Healthy Ageing and Longevity 12
*Series Editor:* Suresh I. S. Rattan

Jonathan Sholl
Suresh I. S. Rattan *Editors*

# Explaining Health Across the Sciences

Springer

# Healthy Ageing and Longevity

Volume 12

**Series Editor**

Suresh I. S. Rattan, Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark

Rapidly changing demographics worldwide towards increased proportion of the elderly in the population and increased life-expectancy have brought the issues, such as “why we grow old”, “how we grow old”, “how long can we live”, “how to maintain health”, “how to prevent and treat diseases in old age”, “what are the future perspectives for healthy ageing and longevity” and so on, in the centre stage of scientific, social, political, and economic arena. Although the descriptive aspects of ageing are now well established at the level of species, populations, individuals, and within an individual at the tissue, cell and molecular levels, the implications of such detailed understanding with respect to the aim of achieving healthy ageing and longevity are ever-changing and challenging issues. This continuing success of gerontology, and especially of biogerontology, is attracting the attention of both the well established academicians and the younger generation of students and researchers in biology, medicine, bioinformatics, bioeconomy, sports science, and nutritional sciences, along with sociologists, psychologists, politicians, public health experts, and health-care industry including cosmeceutical-, food-, and lifestyle-industry. Books in this series will cover the topics related to the issues of healthy ageing and longevity. This series will provide not only the exhaustive reviews of the established body of knowledge, but also will give a critical evaluation of the ongoing research and development with respect to theoretical and evidence-based practical and ethical aspects of interventions towards maintaining, recovering and enhancing health and longevity.

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# Preface

We all have some notion of what a healthy person is or have felt more or less healthy ourselves. And yet, there has been an endless debate about what exactly 'health' is and how it should be defined. Perhaps part of the difficulty is that most standard textbook definitions of health define it in terms of an absence: the absence of disease. As a result, it seems quite difficult to have a science of health, or for health to be considered a scientific concept, since it is supposedly tracking what is not present. On the other hand, what is perhaps the most well-known definition of health outside of the clinical realm comes from the World Health Organization: *health is a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity.* This at least gets around the issue of defining health in negative terms, but it leaves the concept horribly vague and difficult to quantify scientifically. Is anyone ever *completely* healthy?

Is this all there is to be said about health? Should we just abandon the concept entirely? Perhaps we have not been asking the right questions. When the medical sciences are investigating the phenomenon we call 'health,' are they not also tracking the *presence* of some properties, processes or abilities? Wouldn't this latter question force us to clarify what the object of the health sciences actually is? These questions, among many others, were in our minds as we set out to conceive of an interdisciplinary book on 'health.' Through a series of conversations between us—one a philosopher of medicine and the other a biogerontologist—we narrowed down how we might tackle this problem of understanding and even explaining health by bringing together as many different perspectives as we could. We wanted to transport the interdisciplinary conversations we were having into the context of an edited volume where experts in their fields, be they scientific or philosophical, would be challenged to reflect on the implications of their object of study for how to understand and explain health. Now, this is not a question that is often asked outside of the more likely setting of philosophical discussions, and so it required some nudging on our behalf to push the contributors out of their comfort zones. The result is also an interdisciplinary one, though less in terms of collaborations on a given topic and more in terms of the overall composition of the present volume with its mix of scientific and philosophical contributions. This mix produced interesting

challenges and discoveries due to the different expectations of writing in science and in philosophy. We hope that the final composition provides the reader with a diversity of perspectives that complement one another despite their different methods, jargon, topics, and presentation styles.

The volume has been divided into three parts (and a conclusion): one on explaining health from within specific disciplines, one exploring health from the perspective of a bodily system, part, function, or the environment in which organisms are found, and the final part looking at more clinical or practical perspectives. Part I develops the more general evolutionary, biological, and philosophical dimensions of health as discussed in the respective disciplines. Here, the aim is to take a bird's-eye view of health from within an entire field, whether it is evolutionary, molecular or systems biology, or debates within philosophy, and to try to unearth some general insights. The philosophical contributions focus on a range of issues, such as whether there can be a general theory of health and how this pertains to interdisciplinary fields, what philosophers have to say about mental health, and even the relation between healthy aging and authenticity. By and large, the issues raised in these chapters are not ethical ones, but rather issues related to the concepts and models used in the health sciences.

Shifting from entire fields to more specific disciplines within these fields, Part II delves deeper into the structural or systemic aspects, functional aspects, and organismic and environmental aspects of health. The chapters focusing more on localized fields or descriptions present some of the distinct characteristics of a healthy body by, for instance, focusing on a specific part, such as the heart, the mouth, or the microbiome, or on a specific function, such as sleep or sexuality. These internal fields are then complemented by broader organismic and environmental perspectives. There is reflection on how health is correspondingly studied in non-human organisms, such as the famous model organism *C. elegans*, and an analysis of the various challenges facing attempts to unify 'health' across life's diverse forms. The final chapters explore social relations and even public health explanations, providing accounts of the external factors so crucial to understanding health. Part III looks at health from a clinical or practical perspective, with a particular emphasis on the prolongation of health over time, i.e., from health to healthy aging. There is even a reflection of the ancient human dream (or illusion?) of immortality. In these chapters, we find interesting discussions not only about what health is, but how it can be promoted, e.g., through the strategic use of low-dose stressors as described by the notion of 'hormesis.' Finally, Part IV is the conclusion where the editors organized many of the key insights contained throughout the book and extracted some original conclusions and thoughts for future research on health.

Despite these separate parts, the fact that 'health' is a topic that requires interdisciplinary thinking meant that we could not neatly divide the book into science versus philosophy. While the philosophical chapters are largely contained in Part I, there are also contributions by philosophers, or even philosophical contributions by scientists, scattered throughout the other parts. It is in this sense that the composition of the book exhibits interdisciplinarity.

The overarching aim of this volume is thereby to inform, inspire, and encourage intellectuals from various disciplines to assess whether explanations in these disparate fields and across biological levels can be sufficiently systematized and unified to clarify the ever-elusive phenomenon of health. While the result of this volume is a long way from providing a single or unified explanation or even a theory of what health is, we are confident that it is at least one small step in the journey to do so.

Aarhus, Denmark

Jonathan Sholl
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# Contents

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# Part I
# Health Concepts Across Disciplines

# Chapter 1
# Understanding Health from an Evolutionary Perspective


**Thomas B. L. Kirkwood**

**Abstract** Health is a key aspect of the fitness of an organism, both in the everyday sense where fitness refers to general functional wellbeing, and in the more particular sense where fitness refers to competitive success under pressure of evolutionary natural selection. Understanding how evolution influences health is as important for our understanding of chronic, degenerative conditions as it is for gaining insights into the illnesses that arise from the diverse pathogens with which we have co-evolved. This is because selection is subject to constraints, which often involve trade-offs. In particular, the ageing process itself appears likely to have its origins in evolutionary trade-offs involving processes including growth, reproduction and long-term bodily maintenance. This chapter explores what we can learn from an evolutionary perspective on health and what may be the implications for future health at a time when human life expectancy has undergone recent, rapid change.

**Keywords** Health · Evolution · Natural selection · Ageing · Disease · Plasticity

## 1.1 Introduction

How we conceptualise health and its converse, disease, may at first seem straightforward, but in fact is much less so. What exactly is 'disease', and is 'health' merely the state where diseases are absent? Some years ago, whilst working in Africa, I remember greeting a colleague with the everyday question of "How are you this morning?" His reply intrigued me: "Today I am not at ease in my body". Being not at ease, or experiencing "dis-ease", seemed a very good way of expressing that not all was well with him, even though he could not identify himself as suffering from any of the conditions listed in the International Classification of Diseases.

For the World Health Organization, the definition of health is a demanding one: "A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity". By this definition, my colleague was not in a state of health,

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but it was not obvious where the problem lay or how to put it right. On the other hand, a person can be in a state of complete physical, mental and social well-being, even though there may be something seriously wrong with them. One need think only of someone in the earliest stages of incubating a dangerous viral infection, or in whom somatic mutations have started a clone of cells on the road to malignancy.

One lens through which to examine the concept of health is that of evolutionary biology. Evolution is commonly perceived to be an optimising process. But the reality is, of course, that the conditions of life are often far from perfect. Most organisms experience continual challenges to their health throughout most of their lives. Pathogens and parasites are abundant, wounds and injuries are frequent, and health-challenging environmental threats from toxins and stressors are pervasive. The evolutionary perspective on health is thus less a matter of maintaining perfection than of holding diseases and infirmities at bay.

There are perhaps three principal aspects of the interplay between health and disease requiring consideration from an evolutionary perspective. First, what are the evolved mechanisms underpinning the maintenance of health and why do they eventually break down? Second, what part do evolutionary trade-offs play in determining the interplays between health and disease? Third, how is health assured from each generation to the next?

## 1.2 Natural Selection and Its Priorities

Evolution is driven by natural selection. The fundamental principle of natural selection is commonly stated as "survival of the fittest", but the simplicity of this little phrase belies its complexity. To what entity does "survival" refer? By what metric is "fitness" to be defined and measured? These are deep questions and a full examination of them is outside the scope of this chapter. For present purposes, we shall regard the idea of "survival" as referring to the genetic lineage, rather than the individual organism, but even this can become far from straightforward, for example, when considering how it applies to single genes versus genomes.

The idea of "fitness" requires an appreciation that natural selection is fundamentally a numbers game. Even when this is agreed, the definition of fitness is far from elementary. One of the most commonly used metrics of fitness is the intrinsic rate of natural increase of the population in question, also known as the Malthusian parameter. The attraction of this is that it is relatively easy to compute, although to do so generally requires an assumption that the age structure in the population is stable, which will not always be the case. Provided this assumption is made, the relative evolutionary success of different genetic adaptations is judged by comparing their resultant rates of natural increase, the highest being the "winner". Of course, ecological constraints mean that numbers cannot increase indefinitely, but it is possible to surmount this difficulty if the winning adaptation has a zero rate of natural increase when at equilibrium in its environment, whereas the losers have negative rates,

indicating relative declines. Other metrics of fitness include maximising the "carrying capacity" of the environment for individuals bearing a particular adaptation, or minimising the long-term risk of extinction.

When addressing the evolutionary perspective of health, a very important aspect of how natural selection imposes its priorities has to do with age. This is because the population contains a mix of individuals of different chronological ages, i.e. it is age-structured (Charlesworth 1994). The significance of age structure for selection is enormous. This is because mortality is a one-way street. For any given cohort of individuals who were born at the same time, the number of survivors becomes progressively smaller as they get older. This will occur regardless of whether or not the population undergoes any process of intrinsic ageing, or senescence. The result is that natural selection has an age dimension such that it affects the various age groups within the population differentially. The power of selection—that is, its capacity to discriminate in terms of fitness between alternative adaptations (or, more properly, the genes producing them)—declines with age. Put simply (although there are many mathematical nuances that need to be considered for a full analysis), the force of selection at a *younger* age, when a higher fraction will still be alive and a greater proportion of reproductive potential thereby remains in the future, will be greater than at an *older* age, when the converse will be true.

## 1.3 Health, Damage and Repair

Even if we suppose that a new-born individual begins life in perfect health, this state will come under immediate threat from a vast array of mechanisms that cause damage. From without, these include pathogens, UV and other forms of radiation, oxidative stress, toxins and all kinds of injuries. From within, there is an equally threatening, if less immediately obvious, variety of molecular and cellular damage. Much of this internal damage derives from the almost inevitable errors that arise within the fundamental pathways that are responsible for the information transfer and processing reactions that underpin living systems (Kirkwood et al. 1986). Errors are made in DNA replication, RNA synthesis and processing, and in protein translation. To combat the accumulation of these kinds of damage, significant investments are made both in prevention (e.g. proof-reading) and clearance (e.g. autophagy). Overall, the metabolic investments in maintenance and repair to deal with the external and internal threats to health are likely to be very considerable.

Since dealing with damage is costly, we need from an evolutionary perspective to ask: how necessary is it to make this investment? The answer to this question is revealing. On the one hand, it is clearly worthwhile to make sufficient investment that the organism does not suffer significant impairment too soon. The evidence to support this conclusion is apparent from the array of maintenance systems that we see to be at work in all cells and tissues at all times. On the other hand, in the light of the decline in survivorship caused by natural mortality from other causes, it is unlikely to be worth investing more in maintenance and repair processes than is necessary

to keep the body in sound condition for as long as it has a reasonable chance still to be alive. Within a context where death usually occurs from some environmental or accidental cause, such as infection, predation, injury, or cold, life expectancy is often quite short.

The result of the logic just outlined is the concept known as the "disposable soma" theory of ageing (see Kirkwood and Austad 2000). With respect to the somatic tissues and organs of the body, natural selection is expected not to have delivered a greater capacity for maintenance and repair than is needed in the natural environment. For an animal like a mouse, mortality pressure in the wild means that very few individuals survive beyond 1.0–1.5 years (Berry and Bronson 1992). Therefore, the mouse only needs its somatic maintenance systems to secure reasonable health expectancy for this long, as is seen. However, if mice are moved to protected environments, they survive longer, until damage accumulates to cause diseases and eventually death by about 3 years of age. For humans, the exposure to hazard per unit of time is much less than it is for mice. Nevertheless, a similar argument applies, but with roughly a 30-fold expansion of the timescale.

The underlying driver of age-related deterioration is thus seen to be the progressive, lifelong accumulation of molecular and cellular damage of many kinds (Kirkwood 2005). Each of these kinds of damage is a contributor to the biology of ageing. Over the long history of biological research on ageing, there has been a tendency to posit that one or other mechanism is *the* cause of ageing. Such an approach has brought its frustrations, since for each individual mechanism there may be evidence that the hypothesised type of damage does accumulate with age, but generally there is insufficient evidence that it can account for ageing alone. It is now recognised that ageing involves the actions of multiple mechanisms acting in concert, perhaps with synergistic interactions between them.

In addition to the primary mechanisms through which damage occurs, there is also a set of features of biological ageing that should be regarded as secondary. These include impairment and dysfunction of key aspects of normal physiology, such as intercellular signalling, maintenance of tissue homeostasis, immune surveillance, control of gene expression, and basic metabolism (López-Otín et al. 2013). With each of these aspects, the gradual disruption that occurs with ageing results in a progressive deterioration of the fundamental basis of health. In some instances, the damage may trigger the activation of evolved secondary responses, such as inflammation, cell death (apoptosis) or the permanent withdrawal of cells from division (replicative senescence). For these secondary responses, which involve regulatory pathways that detect and coordinate the response to damage, it seems most plausible to suppose that the ultimate evolutionary reason for their existence was to cope with acute injury and stress in younger organisms. The fact that they operate extensively within older organisms as an intrinsic feature of the ageing process is explained rather by the fact that accumulation of damage drives ageing, than because they evolved specifically to cause ageing themselves.

Once it is understood how ageing arises as the result of damage (and responses thereto), it become much easier to explain the major challenges to health that arise in present-day human populations in the form of age-related disabilities and diseases.

For each of these chronic conditions, age is the single biggest risk factor. For each of them also, some kind of damage is associated with the journey from initiating factors to end-stage pathology. As well as age, there are often other risk factors such as genotype, behaviour, lifestyle, smoking and nutrition. The challenge for modern biomedical research is to understand exactly how the damage accumulation resulting from intrinsic biological ageing relates to the pathways causing individual age-related conditions. In addressing this challenge it seems highly likely that attending to the evolutionary background of both of these components will prove rewarding.

## 1.4 The Importance of Trade-Offs

If evolution is an optimising process, it is optimisation within constraints. If there were no constraints, selection might be expected to have produced 'Darwinian demons' that are born with unfailing integrity, grow to reproductive maturity with exceptional speed, generate high volumes of offspring, and live for ever. It is the existence of constraints that prevents this, and that plays an important part in understanding health from an evolutionary perspective. In the previous section, we saw how cost–benefit considerations with respect to investment in somatic maintenance led to the concept of the disposable soma, and thence to the expectation that accumulation of damage should underpin the biology of ageing and its associated diseases. There would be little or no benefit in better somatic maintenance than is needed when the horizon of survival is set by the prevailing level of mortality, and such maintenance is costly. At this level, no explicit mention of constraints was required, but when we recognise that costs of maintenance need to be set against costs of other necessary functions, constraints become readily apparent. The corollary to the existence of constraints is the idea of trade-offs.

Trade-offs are inherent in the realm of evolutionary life-history theory, where the problem of resource allocation is of major importance (Townsend and Calow 1981; Stearns 1992). Organisms acquire resources, chiefly energy, and must use this energy to accomplish different activities, such as growth, reproduction and maintenance. The optimal allocation strategy will be the one that maximises fitness under natural selection. This involves trade-offs. One option, of course, might be to increase the amount of resources available for allocation, but this involves committing greater effort to food gathering, increasing the efficiency of the digestion process, and so on. Such adaptations to boost the availability of resources will themselves involve trade-offs. And, no matter what is the current level of resource availability, it is still important in terms of natural selection to allocate them in the best way. Thus, trade-offs are essential to understanding biological systems.

In addition to trade-offs arising from allocation of resources, there are also expected to be trade-offs that arise when a particular gene-based trait is 'pleiotropic', that is, when it has multiple effects on the phenotype. If, for example, one of the effects is beneficial in early stages of life, but harmful in later stages, such a trait displays 'antagonistic pleiotropy' (Williams 1957). Within age-structured populations, where

the power of natural selection declines with age, selection to retain such a gene on the basis of its early benefits will outweigh any selection to lose it on account of its later harm. This assumes, of course, that selection could not merely inactivate the gene after its benefit has been realised and before harm accrues, but if the harm occurs late enough then selection to do this might not exist. It is plausible, for example, that replicative senescence as a response to damage associated with ageing might be an instance of antagonistic pleiotropy.

There are many, diverse examples where trade-offs are important for the evolutionary perspective on health (Stearns 1999). In sickle cell anaemia, those who carry a single copy of the causative HbS mutation of beta haemoglobin are resistant to malaria. The considerable survival benefit this offered in the African populations where the HbS allele arose is indicated by the fact that the same mutation appears to have arisen four times independently in distinct genetic backgrounds. The down side of the trade-off arises because homozygotes who have two copies of the HbS mutation suffer from the serious and painful condition of sickle cell disease. In parent–offspring conflict, trade-offs arise from the different interests of parents and their offspring despite the closeness of the genetic relationship. A classic instance is the weaning conflict, where it serves the interests of the mother to stop breastfeeding in order to reproduce again, but it is in the interest of the nursing infant to continue. Trade-offs may also arise through processes of 'sexual selection' where a trait such as large body size, physical aggression or extreme phenotypic ornamentation boost the chances for a male of access to mates, but carry a cost of increased mortality. Indeed, the difference in longevity of the human sexes, whereby women not only live longer than men, but also exhibit lower mortality at all ages, seems likely to be the result of trade-offs.

## 1.5 Inter-Generational Health

It goes without saying that over a timescale of generations, health must be preserved. If it were otherwise, the evolutionary lineage would become extinct. Although reproduction and early life are periods of significant risk, with many attendant challenges to health of parent and child, the canonical case is that life begins anew with each generation, according to Weismann's principle of the immortality of the germ-line (Weismann 1891). Of considerable interest, therefore, is how the germ-line seemingly evades the progressive accumulation of damage that causes the ageing of the soma. Germ cells are not immune to the sources of molecular damage that underlie ageing, and many cells of the germ-line do indeed die, but it must be the case that the essential integrity of those cells that contribute to forming the next generation is preserved. There are broadly three ways through which germ-line immortality can be secured: better maintenance, stringent selection in the germ cell lineage (in order to delete cells that are compromised in their molecular integrity), and selection against progeny carrying faults. It seems likely that each of these three mechanisms has some role to play.

Firstly, embryonic stem cell lines (effectively germ-line) of mice and humans exhibit higher levels of cell maintenance functions than the somatic cells into which they differentiate (Saretzki et al. 2008). Secondly, the processes of gamete maturation and competition appear to offer unique opportunities for aggressive selection. In the case of sperm, vast numbers of cells compete to fertilise the egg, which must ensure that only the most viable are successful. In the case of eggs, the mechanisms of competition are less obvious, but many more potential oocytes are present initially in the ovaries than later mature for ovulation, and it seems probable that some form of quality assurance results in the deletion of those that fail to meet the required standard. Finally, new embryos are at significant risk of failure and spontaneous abortion if functionally defective, and infants born with serious developmental or genetic abnormalities would not have survived long in the absence of modern medical interventions.

Although the inter-generational preservation of health is a general necessity, there can be significant impacts on health that are transmitted across generations. Generally, babies are born with their 'age clock' reset to zero. However, it is well known that late maternal age is associated with increasing risk of a genetic abnormality, such as in Down's syndrome. Advanced paternal age has also been linked with some indication of adverse health consequences for offspring (Nybo Andersen and Urhoj 2017). Some infectious diseases, such as HIV, can be transmitted from mother to child, and consumption of noxious substances (tobacco, alcohol, recreational drugs) while the baby is in utero can have lasting harmful impacts.

Of particular evolutionary interest is the possibility that adaptive responses to the parental environment, especially when adverse, can have consequences that may affect the future health of children and even grandchildren. These have prompted considerable interest in the possible evolutionary basis of developmental plasticity (Bateson et al. 2004). For example, for children conceived and carried to term in adverse circumstances, small size and slow metabolism can aid survival, whereas when resources are more abundant it is preferable to grow larger and faster. Where such plasticity operates, the baby who can respond to the mother's condition before birth might be better equipped to manage in an adverse environment. An unexpected consequence, however, of some of the rapid improvements in nutrition and other circumstances that have occurred through socioeconomic development, may be an above-average vulnerability to metabolic disorders (e.g. diabetes, obesity) of those whose parents and grandparents lived in harsher conditions. This is likely to result in a greater burden of age-related chronic conditions and shorter life expectancy.

## 1.6 Conclusion

Evolution has produced health but it has also produced disease. Our co-evolution with the many pathogens that surround us has shaped many of the most important heath challenges that dominated life and death in previous generations. However, evolution has also been responsible for many of the threats to our health that are of ever growing

importance in today's world where we are significantly (if far from completely) safer from infection, but increasingly vulnerable to the chronic deterioration that is ageing.

Understanding how evolution has shaped our life history is of huge relevance for understanding age-related disease. Our bodies are not programmed to die; they are programmed for survival. But individual survival was never a high enough priority for natural selection to maintain our bodies well enough to last forever. Indeed, some of our very survival mechanisms, such as inflammation, may only make matters worse when we reach old age. Within this framework, it becomes possible to understand not only the trajectories of health that play out across the life course, but also how to think about strategies to preserve the thing or property that we call 'health'. Since the damage that will ultimately cause the individual to age and die accumulates progressively throughout life, there is no particular point at which ageing actually begins. Age-related disease begins at the point that some agreed diagnostic threshold is passed. The new emphasis on using the science of ageing to extend 'health span' boils down essentially to trying to enhance maintenance and mitigate damage where it occurs. However, we must be prepared also for side effects that reflect the presence of trade-offs and constraints.

If we can apply our understanding of evolutionary aspects of health to the new challenges that result from demographic change, we may be empowered to make much needed progress.

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# Chapter 2
# An Evolutionary Analysis of Health


**Kenneth R. Arnold, James N. Kezos, Grant A. Rutledge, Thomas T. Barter, and Michael R. Rose**

**Abstract** Most people are interested in achieving or sustaining health. Unfortunately, there are few topics that have been more subject to confusion and contradiction than that of human health. We believe that an evolutionary perspective can make a signal contribution to clarifying the foundations of health, including the prospects for its successful maintenance. Here we provide an outline of how health is defined, the historical progression in the improvement of health, and proposals for remedies that derive from evolutionary research. In the process we will address the critical need for new approaches towards treating chronic diseases, noting the apparent lack of progress made by pharmaceutical research and development. Our evolutionary strategy for improving health is rooted in aging research, including insights into the impact and limitations of altering diet and dietary supplementation.

**Keywords** Human health · Aging · Evolution · Anti-aging substances

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## 2.1 Defining Health—An Evolutionary Perspective on the Meaning of Health

### *2.1.1 What is Health?*

One of the greatest obstacles to scientific dialogue is semantic confusions. Entire disciplines are marred by debates concerning the scope of a term or theory. While these clashes occasionally foster useful distinctions, all too often they are unnecessary if not wholly pedantic. To avoid opacity, we will explore the origins of the word 'health', focusing chiefly on how it pertains to evolutionary biology and 'aging'.

The Old English etymology of 'health,' from hælþ, describes a state of wholeness, of being whole, sound or well. Similarly, the infinitive 'to heal' means to cure, save, and make one whole (Oxford University Press, health). From its roots, the term health has incorporated a notion of completion in all respects that make one well and 'whole'. Though its holistic meaning is often lost in common vernacular, it is nonetheless vital in considering the multidimensionality of health and its deterioration during aging.

### *2.1.2 Aging and Healthspan*

Our focus on aging leads us naturally to the generally perceived decline in health with the passing of time. The term 'aging' is often used to refer to senescence, a deterioration with the passing of time, a term that in turn stems from the Latin root senex or senis meaning 'old' (Oxford University Press, senesce). For most contemporary gerontologists, aging is akin to the breaking down of a car with planned obsolescence—your car disintegrating when your lease or payments contract is effectively done. It is the hope of conventional gerontology that, by targeting the specific physiological mechanisms of damage responsible for their conjectured cumulative physiological breakdown, they will discover how to extend life, including health presumably. However intuitive this strategy may be, notable anomalies cast serious doubt on their core presupposition that aging is indeed neither more nor less than cumulative damage leading to physiological breakdown. Invertebrates that reproduce solely or chiefly through fission do not exhibit demographic or physiological aging, suggesting that ineluctable accumulation of damage is not a sufficient explanation for aging in and of itself (Bell 1984; Martínez 1998). Likewise, numerous experiments have successfully produced populations with extended lifespans, including extended healthspans, by altering the action of natural selection alone (e.g. Rose and Charlesworth 1980; Luckinbill et al. 1984). Furthermore, the physiological machinery that has been altered in longer-lived populations apparently revolves around reproduction and whole-organism stress resistance, not biochemical damage at the molecular level (Rose et al. 2004).

Current evolutionary theory for aging is primarily based on the mathematical principle that the forces of natural selection fall with adult age (e.g. Hamilton 1966; Charlesworth 1980; Rose 1991; Rose et al. 2007). The observed decline in health among aging organisms is explained in terms of falling forces of natural selection, which is closely associated with a pervasive loss of age-specific adaptation and physiological functions. Aging in the context of evolutionary biology is thus defined as the persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration (Rose 1991; Rose et al. 2012). The evolutionary explanation of aging will be further elucidated in later sections.

This view of aging leads us to a revisioning of health in terms of adaptation. That is, our view of health is that it is ultimately derivative from the core evolutionary concept of adaptation. As we will develop below, health in the absence of infection is a manifestation of age-specific adaptation, where adaptation is in turn focused on reproductive success, over the entire lifespan or an age-specific interval. Going forward, our characterization of different ideas of health depends fundamentally on how natural selection shapes adaptation, including the dramatic failure of natural selection to sustain age-specific survival and reproduction, a failure generally called "aging."

Combining health and aging into a unitary metric leads to the general term 'healthspan'. More faithful to the origins of health as a holistic measure of wellness, healthspan describes not only the capacity to survive, but also to function while alive. Many may wish to prolong life, but fail to consider whether some scenarios of prolonged life would be worth living. This brings to mind fates possibly worse than death, such as the 'living dead' common in Western culture since the struldbrugs of Jonathan Swift's *Gulliver's Travels,* if not earlier. In our view, any intervention that aims to combat aging should do so in a way that addresses healthspan, not just survival.

Over many years, the meaning of the word health has been corrupted. Used as a buzzword, especially when conjoined with the marketing of commercial products, it has become a 'good thing' to be strived for. In some fields, there is an effort to redefine health and 'revolutionize the industry' in accordance with corporate or political objectives. Our view is that there is no need to redefine health, but rather a need to restore its initial meaning. With quantitative evolutionary biology guiding the study of healthspan, we should be able to develop a useful foundation for understanding and improving health.

### *2.1.3 Observing Health*

Healthspan can be measured in many ways, and those measurements can have different implications depending on the parameters considered. When performing experiments on evolutionary function or adaptation, choosing appropriate life-history

phenotypes as metrics for fitness is essential. An example of such a quantitative measure of fitness is Ro, which is the summation over all ages of the products of survival probability to a particular age with the fecundity at that age (vid. Charlesworth and Charlesworth 1973). An age-specific evolutionary metric of health is instantaneous fecundity at a specific age. This character gives an age-specific measure of the most essential Darwinian function: net reproduction. Given that natural selection acts on all life-history characters that foster Darwinian fitness, we hold that some quantitative accounting for this relationship between life-history characters and fitness is essential when addressing healthspan. Furthermore, how one chooses to characterize fitness and healthspan quantitatively may alter the implications of one's findings.

Some of the first experimental research linking longevity with inheritance was performed by Raymond Pearl and his associates (Pearl 1922; Pearl and Parker 1922; Gonzalez 1923), who chiefly used *Drosophila melanogaste*r as their model organism. By creating inbred lines with abnormal morphological phenotypes, they were able to demonstrate the effects of genetic background on survivorship patterns. The longevities of the laboratory stocks they used were relatively low compared to those of outbred fly stocks. Laboratory stocks with low effective population sizes undergo accelerated genetic drift, leading to the fixation of recessive deleterious alleles. In effect, loss of heterozygosity reduces longevity. Clarke and Smith (1955) directly tested this interpretation by crossing their inbred fly lines to produce hybrids with improved longevity. The hybridization of inbred lines has a beneficial effect by reintroducing heterozygosity at fixed sites that are unique to each line. Thus, the increased longevity of hybrids reflects a return to more normal conditions, not a "boost" in longevity or lifespan. Furthermore, because the fixation of alleles in inbred lines is a result of the random operation of genetic drift, there is no way of predicting which alleles will be fixed during inbreeding. This random variability makes replication of research results with inbred lines or their hybrids difficult if not impossible.

Another way in which aging and health can be manipulated is through a change in environment. The "healthspan" of any cohort can be subjected to a wide-range of environmental challenges, including dietary change and ambient physical conditions. These effects are particularly extreme in ectotherms subjected to variation in ambient temperature. Laboratory Drosophila, for example, have healthspans that are strongly affected by a long list of environmental factors, from ambient oxygen concentration (Kloek et al. 1976) to larval density and crowding (Lewontin 1955; Lints and Lints 1971). Ambient temperature effects on Drosophila lifespan were demonstrated as long ago as the work of Loeb and Northrop (1917), where the general result is lifespan being inversely correlated with temperature over the range of 10–30 °C (Alpatov and Pearl 1929; Maynard Smith 1963). (The topic of nutrition and pharmaceutical supplementation is explored in greater detail in Sect. 4.2.1).

In order to properly study aging experimentally, it is essential to use genetically appropriate organisms, and to control environmental conditions effectively. Though this is challenging, it is not an impossibility.

## 2.2 Achieving Health: Challenges Confronting Present-Day Medicine

### *2.2.1 The Progress of Medicine in Improving Health*

The medical term "panacea" derives from the Greek goddess of the same name, its etymology coming from "pan akos", or "cure all" (Oxford University Press, *panace*). In some myths, Panacea is the daughter of Asclepius, god of medicine, and is known for aiding the diseased with an elixir or potion of universal benefit. Her presence is notably summoned in medicine's Hippocratic Oath. The idea of searching for such a universal elixir of health, however, is present in most cultures. Its ubiquity illustrates both the pervasive hope for universal cures, along with the common tendency of humans to presume that such simple solutions are possible.

One notable epoch in medicine that approached the level of providing a panacea was the health revolution achieved with the victory of the germ theory for the etiology of contagious disease. The previous medical orthodoxy concerning such diseases had been that they arose from "miasma," or unhealthy vapors. The idea of miasma as a source of disease transmitted through the air dates back to the Greeks, who generally attributed infectious disease to a pollution of the air that in turn arose as a result of a crime or violation of nature. The concept appears, for example, in Thucydides' *History of the Peloponnesian War*. While misconceived in theory, the concept of miasma was sometimes useful in practice. It led to physicians discouraging direct contact with infected individuals, or the close inhalation of their breath, in order to prevent the spread of disease. This usefulness proved insidious in the long-term, however, as it made it more difficult for the germ theory to supplant the miasma status quo. Even after the advent of an explicit germ theory for infectious disease in 1840, miasma continued to dominate medical practice for decades, persisting long after the germ theory became the predominant theory among biologists. The germ theory for contagious disease eventually displaced the miasma theory because it saved lives both in the actual practice of surgery and in public health interventions, such as the provision of water and milk that had been processed to remove bacteria by pasteurization, among other procedures. Identifying specific communicable pathogens as the culprits for infectious diseases was extremely useful for medicine. However, merely taking into account the existence of such pathogens saved lives by itself. Understanding the salience of this historical precedent is important for our discussion of alternative theories of healthspan and aging.

The third major instauration in the progress of medicine took place with the genetic revolution of the twentieth century, especially once it integrated biochemistry with molecular genetics, thanks to the discovery of the nature and role of DNA. With the molecular machinery of genetics sorted out, molecular biologists could tether physiological deficiencies to specific DNA lesions. This reframed the causes of non-infectious diseases. An example is the case of trisomy-3, where the originally hypothesized causes of the disease were mixed up with fetal alcohol disorders and further muddled with notions of race degradation (Patterson and Costa

2005). Some of the difficulties with the explanation of "errors in metabolism" by Archibald Garrod in his 1923 book *Inborn Errors of Metabolism* were elucidated by molecular research on genetic diseases. Many rare genetic diseases that were caused by point mutations had their downstream effects traced to specific metabolic consequences. An example of this is cystic fibrosis, which we now understand is a condition caused by a disabled transmembrane conductance regulator ("CFTR") gene (Rommens et al. 1989, Gadsby et al. 2006). All told, this work is among the most impressive biomedical research of the twentieth century.

### *2.2.2 The Modern Health Crisis*

In broad terms, a central question we must address is why people of our modern age are so unhealthy. For the purpose of clarity, we will focus primarily on the health problems of First World countries. However, recent epidemiological data suggest that the present-day "Second World" countries, such as China or India, are rapidly converging on the chronic disease patterns of Western countries or Japan (Chatterji et al. 2008).

We consider chronic diseases as both causes of death as well as contributory factors in loss of quality of life with age. As such, we define chronic diseases as "a physical or mental health condition that lasts more than one year and causes functional restrictions or requires ongoing monitoring or treatment" (Buttorff et al. 2017). The most pertinent chronic diseases include stroke, heart disease, and cancer, with two-thirds of all deaths in the United States resulting from these diseases alone (Raghupathi and Raghupathi 2018). However, these figures do not reveal the full impact of chronic diseases, as recent studies find rampant comorbidity among major fatal diseases. Additional chronic diseases like hypertension, kidney disease, and diabetes are often found in conjunction with more obviously fatal disorders, like heart disease. The natural inference is that the biological stress posed by having one of these chronic diseases will greatly increase the probability of acquiring another. This means that, while a patient may die of heart disease, the initial cause of the onset of that fatal disease might be fairly attributed to, for example, an episode of renal failure which triggered the decline of other major functions. This scenario illustrates a basic challenge facing physicians in their struggle to diagnose and elucidate the actual cause of illness, in that chronic diseases are often etiologically interconnected.

Currently about 133 million Americans suffer from at least one chronic disease and are at significant risk of acquiring multiple chronic diseases (Tinker 2014). Given that all of these disorders are somewhat preventable, their successful treatment and management could have considerable implications, not only for the wellbeing of the afflicted, but also for the release of funds that could be directed toward the treatment of less manageable illnesses.

### 2.2.3 The Marginal Utility of Current Techniques

The progress made by reductionist molecular biologists in discerning the mechanisms and pathways of single-locus genetic diseases has been invaluable. In addition, by characterizing the machinery of the cause and effect of large-effect mutations in the genome, molecular genetics provided a framework within which the functions of non-afflicted individuals might be explained. But for most non-infectious chronic diseases, the culprit isn't a single genetic defect.

Many misconceptions concerning non-infectious disease stem from the hopes and idealization that prompted the human genome to be sequenced. At its inception, proponents of the Human Genome Project were confident that, by sequencing the human genome in its entirety, we would have a straightforward explanation of all maladies related to chronic diseases (Shreeve 2005). By employing similar techniques to those used to combat rare genetic disorders like cystic fibrosis, detailed above, the hope was to find a few aberrant DNA sequences responsible for each chronic disease, and then treat such chronic disease by making appropriate alterations to such sequences in somatic cells (Rose et al. 2017).

But once the human genome was sequenced circa 2003, after the genomes of nematodes and flies were sequenced in the late 1990s, this technological vision was not achieved. What was discovered instead was that the functional architecture of the genomes of eukaryotic organisms is vastly more complicated than initially presumed. Unlike the traditional notion of the human genome as a neatly organized library of coding genes, genomicists were met with long stretches of intergenic DNA peppered with genes amidst abundant intact and degenerate transposable elements. Not only has it been difficult to associate genic DNA with biological functions and chronic disease, there is even evidence that non-coding regions have functional effects that might be shaped by natural selection, making the genome-wide foundations of health extremely challenging to infer. It became evident to those working particularly with large outbred populations that simple narratives involving a few genes affecting each chronic disease would be the exception, not the rule.

Here we propose a different problematique for medicine. The germ theory for contagious disease has given us antibiotics, antivirals, and vaccinations that have already mitigated most health-related issues that arise from infectious disease. While there is a continuing need for new antibiotics, antivirals, and vaccinations thanks to the evolution of our pathogens, biomedical science fundamentally has the tools to deal effectively with infectious disease. In the same vein, our current approach to addressing rare single-nucleotide polymorphisms is sound, and showing great promise of further progress with the advent of CRISPR technologies (Papasavva et al. 2019). The area of medicine that is in need of substantial improvement is the treatment of chronic, aging-associated, non-infectious diseases, with which contemporary medicine has achieved only halting progress. We believe evolutionary analysis can make a fundamental and non-trivial contribution towards the improvement and

better understanding of health. But, as we will now explain, the biomedical development strategies based on this analysis, and their medical implementation, will be different as well as difficult.

## 2.3 The Evolutionary Approach to Aging and Chronic Disease

### *2.3.1 Natural Selection on Aging*

Having raised the interconnected relationship of aging, chronic disease, and health, a fundamental query that could be asked is, why do organisms age at all. We address this essential question by providing some background on the development of the evolutionary theory of aging. Only then can we make proper inferences into the true causes and future treatment of aging-related chronic diseases.

The fact that aging is observed at all may seem counterintuitive from the view of natural selection. To the layman, the longstanding phraseology of 'survival of the fittest' is often misconstrued as implying the progressive improvement of a species from generation to generation, a doctrine that comes from Lamarck not Darwin. There is no guaranteed arc of progress that inheres in natural selection. Darwin's theory instead provides an explanation for adaptation in those cases where it arises. It is specifically part of Darwinian thinking that organisms will often fail to adapt successfully, and thereby go extinct. Individuals that possess heritable attributes that increase their ability to survive and reproduce are at an advantage with respect to transmitting these attributes to further generations. As a result, advantageous and heritable attributes will become more prevalent within a population. This pattern by which natural selection increases the mean fitness of a population can be demonstrated mathematically (Nagylaki 1977; Ewens 1979).

These ideas in turn lead to the predicament of why so many organisms molded by natural selection exhibit declines in survival and reproduction with increasing adult age. A common supposition is that the absence of aging is simply not possible, because natural selection lacks the necessary genetic variants to produce an organism that does not age. This notion of a universal upper-limit to natural selection's ability to sustain reproduction and survival indefinitely is met with key exceptions among coelenterates, plants, and protozoa, including some hydra, sea anemones, creosote, and juniper (Rose 1991). These organisms too are nevertheless shaped by natural selection, while they also have the same basic eukaryotic molecular biology as organisms that do undergo aging. Yet these species do not undergo demographic aging, when kept in good conditions.

The critical difference between these non-aging species and those species that do age is the *manner* by which they reproduce. Many coelenterates and protozoa undergo a process called "fission," by which these organisms divide to form two new comparably sized organisms, a method of reproduction uncharacteristic of most

eukaryotic organisms. This disparity marks a divide between sexual and asexual organisms in the evolution of aging, as we will now explain.

### 2.3.2 First Proposals of Evolutionary Theories of Aging

Likely the earliest proposal of an evolutionary explanation for aging was provided by Alfred Russel Wallace, co-discoverer of natural selection. Wallace hypothesized a trade-off between an organism's survival in relation to its production of progeny or perhaps their survival (Weismann 1889). Weismann built upon Wallace's work and postulated what could be interpreted as a nascent conceptualization of the force of natural selection with respect to age. A common misconception among these biologists was, however, their justification for aging. Often they viewed aging as a means to weed out the old for the benefit of future generations, discounting the far more impactful role of environment and predation in eliminating older individuals (vid. Medawar 1952).

Taking a different though related tack, Haldane (1941), Medawar (1946, 1952), and Williams (1957) promoted the argument that natural selection operates with less effectiveness on characters that benefit an individual primarily in later life. This principle is perhaps best evinced by a lethal disorder, Huntington's Disease. The prevalence of such a devastating genetic disorder was explained by Haldane (1941) in terms of its late onset, usually in an adult's mid-thirties to mid-forties. Given that most Huntington's victims are able to reproduce early in life prior to the manifestation of clinical symptoms, only now, in an era when many individuals live well past the age of reproduction, are we suffering from its full impact. This disease illustrates the weakened "force" that natural selection has, by failing to remove such late-acting deleterious alleles; it is among the more common genetic diseases. Examples like these provided inspiration for a more formal development of the evolutionary theory of aging.

### 2.3.3 Hamilton Derives the Forces of Natural Selection

William Hamilton (1966) demonstrated mathematically how the weakened forces of natural selection at later ages impact age-structured populations. His chief result is given in Eq. (2.1), showing the impact of natural selection on age-specific survival. Nested within this equation are parameters that can be used to assess healthspan: $l(y)$ is the "survivorship", the probability of surviving from birth to a given age $y$; and $m(y)$ is fecundity at the same age $y$. The survivorship and fecundity parameters of a given population are the values used to solve for the Malthusian parameter $r$ in the Euler-Lotka equation (not shown). In a homogenous population, $r$ gives the rate of population growth.

$$s(x) = \sum_{y=x+1} e^{-ry} l(y) m(y) \tag{2.1}$$

The value of *s(x)* weights the impact of a genetic variant affecting survival probabilities at age *x*, as it represents the expected reproductive output *after* age *x*, as a proportion of lifelong, net, reproductive output. Accordingly, immature individuals benefit from an *s* value of one (1), at ages before anyone in the population reproduces. The *s* function then starts to decline with the onset of reproduction in the population as a whole, finally reaching zero when the reproductive window closes. There is a similar equation for the age-specific force of natural selection acting on fecundity, represented by the following scaling function (2.2).

$$s'(x) = e^{-rx} l(x) \tag{2.2}$$

Equation (2.1) provides a mathematical foundation for Haldane's speculations concerning cases like Huntington's Disease, in that adverse effects of the disorder normally arise only after the end of reproduction. It also explains the lack of aging among fissile organisms: they do not have a decline in the force of natural selection acting on mortality, because as soon as they reproduce there is no residual adult. Each act of reproduction produces two juvenile organisms, in the absence of physiological asymmetry between the products of fission.

Derived from Hamilton's equations (1966), Fig. 2.1 represents the age-specific force of natural selection acting on survival as a percentage of its full force. Natural selection is strongest at earlier ages (a) and begins to decline after the start of reproduction (b). This decline continues until the last age of reproduction (c) of a population's evolutionary history.

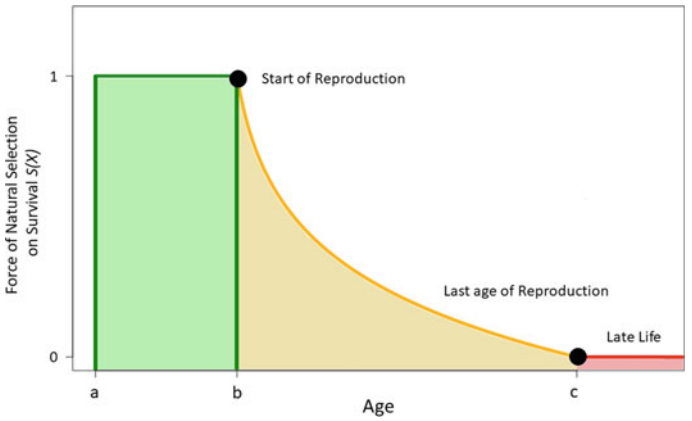


**Fig. 2.1** The scaling of the age-specific force of natural selection acting on survival falling with adult age

The evolutionary explanation of aging does not necessitate any particular biochemical pathways or physiological mechanisms of aging. The evolutionary theory of aging allows any type of failure of adaptation at later ages, whether they involve damage, dysregulation, or the wholesale absence of structures or functions required for continued survival (Rose 1991).

However, one mechanistic possibility particularly emphasized by Williams (1957) and Rose (1985, 1991) is "antagonistic pleiotropy." Put briefly, the concept of antagonistic pleiotropy is one of genetic trade-offs between early reproduction and subsequent aging, where alleles that provide early beneficial effects have pleiotropic deleterious effects in later life. With the preferential focus of natural selection on early ages, arising from the Hamiltonian weighting functions (1) and (2), antagonistic pleiotropy genes have their evolutionary fate determined primarily by their early effects, not their later effects. In this way, evolution by natural selection is biased against survival or reproduction of individuals later in adult life, when natural selection is weakest, providing there is antagonistic pleiotropy among alleles affecting survival or reproduction differentially across the life history.

### *2.3.4 Experimental Implementation of Evolutionary Theories*

The most direct support for the biomedical salience of the evolutionary theory of aging is the creation of "Methuselah Flies," Drosophila lines that achieve a longer lifespan solely by altering the Hamiltonian forces of natural selection through delayed reproduction over the course of multiple generations (Rose et al. 2004). [In terms of Eq. (2.1) above, delaying the start of reproduction in an evolving population increases the age at which the $s(x)$ function first starts to decline.] In addition to increased longevity, these lines feature increased stress resistance, increased total reproduction, as well as improved athletic endurance (Rose et al. 2004). These findings suggest that progress toward enhanced healthspan is achievable without a "Faustian bargain" that exchanges globally depressed biological function for mere extension of longevity. That is to say, the Methuselah Flies that are produced evolutionarily by delaying the first age of reproduction over many generations have functional adaptation, or healthspan, extended to later ages. Their pattern of age-specific mortality is shown in Fig. 2.2 where the "C" flies are from Methuselah Fly populations, and the "A" flies are from populations that reproduced at early ages only.

Two additional features of the biology of these flies are of interest. The first is that such flies exhibit reduced very early reproduction, in conformity with the antagonistic pleiotropy hypothesis. The second is that genome-wide analysis of single-nucleotide, transposable-elements, and structural-variant polymorphisms reveals that many sites in the genome underlie this demographic transformation (Graves et. al 2017). Other functional and omic research with fruit flies corroborates these results (Remolina et. al 2012). Thus, many of the earliest intuitions of Medawar (1952) and Williams (1957) about the evolutionary control of aging have been strongly supported by

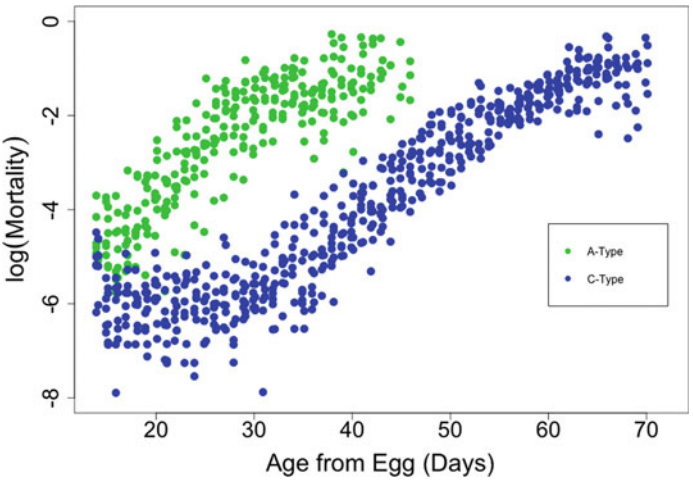


**Fig. 2.2** Adult age-specific mortality in females from 10 A-type and 10 C-type selected populations. Points represent log-transformed mortality rate per population in each selection treatment. Data from Burke et. al (2016)

strong-inference experiments: there are genetic trade-offs between early and late ages; and the underlying physiology of aging is complex.

Rose has repeatedly proposed the use of such Methuselah model organisms as a starting point towards understanding and improving human healthspan. A first step in this direction has been the use of homology to proceed from genomic and other omic differentiation in Methuselah Flies to corresponding human genetic variants (Rose et al. 2010). But few laboratories have taken such steps, to date.

## 2.4 Evolutionary Healthspan Interventions

### *2.4.1 Diets Out of Time and Evolutionary Mismatch*

Our dietary proposals for how to prevent and mitigate the effects of chronic disease are founded on the intersection of the evolutionary theory of aging with the concept of evolutionary 'mismatch' (Gluckman et al. 2019; Rutledge 2018). Thanks to the implementation of practical insights that derive from the germ theory of disease, industrial civilization has greatly extended mean lifespan and improved the quality of life, especially by providing access to clean water and sanitation. Some of these industrial alterations in the human lifestyle, however, are proving to be deleterious. For many physicians the modern lifestyle, often laden as it is with high fructose corn syrup, trans fats, and sedentary habits, is believed to be responsible for the increased incidence of heart disease and dementia (Lindeberg et al. 2007; Davis

2011; Perlmutter 2013). Here we see a clear connection to healthspan, wherein the mortality risks of heart diseases are comorbid with the loss of quality of life found in dementia. The evolutionary explanation for this is that we are simply ill-equipped genetically to handle such radical novelty.

The remedy is apparent, but unlikely to be popular. Changing diet and lifestyle to fit our ancestral adaptations are commonly supported options among anthropologists (Eaton and Konner 1985; O'Keefe and Cordain 2004; Jönsson et al. 2009; Lindeberg 2010). Though evolution has been demonstrated to occur rapidly under experimental conditions (Burke et al. 2016), human adaptation to the twentieth century lifestyle is still many generations away. We are simply stuck with our current genomes, facing complex and chronic diseases that are exacerbated by modern diets and modern inactivity.

However, evolutionary theory leads to a further subtlety. Hamilton's forces of natural selection scale the rate of adaptation to a new environment *as a function of adult age* (Mueller et al. 2011, Chapter 11). Juvenile and early adult ages are expected to adapt quickly to a new environment, and should therefore be healthy in that new environment, when Hamilton's forces of natural selection are strong, whether that new environment features different ambient conditions or a new diet. But later ages are expected, on Hamiltonian principles, to adapt at a slower rate. This implies that a species which has adopted a new diet will adapt to that diet rapidly at early ages over some hundreds of generations, but only slowly or not at all at much later ages. Therefore, the health of such a species will be even worse at later ages than expected relative to other species that have undergone selection in that environment over a very large number of generations.

It turns out that the stocks of the Rose laboratory (vid. Rose et al. 2004) have been inadvertently subjected to just such a dietary transition, switching from centuries on rotting apples to a synthetically "rotten" banana diet. Rutledge (2018) tested whether there has been an interaction between the forces of natural selection and diet in the Rose laboratory stocks. Specifically, evolutionary analysis suggests that stocks which had strong natural selection only at early ages should lose adaptation to banana at later ages, while stocks that had sustained strong natural selection to later ages should not. Rutledge (2018) found experimentally that this pattern was indeed sustained among laboratory cohorts subjected to different diets: at later ages, stocks that had weak forces of natural selection at later ages were better adapted to a laboratory emulation of their long-abandoned ancestral diet.

The implication for the human case is straightforward, because the experiments that Rutledge (2018) performed constitute a strong-inference test of the general hypothesis of age-specific weighting of the speed of adaptation by Hamilton's forces of natural selection. Eurasian populations of humans have switched from hunter-gatherer diets and lifestyles to agricultural diets and lifestyles over the last twelve thousand years. Young Eurasians should be well-adapted to "organic" agricultural diets and patterns of activity. But much older individuals of Eurasian ancestry probably are not particularly well-adapted to agricultural diets. For such individuals, reversion to a modern-day emulation of a hunter-gatherer diet, with greatly reduced

consumption of grains and milk-derived foods, will probably benefit their health significantly.

However, individuals with ancestry from populations that have not sustained agricultural practices for thousands of years probably lack sufficient adaptation to agriculture at *all* ages. These would unequivocally include the original indigenous populations of Australasia and equatorial Africa. As reviewed by Lindeberg (2010), reverting to emulations of hunter-gatherer diets greatly improves the health of such individuals in small trials. Populations that have more recently adopted agriculture, such as those of the pre-Columbian New World, are probably intermediate. For such individuals, less-agricultural dietary practices even during early adulthood might afford some benefits, with still greater benefits accruing at later adult ages.

In general, this line of evolutionary analysis suggests that the specific evolutionary histories of human population are relevant to their best dietary and activity patterns for enhancing healthspan. Nonetheless, as this is a new direction for evolutionary research, much work remains to be done.

### *2.4.2 Pharmaceutical Strategies*

As alterations in diet have demonstrated clear impacts on healthspan, a natural question is what the evolutionary analysis of healthspan suggests concerning the development and use of pharmaceuticals. Monetary investment in the discovery of new drugs is drastically increasing, but with only marginal returns (Pammolli et al. 2011). Thus far, pharmacological and medical research on chronic disease has been rooted in physiological theories of aging, with a clear bias in favor of searching for simple molecular etiologies for chronic disease, after the fashion of the etiologies of single-locus genetic disease. By contrast, genomic research like Genome-Wide Association Studies reveals the involvement of many loci of individually weak effects on chronic disorders, like cardiovascular disease. Reductionist molecular genetics offers few tools for investigating, much less treating, such chronic disease.

Experimental evolutionary genomics research suggests that this problematic situation is indeed rooted in basic aspects of the machinery underlying chronic disease. For example, experimental evolution of different rates of aging in Drosophila populations is underlain by changes at hundreds of sites in the fruit fly genome (Burke et al. 2010; Graves et al. 2017), as already mentioned. That is, to make a fly live about twice as long, it takes genetic change at hundreds of sites. Transcriptomic analysis likewise reveals that such a transformation in healthspan is associated with more than 600 differences in transcriptome abundance in mid-life (Barter et al. 2019). Metabolomic research still ongoing does not indicate a narrowing of complexity at that omic level either. Overall, the reality is that most chronic disease is underlain by omic complexity, and thus physiological complexity (Figs. 2.3 and 2.4).

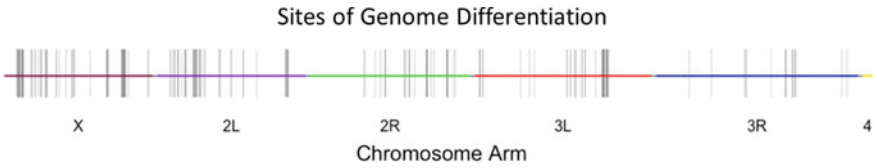


**Fig. 2.3** Sites of genomic differentiation between 10 A-type and 10 C-type selected populations. Each line represents the location of a differentiated SNP region (50 kb) within the Drosophila genome. Each chromosome arm is color coded with a designated color. Data from Graves et. al (2017)

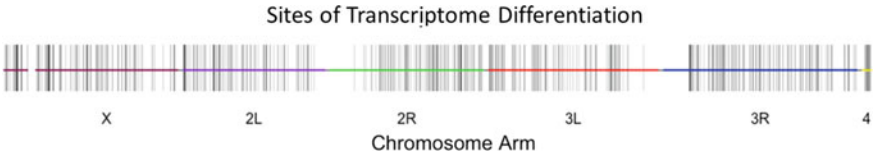


**Fig. 2.4** Sites of transcriptomic differentiation between 10 A-type and 10 C-type selected populations. Each line represents the location of a differentiated SNP region (50 kb) within the Drosophila genome. Each chromosome arm is color coded with the same designated colors. Data from Barter et. al (2019)

### *2.4.3 The Example of Heart Disease: From Drosophila Hearts to Human Hearts*

A major barrier to understanding chronic diseases is the lack of experimental platforms enabling the rapid and large-scale exploration of gene function on organ function. Experimentally probing *D. melanogaster* physiology via selection experiments has demonstrated the value of this complex metazoan as an experimental model for the study of health and disease. Unlike most microbial models, the physiology of Drosophila is both complex and broadly analogous to some features of vertebrate physiology. A growing body of evidence has demonstrated that fundamental human cellular and physiological processes, including heart function, operate in a similar fashion in Drosophila. Over the past 30 years, Drosophila has become the invertebrate system of choice to study heart development, function, and aging, as well as obesity-related disorders. The tube-like heart structure in Drosophila separates this model species from other common invertebrate model species, making Drosophila the simplest model organism that can be used for heart function studies (Bier and Bodmer 2004). There are important differences between Drosophila and mammalian cardiovascular structure and function, for example, open versus closed circulatory systems. But the conserved mechanisms of heart development and function between Drosophila and vertebrates nonetheless supports the use of this model for heart research (Bodmer 1995; Bodmer and Frasch 1999; Bodmer et al. 2005; Cripps and Olsen 2002; Harvey 1996). There are similarities in (a) early heart development, (b) age-dependent decline in heart function, and (c) the genes associated with heart

development, function, and diseases (Bodmer and Venkatesh 1998; Cripps and Olson 2002; Zaffran and Frasch 2002; Bier and Bodmer 2004; Bodmer et al. 2005; Ocorr et al. 2006, 2007, 2017; Nishimura et al. 2011; Wolf and Rockman 2011; Diop and Bodmer 2012).

The *D. melanogaster* heart has been used as a model for identifying single genes that cause heart disease (e.g. Wolf et al. 2006). Drosophila shares some of the genes that underlie its cardiac performance with those of human cardiac genetics, such as *tinman* (Bodmer 1993, 2006) and *opa1* (Shahrestani et al. 2009). But other types of heart disease undoubtedly involve many genes and thus many biochemical pathways. The kinds of heart disease that are common among present-day human populations are unlikely to result from deleterious alleles of major effect. It would be impossible for these alleles to rise to high frequencies in outbred populations, because of natural selection acting to remove them. Therefore, it would be better to study heart function in large outbred populations that differ in allele frequencies at many loci, rather than just at single loci of large effect. Such Drosophila populations have been produced through experimental evolution in which specific selection protocols are used to produce phenotypic divergence with relative ease in comparison to higher order vertebrate model systems (Garland and Rose 2009; Rose et al. 2004). One approach is to create obese populations via selection. Such starvation-resistant and obese Drosophila populations are a powerful tool not only for studying the evolution of starvation responses, but also for studying metabolic disorders and related cardiac dysfunction. Hardy et al. observed dilated hearts and reduced contractility in their three evolved obese populations after 65 generations of selection for starvation resistance. Fruit flies with increased lipid content in other studies display hyperglycemia, insulin resistance, reduced cardiac contractility, and cardiac arrhythmias (Birse et al. 2010; Hoffmann et al. 2013; Na et al. 2013; Trinh and Boulianne 2013).

The types of heart disease that are prevalent among present-day human populations are unlikely to result from deleterious alleles of major effect, instead involving many genes and thus many biochemical pathways. It is therefore important for our understanding of human heart disease to study heart function in these large outbred populations of *D. melanogaster* that differ in allele frequencies at many loci. The use of multi-omic tools with these Drosophila populations across multiple ages could help parse the genetic and molecular underpinnings of heart function, heart disease, and other obesity-related disorders. Recently, Hardy et al. (2018) and Kezos et al. (2019) have published studies of the genomic foundations and cardiac effects of selection for extreme obesity in Drosophila. Once again, many sites in the genome are involved. However, as we discuss below, we now have machine learning tools that can help us make sense of the physiological complexity underlying healthspan and chronic disease in such well-defined experimental systems.

### *2.4.4 Machine Learning in the OMIC Age*

The immense omic complexity underlying chronic disease suggests that to make progress machine learning is a necessary resort. Over the last decade, omic-centered publications have demonstrated the omic complexity underlying extended healthspan, even in model organisms (e.g. Graves et al. 2017). Machine-learning tools like "FLAM" (for Fused Lasso Additive Models) have nevertheless shown success in parsing genome-wide differentiation to identify the causal links between omic differentiation and functional characters (Mueller et al. 2018). Analyses such as these will allow the integration of phenotypic, transcriptomic, metabolomic, and genomic data from highly differentiated populations. In particular, FLAM can identify the specific pathways which underlie each kind of chronic dysfunction, such as those of heart disease. By identifying the causal foundations of healthspan at the genomic, transcriptomic, and metabolomic levels using machine learning, we can begin to identify opportunities for improving healthspan further using appropriate medications.

## 2.5 Unification of Health: The Evolutionary Paradigm for Health Relative to the Prospect of an 'Integrated Theory of Health'

Unified theories are difficult to develop. The stark reality of our current understanding of healthspan is that its physiology, from genome to organ system, is often complex. Indeed, far more complex than the unaided human mind can parse. As a result, most progress with understanding, much less ameliorating, human healthspan will hinge on the ability of researchers to utilize machine learning to parse vast caches of data at the dawn of this new 'omic' age of biological research.

A unified understanding of health requires the solution of a puzzle with many pieces. Even if some might argue that we have most of those pieces now, we must not be too quick to claim that we know how they all go together. From the standpoint of concrete research methods, we believe that assembling the causal biological networks that underlie health will require the use of large bodies of data from human and model system populations, where such data must include both functional phenotypes and the various "omics" that are the current obsession of biological research. Specifically, omic findings from the field of experimental evolution will be at least partially transferable to human populations, thanks to the kind of homology that we have illustrated here with the case of heart health.

However, twenty-first century biology is developing with remarkable rapidity in unanticipated directions. We are confident that the study of health, in particular, will feature startling new discoveries based on technologies that at present are far from full development.

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# Chapter 3
# What is a Healthy Body? A Biodemographer's View


**S. Jay Olshansky**

**Abstract** A formal definition of disease defines by its absence, a formal definition of health. This may have been a productive concept in the early twentieth century when many of the diseases we faced were acute and fatal, but in today's world it's evident that how we define disease and disability—and by extension, a healthy body—should be determined not just by the presence of a disease, but also by how any given disease influences physical and psychological functioning. Complicating the definition of a healthy body is a set of events we willingly brought on ourselves—life extension caused by advances in public health and medicine, and population aging caused by lower fertility and declining old-age mortality. Technology has managed to transform many conditions that in previous generations would have been either completely debilitating or fatal, into little more than nuisances that are often no longer perceived. A biodemographic perspective of the definition of a healthy body is one based on a more complete understanding of the various ways in which humans adapt to inevitable changes in our bodies that occur with the passage of time.

**Keywords** Healthy aging · Longevity · Mortality · Health · Aging

Health was originally defined by the World Health Organization (WHO) in 1948 as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948). In 1986, this definition was augmented by the WHO to read: "A resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities" (WHO 1986). The presence of "health"—which includes both body and mind—was originally considered a resource or commodity, and healthy lifestyles (however that is defined) was the means to increase the resource of healthy life.

The WHO definition of health was intended to foster the notion of health for everyone; for each person individually and at the population level. The implication of the original definition was that if healthy lifestyles were adhered to throughout life by everyone, diseases would be held at bay; physical and mental well-being could

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be maintained until life ended; and implicitly the maximum lifespan and healthspan for the population would be achieved. However, once people began surviving with regularity into older ages during the twentieth century, and as our scientific understanding of aging and biology developed more fully as a result, it became evident that the WHO definition of health was not just narrow, but plausibly naïve.

The premise that everyone has the potential to achieve optimum health implies that all of us are living life on the same aging trajectory, and that any definition of optimum health that might theoretically apply to one person, applies equally to all of humanity. Humans are not genetically identical; we do not all live life under the same conditions; we were not all born at the same time; and even if those conditions were met, the random component to aging means that variation in health and duration of life is inevitable (Finch and Kirkwood 2000). The WHO definition of health is not possible to achieve in the real world, and holding up an ideal of what it means to be healthy, or what the vision is of a healthy body, means that almost everyone will fail at some point during life in the pursuit of perfection.

What is missing from the WHO definition of health? The recognition that human bodies change in relatively predictable ways overall with the passage of chronological and biological time. However, while there is variation in the rate of change in the way in which all of us grow older, there are attributes of aging that are associated with developmental events that are resistant to interventions. Examples include biological transformations associated with puberty and reproduction, but the end of the reproductive window (menopause in women) marks a particularly unique attribute of human development that is baked into our genome. Changes in bone density, muscle atrophy, and losses associated with neurological conditions, are directly associated with growing older, although scientists recognize that some physical attributes of aging can be slowed or reversed through diet, exercise, and with therapeutic interventions (Blagosklonny 2018; Garau et al. 2018). However, even with optimum diet and exercise regimens in place, some age-related loss in these attributes of the body is inevitable (Carnes et al. 2003).

Sensory impairments are another element of human aging that are largely inevitable. Loss of hearing and impaired vision is a normal part of biological aging, and problems with knee and hip joints are a byproduct of both use and overuse. The loss of functionality of key components of the body with time should not be portrayed as a loss of health as the WHO definition implies, but rather, as a normal byproduct of pushing out the envelope of human survival into age windows rarely experienced by our ancestors. In a way, the rise of age-related health challenges is a product of success as survival to older ages is required for these challenges to become visible. On the one hand we want to live a long life, but we don't want the infirmities that often accompany extended survival.

In recent discussions on this topic, survival tradeoffs can be thought of as a Faustian bargain (Olshansky 2017). The rise in life expectancy in the twentieth century occurred swiftly because the primary early beneficiaries of public health and medicine were infants and children. As communicable diseases waned, humanity secured a 30-year rise in life expectancy at birth and we achieved what we wanted most—saving and extending the lives of our children. This led to the first longevity

revolution, and there is no disputing the value of the life extension achieved for both individuals and populations. In fact, even the wealth of nations can be directly tied to our rising levels of health and longevity (Bloom and Canning 2000).

However, rarely does something so desirable—such as extended life—come without a price. There were certainly clues back in 1850 that longer lives would be accompanied by challenging health issues. There have always been older people, so we could see even thousands of years ago that long life was accompanied by undesirable infirmities (Thomas et al. 2015). As such, the modern rise of heart disease, cancer, stroke, Alzheimer's, diabetes, and a long list of non-fatal disabling conditions, could have been anticipated when the first longevity revolution began. The first Faustian bargain was exactly what humanity longed for.

The WHO definition of what is "unhealthy", or the absence of health is exactly what humanity set out to achieve, indirectly and inadvertently, as the first longevity revolution was launched. The question we face now is, what trade-offs lie ahead? Cardiovascular diseases yielded to the pressure imposed by improved lifestyles, early detection, pharmaceuticals, and improved surgical interventions, but recent evidence indicates that improvements in health and longevity have decelerated and frailty and disability are on the rise (Case and Deaton 2015; Crimmins 2015; Reither et al. 2011). Certain forms of cancer have waned, but others have risen. Alzheimer's disease has ascended as a result, and now we're witnessing a rapid escalation in the prevalence of nonfatal disabling conditions expressed at later ages (Vos et al. 2016).

When we modulate disease risk through earlier detection and better treatments, this success has no influence on the rate at which we age. This means that successful efforts to combat one disease allows the survivors to live long enough to experience other age-related conditions. The longer we live, the more diseases we accumulate in bodies that were not "designed" for long-term use (Olshansky et al. 2001). This is an epidemiological game of whack-a-mole: when one disease is knocked down, two or more rise to take its place. This phenomenon of escalating "competing risks" in a rapidly aging world cannot be understated. People who routinely live past age 65 in long-lived populations today and in the coming decades will face a Faustian challenge unlike anything humanity has ever seen, and the further we push out the envelope of survival, the higher the probability that we'll face increasingly more undesirable trade-offs.

In an aging world brought forth by our own hand, the rise of an "unhealthy" population is an inevitable byproduct of success. The WHO definition of health and a healthy body did not take aging into account, nor did they consider how life extension and shifts in the age structure (population aging) that humanity gladly brought onto itself as a product of the first longevity revolution, would influence the observed health of future cohorts. From the perspective of aging biology alone, the definition of health and a healthy body must consider more nuanced definitions that include shades of grey between the complete absence of disease—which is exceedingly rare—to the presence of disease and how people adapt to them.

## 3.1 Adaptation

One important shade of grey between perfect health and disease is how medical science and basic ingenuity have led individuals and populations to adapt to the changes that occur to our bodies with the passage of time—essentially nullifying or lessening the impact of a disorder on functional ability. For example, dentistry in one form or another has been in existence for more than 9000 years (Wildwerding 2001), but the practice of dentistry as we know it today began in the early nineteenth century. Part of the field of dentistry includes learning how to better care for our teeth so that they last longer in a functional state rather than just finding ways to replace them with serviceable alternatives. The simple acts of flossing, brushing, and regular visits to the dentist now make it possible for many lifelong problems that we used to have with our teeth to never occur at all for many. When problems do arise, the field of dentistry has evolved to the point where dental implants can now create perfectly functional replacement teeth for the duration of life—essentially transforming this unhealthy state into one that is now more akin to routine maintenance.

Another part of the body known to change with age is one of our senses—sight. In the absence of adaptation, most people that reach middle or older ages would essentially be blind and according to the WHO definition of health, in a disease state. The invention of alternative methods of adapting to this change in our body comes from the time of the Roman empire when globes of water were used to magnify objects; but this evolved to the creation of glass spheres about 1000 AD (called reading stones) that were placed over written material for magnification (Rosen 1956). Eyeglasses as we know them today were first invented in the seventeenth century, and Benjamin Franklin was famously known for having invented bifocal lenses in 1784. Now with corrective surgery, it becomes possible to restore near perfect vision for the remainder of a person's life with no additional devices required. This is another example of how humans have adapted to a normal change that occurs in our body with the passage of time that might ordinarily be considered a disease according to the WHO definition, but which is rendered a non-issue through adaptation.

Other examples of adaptation include surgical procedures to treat normally fatal or disabling conditions such as appendicitis or hernias; the use of drugs such as hypertensive medications or statins that can render cardiovascular disease nearly irrelevant; and cancer treatments that lead to effective cures. Vaccines and antibiotics render many of our ancient sources of disease almost completely irrelevant. Organ and body part removal or replacement—such as knees and hips and mitral valves—are just a few of thousands of examples of how humans have found ways to adapt to the disease states that would normally define us as unhealthy.

Finally, consider some of the simple adaptations that have emerged in our modern world. People that live in two- and three-story homes can now move from one level to another with the use of assistive devices that carry a person up and down their stairs without the need for climbing. Buses have been adapted to dip the front end down to the ground, so it becomes easy to walk on and off the bus. Smart homes

have evolved to the point where computers can keep track of our daily activities, including reminders to remain hydrated.

Without these forms of adaptation that humans have built around and within us, the WHO definition of health would have most of us defined as in a disease state. It is now possible to eliminate many of these disease states through human ingenuity manifested through basic knowledge of public health, science, medicine, and both simple and complex adaptation to the world around us as we age. I'm confident that adaptation will continue to render many existing disease states as little more than nuisances in the coming years—yielding even less relevant our current notions of what it means to have a healthy body.

## 3.2 Happiness

A colleague of mine in the demographic sciences told me a story about his aging wife that had developed a severe case of Alzheimer's disease. She eventually forgot that she was married and didn't know that the person visiting her frequently was her husband. Eventually she came to believe that her husband had died, and she was free to have a relationship with someone else, so she chose the man that was visiting her often as her new companion. They had many relatively happy years together in this new relationship, recognizing the limitations imposed by the frequent problems that accompany acute cases of Alzheimer's disease.

I was reminded of cases like this last year when giving a presentation on aging at a conference overseas where the issue of rising levels of frailty and disability are expected among future cohorts of older people. The message from several people in the audience was to be careful about language, because the presence of frailty and disability in an individual does not mean they're not happy and/or living what they consider to be a productive life. Examples of how people with multiple sclerosis and their caregivers give meaning to life beyond the disease itself represents a perfect example of how happiness should play a role in our understanding of what it means to be healthy (Fave et al. 2017).

## 3.3 Conclusion

The WHO and many other health-related organizations around the world spend considerable effort setting health goals for the future. This is laudable to be sure, but it should be evident by now that the definitions of a healthy body and a healthy population must embody much more than the presence or absence of disease. The hard truth is that humans are not in possession of bodies that are capable of surviving to later ages in the absence of pathology related to aging and inherited and acquired risk factors that influence diseases that are common in long-lived societies. Humanity sought out longer lives through advances in public health and modern medicine, so

the experience of aging and everything that goes along with it, both good and bad, is something that has always been desirable. The alternative was high mortality among infants and children, so humanity made a reasonable Faustian bargain 150 years ago to obtain the 30-year rise in life expectancy at birth that occurred since then.

Looking back on the original WHO definition of health, it's easy to see why they were pressed to formulate language designed to generate consensus on what it means to be healthy. My view is that concepts of health should be fluid; evolving in concert with the development of technologies that allow us to treat diseases more effectively or live with them as increasingly more benign changes in our bodies.

Now that developed nations have experienced both life extension and shifts in age structure toward rapid population aging, definitions of health and healthy bodies must also evolve by taking into consideration how our modern world adapts to new health challenges that arise as a byproduct of using our bodies beyond their biological warranty period, and the complex psychology underlying notions of frailty and disability.

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# Chapter 4
# Biological Health and Homeodynamic Space


**Suresh I. S. Rattan**

**Abstract** The concepts of homeodynamics and homeodynamic space encompass both the theoretical and practical aspects of defining and measuring health at biological levels. The three characteristics of the homeodynamic space—stress response, damage control and constant remodelling—provide measurable biomarkers reflecting the survival ability, robustness and resilience of a biological system. A biological definition of health thus involves measures of functionality, tolerance and adaptation.

**Keywords** Ageing · Health-span · Hormesis · Longevity · Homeodynamics

## 4.1 Introduction

One of the main characteristics of living systems, which distinguishes them from the inorganic and non-living systems, is their intrinsic ability to respond, to counteract, and to adapt to the external and internal sources of disturbance (Luisi 1998; Huber 2015). A traditional and most commonly used term to describe this ability is homeostasis, which is based in the "body as a machine" paradigm (Cannon 1926; Cannon 1932). Homeostasis is also the usual basis of defining the health of a living system, from a cell to an organism and even of a population. However, a static and simplistic view of homeostasis and the machine paradigm do not sufficiently take into account the dynamic nature of information- and interaction-networks that underlie the complexity of biological systems (Nicholson 2019).

Following a more nuanced view of homeostasis as 'dynamic stability', the term homeodynamics encompasses the fact that, unlike machines, the internal conditions of biological systems are not fixed at a stable equilibrium, and are under constant dynamic regulation and interaction among various levels of organization (Yates 1994; Lemoine 2015; Nicholson 2019). Other concepts, such as robustness, resilience and allostasis have also been put forward to further emphasize the above fact (Kitano

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2004; Kitano 2007; McEwen and Wingfield 2003; Sterling 2004). For example, according to the allostasis model, "stability through change" is the most realistic situation for living biological systems by taking into account the characteristics, such as reciprocal trade-offs between various cells, tissues and organs, accommodative sensing and prediction with respect to the severity of a potential stressor, and the final cost of making a response and readjustment to bring about the necessary change (Sholl and Rattan 2019). Every act of allostasis adds to the allostatic load in terms of, for example, unrepaired molecular damage, reduced energy deposits and progressively less efficient or less stable structural and functional components (Sterling 2004).

The aim of this article is to discuss the concept of health within the framework of homeodynamics and homeodynamic space (HS) in biological systems, which can be the basis of measuring health at various stages of life.

## 4.2 Homeodynamic Space

The concept of a HS tracks all of what is currently known to constitute the abilities of the organism to survive and meet the demands of its environment (Rattan 2012, 2013, 2020). As discussed previously (Sholl and Rattan 2019), Fig. 4.1 describes a parametric view of health in which the phenotypic parameters characterize the performance of a biological system—from a single cell to cell populations, tissues,

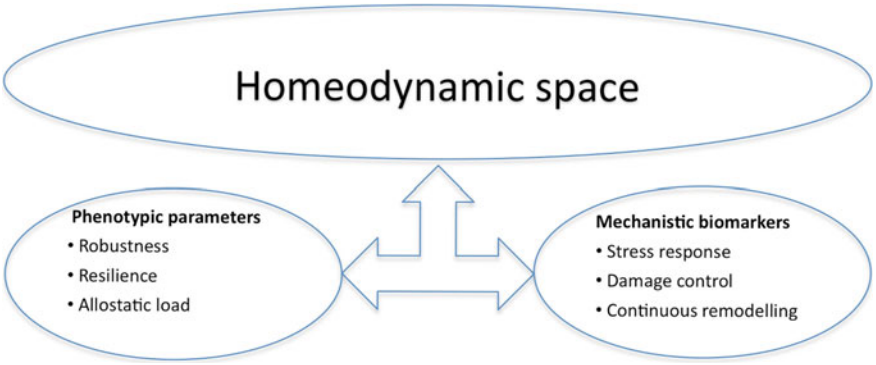


**Fig. 4.1** The overall abilities of an individual are described by the homeodynamic space (HS). This is in turn broken down into the phenotypic parameters that characterize the individual (or subsystem's) performance with respect to a specific perturbation. Finally, the mechanistic biomarkers are the measurable changes that help distinguish the different parameters and their contributions to the HS. *Reprinted with permission from:* Sholl and Rattan (2019)

**Table 4.1** Mechanistic biomarkers of the homeodynamic space and the main processes of maintenance and repair

| Characteristic | Main processes involved |
|---|---|
| Stress response | Autophagy, DNA repair response, oxidative stress response, unfolded protein stress response, nutritional stress response, inflammatory response, energy deficiency stress response |
| Damage control | DNA repair, protein repair, free radical scavenging, molecular turnover |
| Constant remodeling | Cellular turnover, wound healing, immune remodeling, bone remodeling, tissue regeneration |

organs and the whole body—with respect to a specific perturbation. The mechanistic biomarkers in this context are the measurable changes at molecular, biochemical, and physiological levels that help distinguish the different parameters and their contributions to the HS (Sholl and Rattan 2019).

The three main mechanistic biomarkers of the ability to maintain these phenotypic parameters through time are listed in Table 4.1, and are described briefly as follows:

1. *Stress response (SR):* how far a system can tolerate perturbations and stressors. At a single cell level, there are at least 7 main SR pathways, as defined by the nature of the stressor(s) (Bhattacharya and Rattan 2019; Bhattacharya and Rattan 2020). For example, stressors which cause protein denaturation induce the so-called heat shock response, whereas oxidative damage-causing stressors induce the anti-oxidative SR mediated by Nrf2, and nutritional deficiency induces the autophagic SR, and so on (Demirovic and Rattan 2013; Demirovic et al. 2014). Most commonly, each SR is studied and analysed individually and provides detailed information about the kinetics of that specific SR only. However, in a complex biological system (even at the level of a single cell), the stress-specific primary and immediate SR is almost always followed by the delayed or secondary SR (Demirovic and Rattan 2013). Therefore, in order to fully understand how SR can be a useful biomarker of the HS of a biological system, it is essential that all SR pathways are analyzed simultaneously, and a complete SR profile is established under a given condition, such as cell type, age and the severity of stress (Rattan et al. 2018).
2. *Molecular damage control:* repair processes turning on after a system has been severely perturbed by internal and external sources of damage, including free radicals, nutritional metabolites, and environmental toxins. A positive relationship between the extent and efficiency of various molecular damage control processes and the species lifespan are well documented (Kapahi et al. 1999; Barja 2002; Rattan 2006; Perez et al. 2009). In contrast, a negative correlation has been demonstrated between species' lifespan and the rate of molecular damage accumulation, including mutations, epimutations, macromolecular oxidation and aggregation of metabolic by-products (Holliday 2006; Rattan 2006; Bhattacharya and Rattan 2019). A similar relationship may also exist at the level of an individual, for which enough data are yet to be collected.

3. *Constant remodeling:* the ability to compensate by constant remodeling of the molecular heterogeneity within a cell, and of cellular heterogeneity within a tissue/system during growth, maturation and ageing. Constant remodeling as a crucial feature of the HS of an individual system can be best seen in the case of cellular turnover within a tissue, wound healing, bone remodeling and immune system remodeling (Duscher et al. 2016; Raggatt and Partridge 2010; Franceschi et al. 2000; Bellavista et al. 2014).

All these processes, which comprise the HS, involve hundreds of genes and gene products, that collectively are known as the longevity assurance genes (LAG) (Jazwinski 1998; Martin 2007) or vitagenes (Rattan 1998; Calabrese et al. 2010). Numerous genome wide association studies (GWAS) are being performed in order to correlate genetic variations with the longevity of the individuals within a population (Deelen et al. 2014; Price et al. 2017; Wright et al. 2019). Thus, it may be possible to create a genetic profile of the HS of an individual, population and the species.

A certain volume of the HS is essential in a newborn organism, without which its survival is impossible. Various genetic, epigenetic, pre-natal, and post-natal factors determine the size and the extent of the HS of an individual (Rattan 2020). Furthermore, the HS expands and reaches its optimal during growth, development and maturation enabling the survival of an individual to attain a reproductive age, as determined by the evolutionary life history of its species. Such natural lifespan of a species is known as the "essential lifespan" (ELS) (Rattan 2000), or the "warranty period" of a species (Carnes et al. 2003). Species undergoing fast maturation and early onset of reproduction with large reproductive potential generally have a short ELS, and thereby a smaller HS. In contrast, slow maturation, late onset of reproduction, and small reproductive potential of a species is concurrent with its long ELS (Finch and Kirkwood 2000, Finch 2009), implying having a large HS.

## 4.3 Imperfections of the Homeodynamic Space

Evolution neither aims for nor requires perfect systems (Finch and Kirkwood 2000). Spontaneous errors, intrinsic infidelity of the biochemical processes, and progressive thermodynamic increase in entropy are both the basis of evolution and the ultimate reason of demise of a living system (Hayflick 2007; Demetrius 2013). The three components of the HS are also not perfect, and therefore, even in an apparently normal newborn organism, there is a "vulnerability zone" representing the imperfections which allow the structural and functional deviations, disturbances, impairments, and death before ELS.

Owing to the imperfections of the homeodynamic machinery, progressive occurrence and accumulation of molecular damage is intrinsic to life processes. Table 4.2 gives examples of some types of molecular damages which have been detected and measured so far in a wide range of biological systems (Rattan 2006; Rattan 2008; Moskalev et al. 2012; Hause et al. 2018; Gubina et al. 2019).

**Table 4.2** Molecular damages reported to accumulate during lifetime

| Macromolecule | Examples of damage |
|---|---|
| DNA (nuclear and mitochondrial) | Mutations, epimutations, base modifications, strand breaks, loss of telomeres |
| RNA | Base modifications, miscoding, missplicing |
| Protein | Amino acid modifications, misincorporation, misfolding, aggregation |
| Carbohydrates, lipids, and molecular conjugates | Advanced glycation end-products (AGE), lipofuscin, aggrosomes |

Molecular damages occur all the time in all biochemical processes, including in the maintenance and repair systems supposed to protect from the damage (Rattan 2008). The extent of damage accumulation during the period of growth, development, maturation and survival until reproduction is generally without any significant demonstratable negative effects on health. However, during the period of survival beyond species' ELS, molecular damage accumulation happens exponentially because of the internal amplification loop generated by the damaged damage-control processes (Rattan 2008). This accumulation of molecular damage becomes manifested progressively as functional impairments, reduced physiological capacities, frailty, pathologies and eventual death. This is exactly how biological ageing is identified, characterized and defined (Lopez-Otin et al. 2013); and in terms of HS, ageing is the progressive shrinkage of the HS concurrent with an increase in the scope of the vulnerability zone (Rattan 2012, 2013).

## 4.4 Homeodynamics-Based Pragmatic Definition of Health

Health of an individual is often described either in the context of the absence of one or more diseases or as an undefined notion of well-being, without having any objective measures for that (Rattan 2013; Sholl and Rattan 2019). Although various parameters of frailty have been proposed (Mitnitski et al. 2017; Kim et al. 2017; Ding et al. 2017; Cardoso et al. 2018; Jazwinski and Kim 2019) direct measures of health largely remain undefined. Since one of the crucial aspects of health is the functionality of the living system, health could be defined as a state of *absolute* physical and mental independence in activities of daily living (Rattan 2013). However, absolute health is an idealized state, which no one can have. Therefore, being healthy, in practical terms, means having *adequate* physical and mental independence in activities of daily living; and this state may vary widely but can be established objectively (Rattan 2013; Sholl and Rattan 2019). This pragmatic definition of health as a state of having adequate physical and mental independence in activities of daily living requires identifying a set of measurable parameters at the most fundamental level of biological organization.

Analysing the components of the HS can be an objective way to quantify health at the level of cells, tissues and the body.

As discussed previously (Sholl and Rattan 2019), the following three lines of investigation may be useful to develop evidence-based biological markers of health:

1. Establishing immediate and delayed stress response profiles of cells, organisms and humans at different ages (Demirovic and Rattan 2013). This will also include developing methods for measuring resilience and robustness (Kitano 2007; Kriete 2013).
2. Developing methods for measuring the limits of health at the individual level. This will involve establishing relationships between stress tolerance, recovery, survival, innate immune response and longevity at different levels and ages. This could also lead to converting multidimensional information about the number of determinants of health at different levels to a single number expressing the biological age or the frailty status or the size of the homeodynamic space, by applying bioinformatics and mathematical modelling (Belsky et al. 2015; Tacutu et al. 2010).
3. Developing physiological criteria and methods to monitor health improvement by physical, nutritional or other interventions.

To conclude, the concept of HS encompasses both the theoretical and practical aspects of defining and measuring health at biological levels. The three characteristics of the HS—stress response, damage control and constant remodelling—are measurable both quantitatively and qualitatively. These characteristics can be the basis of defining health and the health status of a biological system at the levels from a single cell to the tissue, organs, system and the whole body. Furthermore, any interventions in the maintenance, recovery or enhancement of health can also be monitored for their efficacy using this concept of the homeodynamic space.

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# Chapter 5
# Healthy Biological Systems


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**Abstract** Health and pathologies are multifactorial states characterizing how well biological systems function in a range of conditions and facing various stressors. Depending on how flexible the definition of a state is, systems may have multiple healthy and stable states. However, keeping homeostasis requires parameters dynamically fluctuating within a physiological range. On the molecular level, states depend on the combined effect of a myriad of genetic, epigenetic and environmental factors, and in response to a time-varying signal from the exposome, the system may transit between states of health, states with better or worse fitness, and disorder states. In this chapter, we discuss how differences in heritable components, repair mechanisms, and exposure to events in early or adult life, influence healthspan, longevity and susceptibility to pathologies. We also review the genomic, methylomic, transcriptomic and metabolomic changes that accumulate with age, and discuss them as potential drivers of shifts towards pathological phenotypes. Lastly, we hypothesize that transitions are generally small and slow during ageing and more dynamic in disease emergence or progression, with both cases being characterized by system-wide changes in the expression and function of their components, the topology of their interactions, and the system's overall robustness.

**Keywords** Systems biology · Healthy systems · Genomics · Transcriptomics · Metabolomics · Networks

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## 5.1 Introduction

Defining health is still controversial, however, a practical definition implies that a healthy organism should function optimally in a range of conditions, including when facing physical, biological, psychological and social stressors. At the same time, health is tightly connected, antagonistically, to pathologies, and perhaps more subtly to disease susceptibility—as high susceptibility should not be compatible with health, but rather a characteristic of pre-diseased states. Being in a healthy, pre-diseased or diseased state, depends on the combined effect of many genetic and environmental factors, the latter including interactions that occur either as adults or in early life (Jirtle and Skinner 2007). In this chapter, health is analyzed mainly from a systems perspective, biological systems are seen as a whole, and the states of health and pathology include all the characteristics that determine system functionality.

Generally, complex systems are defined by their constitutive parts, interactions between components, and other external interactions. In particular, for biological systems, the parts include coding components, changing relatively little throughout life, and more dynamic and sensitive parts, responsible for the system's functionality at a certain time. The combined measure of all these dynamic parts determines the phenome, i.e. the full set of phenotypes (Houle et al. 2010). It includes behavioral, morphological (anatomical, histological, imagistic), physiological (organ systems functioning parameters), and molecular phenotypes, acting together as a very complex, high-dimensional representation that can describe the biological system state. Complementarily, the "exposome" is formally the "ome" that captures all the exposure to environmental factors (Smith et al. 2015). Through a genome-phenome map, the genome largely determines the phenome (Houle et al. 2010). The phenome is also heavily shaped by the exposome through all prior life events and the genome may be altered, even though to a lesser extent, by phenome dysregulations or environmental interactions. Thus, the actual state of a biological system is determined by the combined states of the genome, phenome and current exposome. With the latest advances in molecular techniques (in genomics, transcriptomics, epigenomics, proteomics and metabolomics), the genome and much of phenome are now assayed with relatively high accuracy. Although directly capturing environmental factors using specifically tailored sensors is still unrealistic for the moment, exposomics can be instead measured indirectly using similar molecular techniques (metabolomics, adductomics, stress measurements, inflammatory markers, etc.).

An individual should be considered in a *healthy* state if its genomic and phenomic state: (1) allow for physical, mental and social well-being, under a range of non-extreme conditions (*normal functioning*); (2) are not characterized by any major dysfunctionalities (*not pathological*); and (3) can withstand non-major alterations caused by a range of external stressors (*robustness, lack of disease susceptibility*). Further extending the concept to *healthy life*, a system can be considered healthier if, due to its internal properties, it is less likely to transition out of healthy states throughout its lifetime, thus having an increased expected healthspan, given random exposomes. It should be noted that the above statement does not necessarily exclude

accumulation of minor dysfunctionalities or medical conditions during life, as long as these do not interfere significantly with overall system performance. Also, in a population there is variability amongst individuals and health can be achieved through multiple genome/phenome configurations.

For most people, except perhaps individuals born with degenerative conditions, there is a point in adult life, when the organism reaches a personal peak in fitness, and when despite potentially having minor affections or susceptibilities, the individual can be considered healthy (Cutler and Mattson 2006). After reaching this peak and with the passing of time, the organism's robustness starts to decline, and its components start showing signs of fragility (i.e. risks of becoming dysregulated or malfunctioning), increased risk of injury and susceptibility to diseases. In particular, age is a risk factor that increases non-linearly the probability to develop various chronic pathologies, including cardiovascular diseases, cancers, neurodegenerative disorders, type 2 diabetes, etc. Other more subtle processes, like cellular senescence, oxidative stress, or chronic inflammation, also start to creep into the system, although less visibly, reducing its performance. Before the end of life, the state of the organism for most individuals will have shifted away from the healthy state and becomes cataloged as diseased (Kinzina et al. 2019).

In the next few sections, we discuss how differences in the heritable components influence health and longevity, how pre- or post-natal early life events can impact the risk of developing adult diseases, and how a biological system repairs itself continually to counteract incoming damage and keep its robustness. Next, we discuss how despite repair there is a systemic health decline with ageing, and how the system transitions to other states, characteristic for age-related pathologies. Lastly, we give an overview of the genomic, methylomic, transcriptomic and metabolomic changes that accumulate with age, and we discuss how the separate changes could be analyzed and understood together with the use of networks and systems biology.

## 5.2 The "Starting Kit"

One prerequisite for health is starting life with proper genetic and epigenetic tools, a "starting kit" that ensures harmonious development, growth and later, homeostasis. This kit is inherited from parents and includes: (1) the "coding" components (mainly nuclear DNA, but also components like mitochondrial DNA), and (2) epigenetic traits, shaped during early embryogenesis and development by the fetal-maternal interaction.

### *5.2.1 Genetic Heritability*

The human genome is highly variable, with hundreds of different loci scattered throughout twenty-three chromosomes, more than twenty thousand genes, different

alleles and at least 11 million SNPs (Jackson et al. 2018). This variation is inherent to the genome and generally does not affect health significantly. The complexity is further exacerbated by "missing heritability", the heritability of health and disease traits being only superficially explained by genetic variants, which might be due to epistasis among loci (Zuk et al. 2012). Nevertheless, health has a genetic component, with multiple loci being associated with healthspan (Zenin et al. 2019) and lifespan (Budovsky et al. 2013), and the number of de novo mutations in the offspring correlating even with the parents age (Goldmann et al. 2019), and arguably health.

*Longevity and health are partly heritable:* Individuals who start with good genetics are also less affected by diseases and health problems during their lives. For example, centenarians generally avoid chronic diseases even after a lifetime of serious health risks, including smoking, drinking, sedentarism or obesity, which is probably due to genes that protected them from carcinogens or naturally accumulating mutations (Milman and Barzilai 2015). Additionally, offspring of long-lived parents are likely to have longer lifespans (Vågerö et al. 2018). It seems that the heritability of longevity increases with survival to much older ages, and is higher in long-lived families, while environmental factors are more important in sporadic longevity (van den Berg et al. 2019). Lastly, this also extends to health heritability as centenarian offsprings have better cardiovascular ageing as well (Adams et al. 2008).

Analyses on the families of New England centenarians showed that siblings of a centenarian are four times more likely to live past 90 than the general population, and 150 genetic variations were used to accurately predict reaching 100 (Sebastiani et al. 2009). Considering non-centenarians, in a longitudinal cohort of ~20,000, the University of Michigan Health and Retirement Study found that the all-cause mortality consistently declined by 19% for each decade that participants' mothers had survived beyond 65 (14% per decade for fathers) (Dutta et al. 2013).

*Several genome-wide association studies (GWAS) have aimed to identify longevity determinants:* Of particular interest are the genes or alleles associated with increased lifespan and healthspan (Zenin et al. 2019), and many GWAS have studied centenarians and their families to identify longevity variants (Sebastiani et al. 2012). For example, *APOE*, which is involved in fat metabolism and cholesterol transport shows a strong association with longevity, in various geographic populations. One of its four alleles (ε2) is linked with increased odds for extreme longevity (genotypes ε2ε2 or ε2ε3), while carrying ε4 poses an increased mortality risk even within the 1% longest-lived individuals (Sebastiani et al. 2019). *FOXOA3* is another longevity-associated gene, with one variant found much more often in centenarians, albeit not in all populations (Bae et al. 2018). Due to epistasis effects, many other longevity variants might be harder to identify. This is the case of *FNDC5*, which synthesizes a hormone upregulated by muscular exercise, and extends lifespan dependent on *FOXO3* and *APOE* (Fuku et al. 2017). Insulin resistance increases with age, however IGF-1 is decreased in subjects that are 90 or older (Paolisso et al. 2001), suggesting that long-lived subjects have higher insulin sensitivity (Vitale et al. 2019). A link between living to 100 and inheriting a hyperactive version of telomerase was also reported on Ashkenazi Jew centenarians (Atzmon et al. 2010). Overall, for centenarian GWAS, with

the exception of APOE and FOXO3A, the results have been inconsistent and localized to certain populations, revealing only a small part of the exceptional longevity and health (Brooks-Wilson 2013). It seems though that longevity is highly polygenic, with complex interactions and synergies, in many cases determined by genes involved in cellular senescence, inflammation, lipid metabolism and cardiovascular conditions (Pilling et al. 2017).

*The detrimental effect that genetics may have on adult health*: While the above examples show links between genetic characteristics and healthy traits, the reverse also exists. Indeed, many genes are associated with the onset and determination of diseases, with an extremely extensive list of disorder-gene association pairs that could form a network (Goh et al. 2007). For example, mutations in three of the five RecQ helicases (highly conserved genes involved in DNA repair and genome maintenance) lead to premature ageing phenotypes (Bernstein et al. 2010). In fact, many of the progeroid syndromes, rare genetic disorders that display features of accelerated physiological ageing are linked to DNA repair defects (Navarro et al. 2006), and broadly, progeria are grouped in two large categories: (1) gene mutations in DNA-repair pathways, such as the case for Werner syndrome, Bloom syndrome, or Cockayne syndrome, and (2) compound alterations in the nuclear envelope, leading to the Hutchinson-Gilford syndrome, Néstor-Guillermo syndrome, or mandibuloacral dysplasia (Carrero et al. 2016).

These are a few extreme examples of genetic-driven pathologies that significantly impair health. However, much more heritable genetic variations (too many to thoroughly review) can influence health, either as part of multifactorial diseases, or perhaps in more subtle ways, increasing or decreasing the susceptibility or vulnerabilities to a certain exposome. Perhaps one of the best examples is that of the blood groups. Blood group antigens represent polymorphic traits inherited among individuals and populations, with 34 human blood groups currently known and hundreds of individual blood group antigens and alleles. While not having a strong impact on overall health, blood types can influence the sensitivity to various infections or modulate the innate immune response. Blood groups can serve both as coreceptors and/or receptors for microorganisms, viruses, and parasites, and so, many antigens facilitate intracellular uptake, signal transduction, or adhesion through the organization of membrane microdomains (Cooling 2015).

Overall, the above examples prove that genetic makeup is important for both lifespan and healthspan. Better genetic tools can significantly contribute to long, healthy lives, despite environmental risks, while an unlucky set of genes or alleles can easily predispose to a wide array of susceptibilities or even pathologies.

### *5.2.2 "Epigenetic" Heritability*

The Fetal Origins of Adult Disease (FOAD) hypothesis suggests that developmental stressors permanently alter structure, metabolism and genetic expression, resulting in cognitive, behavioral and body composition changes, potentially leading to future

adult diseases (Barker 1992). For example, in addition to being at increased risk for developing metabolic derangements, being large for gestational age at birth is associated with an increased risk of cancer, including breast, ovarian, prostate, testicular, and colon (Calkins and Devaskar 2011). On the other hand, infants born small for gestational age are associated with increased risk for developing obesity, type 2 diabetes, coronary artery disease, hypertension, kidney disease, premature pubarche, polycystic syndrome, dyslipidemia, short stature, and osteoporosis (Calkins and Devaskar 2011). All living creatures have increased plasticity in early life, so that the same genotype may differentiate into various phenotypes depending on early-life environmental conditions (Langley-Evans 2009). These phenotypes are tailored to optimize the physiological responses to the anticipated adult lifestyle demands; however, a mismatch between the "predictive" adaptations made during early-life and the actual realities later in life may be a cause of disease (Gluckman and Hanson 2006). The difference between the Dutch famine and the Leningrad siege, two natural disasters, is a great example. After the disaster, the fetal survivors in Leningrad developed a "thrifty phenotype", adjusted for the prenatal malnutrition, which served them well in their extrauterine life, as the same conditions continued after the war period. By contrast, their Dutch counterparts who suffered famine only for a short period of time started to display increased rates of insulin resistance, dyslipidemia, hypertension later in life due to the high-calorie intake (Hales and Barker 2001).

Fetus growth depends on the maternal placenta's ability to supply nutrients (amino acids, glucose, fat, oxygen, and growth-stimulating hormones) and can even be influenced by the mother's own in utero experience (Jimenez-Chillaron et al. 2009). So, the consequences of fetal "reprogramming" may extend beyond one generation. Among potential causes impacting later adult life may be alterations in diet composition, inflammation, infection, glucocorticoids, hypoxia, stress, and toxins (Calkins and Devaskar 2011).

Strong relationships exist between early-life conditions and adult health, including the incidence and severity of age-related diseases, and epigenetics is the key factor mediating these links (Gravina and Vijg 2010). Epigenetic determinants are in turn influenced by nutrition and other environmental interactions, whose modulation may promote health and prevent disease (Niculescu and Lupu 2011). The alterations undergone during gametogenesis and early embryogenesis include unique changes in the lineage-specific patterns of gene expression (Vickaryous and Whitelaw 2005) and in epigenetic pathways, which connect early development to adult disorders, such as neurodegenerative diseases and type 2 diabetes (Gluckman et al. 2011).

Infections in early life that train immunity and prevent the development of pathological immune responses, may also have adverse impacts on health later in life (Crimmins and Finch 2006). More generally, this type of "programming" applied during early development, enables permanent changes that persist throughout the whole lifespan. The disadvantage is that, over time, part of the "plasticity" is lost, and the response to environmental or pathologic challenges becomes constrained (Calkins and Devaskar 2011).

## 5.3 Health Changes Throughout Life

### *5.3.1 Health Peak, the Ageing Decline, and Age-Related Diseases*

The age-dependent mortality is a convex curve, indicating an increased rate of mortality during very early and late-life, with the minimum value attained approximately before puberty. While it is still debatable whether the curve is a Gompertz function (Gavrilova and Gavrilov 2015; Barbi et al. 2018), there is a clear time point, around puberty, at which an organism seems maximally fit for survival. This is in fact an aggregate fitness, as different system components peak at different times: hearing (5yo), smell (10yo), taste (10yo), flexibility and balance (13yo), muscle strength (18yo), tissue repair (13yo), short term memory (20yo), immune response (13yo), lung capacity (20yo) (Cutler and Mattson 2006).

With ageing, all these functions start declining after the peak. Accumulation of molecular damage yields functional deterioration, both physiologically and anatomically. While the reserve capacity and repair mechanisms mask physiological deterioration from becoming visible early on, adulthood is accompanied by ageing and a gradual deterioration of physiological functions. To name only a few, ageing leads to a decrease in gain and redistribution of fat, decreased melanin production, sarcopenia, progressive loss in bone mass, deficits of sensory pathways (hearing, vision, etc.), motor functions (reaction time, coordination), and cognitive performance, decline in cardiovascular and pulmonary function, decrease in resting metabolic rate, and many more changes (Boron and Boulpaep 2016). Up to date, approximately 350 physiological changes and thousands of molecular changes have been reported during ageing, according to the Digital Ageing Atlas (Craig et al. 2015).

One important question is whether ageing, and implicitly the decrease in health, results from a single underlying cause, leading to all these changes and acting synchronously, or whether there is a mix of independent causes. It should be noted that while all physiological functions start declining at different times and have different rates this is not enough to conclude the existence of multiple mechanisms (Miller 1999). Cell proliferation decreases for example in mice, similarly in epithelial cells of gingiva, tongue, buccal mucosa and skin, but also in liver and kidney (Enoki et al. 2007). Using GTEx transcriptomics data, a tight synchronization in ageing patterns was found for lung, heart and blood tissues (Yang et al., 2015). Perhaps the most compelling are studies of lifespan extension (genetic interventions and caloric restriction), which do not only improve the health of a single organ or cell type – for an extensive list of studies see: GenAge and GenDR (Tacutu et al. 2018).

All system parts have to withstand damage accumulation from environmental interactions, DNA damage from ROS, UV radiation and environmental mutagens being well-known causes for ageing and cancer (Vijg and Suh 2013). The decay in physiological fitness is further amplified by the deterioration of repairing mechanisms caused at a minimum by stochastic damage that accumulates with age (Chen et al. 2002). Protein recycling and antioxidant mechanisms have also been shown

to decrease with age in multiple tissues (Cuervo and Dice 2000). Although young organisms are able to clear senescent cells through mechanisms of senescence surveillance, age-related immunosenescence impedes these beneficial clearance processes (Soto-Gamez and Demaria 2017).

The frequency of major life-threatening degenerative pathologies and conditions, including atherosclerosis, cancer, neurodegeneration, type 2 diabetes, osteoporosis, sarcopenia, progressively increase in humans in the post-reproductive period (Cutler and Mattson 2006). It is natural to assume that there is a relationship between the risk to develop these diseases and the ageing-related decline in health. At a molecular level, hundreds of genes are jointly involved both in ageing, longevity, and age-related diseases, as well as in other ageing-associated conditions such as oxidative stress, chronic inflammation, and cellular senescence (Tacutu et al. 2011; Fernandes et al. 2016). Recent studies showed that in most pathological conditions it is the dysregulation of complex gene networks rather than a problem with single gene dysregulations that causes its emergence or progression (Smith and Flodman 2018). This is in line with genes impacting lifespan being highly evolutionarily conserved and enriched in multi-factorial processes like translation, energy metabolism, and DNA repair (Yanai et al. 2017), and with both these genes and the genes involved in ageing-associated pathologies forming networks (Budovsky et al. 2007; Tacutu et al. 2010a). For diseases, it seems that the degenerative decline in health, personalized to each individual's genome, phenome and exposome, brings the system to a divergence path, leading it towards the development of one pathology or another (Demetrius et al. 2014). As such, age-related diseases could be viewed as extreme manifestations of the health decline that occurs during normal ageing (Tacutu et al. 2010b).

### *5.3.2 Healthy Genomics*

*The nuclear genome:* Heritability influences various health traits and age-related diseases, through genes and their variations, but the stability and consistency of the nuclear genome throughout life is also extremely important for the health of an entire system. This healthy genome state is determined by many factors, including SNPs, de novo mutations (DNMs), copy number variants (CNVs)—including tandem repeats, microsatellites and minisatellites, CpG sites, transposable elements and chromosomal abnormalities. Human germline DNMs, which appear in an individual's genome either due to a mutation in a parent's germ cell, or due to a variant that arises during early embryogenesis, can drive genetic diseases (Sasani et al. 2019). DNMs are a complex mixture of mutations that arise through different biological processes acting at different times during human development and life (Goldmann et al. 2019).

CNVs are repeated genome sequences (typically above 1000 bp), usually resulting from duplications or deletions, and their number varies across individuals (McCarroll and Altshuler 2007). Recent research indicates that approximately two-thirds of the entire genome is composed of repeats (de Koning et al. 2011) and 4.8–9.5% can be classified as CNVs (Zarrei et al. 2015). Additionally, approximately 1–2%

of children have a de novo CNV > 100 kb (Jackson et al. 2018). In mammals, CNVs play an important role in generating populational variation, however, they also have an impact on disease phenotypes, being linked to neurodegenerative and neurodevelopmental disorders, including familial Parkinson's disease, autism, and syndromic mental retardation (McCarroll and Altshuler 2007).

Tandem repeats, repeated nucleotide sequences that are directly adjacent (generally with units > 50 bp), are another relatively common type of CNV that may contribute to human genomic variation and disease risk (Bruce et al. 2009). A particular case of tandem repeats is that of microsatellites and minisatellites. Microsatellites, sequences of one to six base pairs, repeated about a variable 5–50 times, have a relatively high mutation frequency, with gain or loss of repeat units occurring in roughly 1 per 1000 microsatellites, per gamete per generation (Jackson et al. 2018). Microsatellites can be found in thousands of genome locations and have a higher mutation rate than other DNA areas (Brinkmann et al. 1998). No universal rule can explain the instability of repetitive sequences, each sequence being influenced by local and general factors that determine its level of instability (Debrauwere et al. 1997). In health diagnostics, however, tandem repeats have been used to identify the genetic linkage between specific gene locations or mutations and given traits or diseases (Hannan 2018).

CpG sites, regions of DNA where a cytosine and guanine are sequentially adjacent, are another genomic peculiarity, with larger regions of frequent CpG sites being called CpG islands. In mammals, 70–80% of CpG cytosines are methylated (Jabbari and Bernardi 2004) and the methylation of CpG sites is found throughout the whole genome (Takai and Jones 2002). Importantly, the density of CpG sites in many mammalian gene promoters, which can be targeted for DNA methylation (and hence silencing), correlates with lifespan (Mayne et al. 2019). So it is not surprising that CpG sites have been associated with ageing and various diseases (Marttila et al. 2015). For example, DNA repair genes are frequently repressed in cancers due to hypermethylation, leading to a genetic loss of function (Jin and Robertson 2013). On the other hand, hypomethylation causes over-expression and may also lead to numerous cancers.

Transposable elements (TEs) are DNA sequences that can change position within the genome, in some cases creating or reversing mutations, and altering the cell's genetic identity or genome size (Bourque et al. 2018). Approximately, 44% of the human genome contains transposons with a small part (<0.05%) being active (Mills et al. 2007). Even though transposons are mutagenic and may lead to genetic diseases, it is assumed they are important for genome function and evolution (Bucher et al. 2012). In many cases, transposition results in duplication of the same genetic material, and transposon or retrotransposon insertion into a functional gene might alter its expression (Belancio et al. 2008). Transposon removal may cause gaps that are not repaired. Multiple copies of a transposon might interfere with proper chromosome pairing during mitosis or meiosis, resulting in unequal crossovers, one of the main reasons for chromosome duplication. TEs are found to cause diseases such as hemophilia A and B, severe combined immunodeficiency, porphyria, predisposition

to cancer, and Duchenne muscular dystrophy (Kazazian and Goodier 2002). Moreover, TEs might contain promoters that drive transcription of their own transposase. These promoters are able to change gene expression, causing disease or mutant phenotypes (Chuong et al. 2017).

Lastly, chromosomal anomalies, including missing, extra, or irregular portions of chromosomal DNA can arise from a typical number of chromosomes or a structural abnormality in one or more chromosomes, with wide implications in cancer (Santaguida and Amon 2015).

The human genome undergoes one million individual molecular lesions per cell, per day, as a result of normal metabolic activities and environmental factors (Lodish et al. 2004). The accumulation of somatic mutations with advanced age or of damage repair failures leads to: cellular senescence, apoptosis or unregulated cell division, which then leads to tumorigenesis. DNA damage processes increase cancer risk and contribute to the functional decline in health. The DNA repair ability of a cell is vital to the integrity of the genome. Thus, during evolution, organisms have allocated many resources to repairing mechanisms, and many genes initially shown to influence healthspan and lifespan were involved in DNA maintenance (Browner et al. 2004). Despite overall efficiency, repair processes sometimes fail, and when cellular apoptosis does not occur, irreparable DNA damage may occur, including double-strand breaks and DNA cross-linkages. This may eventually result in malignant tumors or cancer (Jeggo et al. 2016). The rate of DNA repair depends on many factors, including the cell type, the age of the cell, and the extracellular environment.

*The mitochondrial genome:* Mitochondria are essential cytoplasmic organelles involved in many functions of the cell, including energy production, intracellular signaling and apoptosis, reactive oxygen species (ROS) production, heat generation, calcium storage, metabolism of amino acids, lipids, cholesterol, and steroids (Apostolova et al. 2011). Based on accumulated data of full mitochondrial genomes (Toren et al. 2016) many mtDNA parameters, including resting metabolic rate, body temperature, rates of ROS production and scavenging, mitochondrial DNA (mtDNA) damage and repair, often exhibit correlations with longevity (Lehmann et al. 2013; Szczepanowska and Trifunovic 2017). As such, it is probable that the health of mitochondria directly influences the health of the overall system.

Mitochondrial mutations for example have been linked to the ageing process and age-associated pathologies (Alexeyev et al. 2004), and the accumulation of somatic mtDNA mutations has been documented in animals, from worms to humans (Melvin and Ballard 2017). This has been suggested to play a causal role in ageing and age-related diseases (Wallace 2005; Szczepanowska and Trifunovic 2017). To ensure mitochondrial homoplasmy, cells usually pass on only one mtDNA haplotype, with many identical mtDNA molecules present in a single cell. During evolution, populations accumulate a high number of non-pathological mtDNA base substitutions that radiate along maternal lineages (Mueller et al. 2012). The existence of different haplotypes (heteroplasmy) in mtDNA populations can be naturally inherited or due to de novo mutations (Payne et al. 2013). The within-cell and between-cell distributions of heteroplasmy may dictate the onset and severity of diseases (Burgstaller

et al. 2015) and are influenced by complicated stochastic processes within the cell (Burgstaller et al. 2014; Johnston et al. 2015).

Many studies have focused on mtDNA point mutations, deletions or levels of oxidized nucleotides with regard to species-specific longevity. In particular, maximum lifespan was found to be inversely correlated with the steady-state levels of 8-oxodG (a marker for oxidative damage) in the heart and brain mtDNA (but not in nDNA) across several mammalian species (Barja and Herrero 2000). Mutations in mtDNA may lead to an alteration in the coding instructions of some proteins (Taylor and Turnbull 2005), which may have an effect on metabolism and fitness. Diseases caused by dysfunctional mitochondria are potentially severe and incurable (Burgstaller et al. 2015). Among specific pathologies linked to mitochondrial mutations are exercise intolerance and Kearns–Sayre syndrome, which causes loss of function of heart, eye, and muscle movements (Tsang et al. 2018). Mutations in mitochondrial tRNAs have been linked to severe diseases like the MELAS and MERRF syndromes (Taylor and Turnbull 2005).

In summary, the accumulation of mutations in nDNA or in the population of mtDNAs, together with a stochastically driven decline in the DNA repair mechanisms, are probably important promoters of health decline during life.

### *5.3.3 Methylomics Changes in Ageing*

The epigenome profile changes dramatically with time. This has been the basis for the epigenetic theory of ageing and for the development of methylation ageing clocks (Horvath and Raj 2018). Briefly, a methylation clock (DNAm) refers to a function estimating age (either chronological or biological) based on DNA methylation levels. Among molecular phenotypes, methylation clocks record currently best performance (Horvath 2013; Putin et al. 2016), with microbiome clocks performing almost similarly well (Galkin et al. 2018). Most clocks are tailored for adults, but models that work across the entire lifespan and children-specific clocks also exist (Wu et al. 2019a). The most popular so far has been the multi-tissue DNAm, estimating chronological age, developed by Horvath, whose estimations do not vary significantly for different tissues (Horvath 2013). This suggests that the clock does not reflect mitotic age (Horvath and Raj 2018), in contrast to telomere length (Lowe et al. 2016). The clock also seems to slightly underestimate age acceleration variation with age, the bias being partially explained by the increased saturation of CpG methylation sites, so including age as a covariate is recommended (El Khoury et al. 2019).

Clocks for biological age estimation also exist (Levine et al. 2018) and can be seen as indicators of health, reflecting the continuous accumulation of system changes. For example, methylation measurements of ageing acceleration have been associated with cognitive decline in attention and visual memory (Beydoun et al. 2019). It should also be mentioned that the epigenome profile is strongly influenced by the environment, with factors like smoking increasing the epigenetic age of airway cells

by an average of 4.9 years and lung tissue by 4.3 years (Wu et al. 2019b), and hence it can also capture part of the exposome.

The age-specific drift in DNA methylation can be divided into global hypomethylation and local hypermethylation (Jung and Pfeifer 2015). Global hypomethylation events are enriched for repetitive DNA sequences and may lead to the reactivation of transposable genome elements with ageing, building up genomic instability (Howard et al. 2008). Sites of local hypermethylation are often found near tumor suppressor genes and are linked to tumorigenesis (Ohm et al. 2007). Additionally, the rate of DNA methylation changes and is influenced by factors like inflammation and the environment (Bind et al. 2014). Diet and nutrition also have a significant role, potentially related to the metabolism of methyl groups. Nutrients like folic acid, vitamin B12, and methionine have also been suspected for the aberrant evolution of DNA methylation with age (Choi et al. 2013).

The importance of methylation for health comes mainly from the link between methylation and transcriptomics. Considering the ageing changes assessed by the DNAm, 193 CpG sites that correlate positively with age are located in promoters, while 160 sites with negative correlation are located in enhancers (Horvath 2013). Moreover, with ageing, cells start to show increased transcriptional heterogeneity, possibly because of promoters with increased methylation heterogeneity (Hernando-Herraez et al. 2019). Another consideration is that many daily activities require biological rhythms which exhibit cyclical behavior, like the circadian rhythm, and this involves cyclical epigenetic modifications. Interestingly, a significant overlap was observed between DNAm sites that vary with age and sites that exhibit circadian cyclic behavior (Oh et al. 2018).

Lastly, in contrast to methylation being a drift phenomenon, the existence of an epigenetic maintenance system was also hypothesized. That is, once damage accumulates during ageing-related health decline, it is possible that an epigenetic maintenance system activates and modulates methylation levels in an attempt to control the damage and maintain stability (Horvath and Raj 2018). While this possibility is quite appealing, as externally triggered mechanisms might be discovered, for the time being, more research is needed to clarify this aspect.

Of note, this section refers only to DNA methylation, however very recently RNA methylation was also reported. Since this novel type of regulation is not directly involved in protein translation, but in how DNA is stored and transcribed (Liu et al. 2020), it is still unclear what its ramifications are for health.

### *5.3.4 Transcriptomics Changes in Ageing*

The transcriptional profile shifts with ageing as a response to accumulated damage or changes in the environment, either due to genetic or epigenetic modifications. On a cellular level, this translates to different effects, including downregulation of genes encoding mitochondrial proteins, downregulation of the protein synthesis machinery,

dysregulation of immune system genes, reduction in growth factor signaling, constitutive responses to stress and DNA damage, dysregulation of gene expression and mRNA processing (Frenk and Houseley 2018).

In addition to age-related changes per se, the variability of both transcriptomics and methylomics changes with age. As such, the ageing decline leads to a large proportion of system components, genes or mRNA, becoming hyper- or hypo-variable, either by relaxing or constraining the transcriptomic response (Bashkeel et al. 2019).

In recent years, more and more transcriptomic studies have been performed and the repositories for gene expression data have been expanded. One resource worth mentioning is GTEx, a data portal with tissue-specific gene expression data (GTEx Consortium 2013), which provides comprehensive insights into the specific transcriptomic dynamics and transitions during ageing or pathogenesis.

In particular, single-cell technologies add more granularity to the sequencing data, allowing researchers to explore transcriptome dynamics in a cell type dependent manner. This led to the observation that ageing is associated with increased transcriptional dysregulation and loss of identity at the single-cell level. In the pancreas it was found that cells from older donors have increased transcriptional noise and signs of fate drift, endocrine pancreas cells display an oxidative stress-related mutational signature, and cellular stress and metabolic genes get an increase in expression with the accumulation of errors (Enge et al. 2017). In another study, single-cell sequencing was integrated with mass spectrometry to jointly quantify transcriptional and protein changes across 30 cell types from the lungs of young and old mice. This revealed that ageing increases transcriptional noise and cholesterol biosynthesis in various cell types, and alters the frequency of airway epithelial cells (Angelidis et al. 2019). In the mouse brain, gene signatures are regulated in a cell-type specific manner, sometimes even moving in opposite directions; however, the variation seems to be coordinated across cell types (Ximerakis et al. 2019). Similarly, both common and unique transcriptional features of ageing were found across cell types that analyzed three mouse tissues (Kimmel et al. 2019). Cell-specific changes found across 18 mice tissues and organs revealed ageing to be linked to senescence, activity changes in metabolic pathways, depletion of stem-cell populations, genomic instability and inflammation, and changes in the immune system (The Tabula Muris Consortium et al. 2019). The immunological activation that drives a conserved transcriptomic response is also affected, leading to perturbations in the core response and increased expression heterogeneity across populations of cells. Thus, increased cell-to-cell transcriptional variability is a feature of health across most, if not all, mammalian tissues (Martinez-Jimenez et al. 2017).

Single-cell studies of transcriptome dynamics during ageing are also beginning to emerge. Such data was compiled for example into an atlas for adult fly brains (Davie et al. 2018). Using this atlas, an exponential decline of gene expression magnitudes was observed with ageing, although this is somewhat in contrast with prior studies (Enge et al. 2017).

As a conclusion, ageing and the decline in health results in widespread molecular changes (thousands of genes differentially expressed), but the changes are in most cases cell type-specific, making universal patterns harder to find.

### *5.3.5 Metabolomics*

Complementary to other less dynamic omics, metabolomics can connect the system state to the exposome as a step towards personalized medicine (Karczewski and Snyder 2018). The metabolome is the set of all low-molecular mass (<1000 Da) compounds synthesized by an organism (Oliver et al. 1998) and many studies have linked various metabolites to health. The biochemical diversity of metabolites (polar, nonpolar, organic, anorganic, endogenous, exogenous) makes it more sensitive and dynamic to study biological systems (Koo et al. 2014), and the metabolite phenotype (metabotype) can be an important marker of health.

By combining GWAS and metabolomics, many genetic variants in enzyme-, transporter- and other metabolism-related genes were shown to affect metabolic capabilities and disorder aetiology (Suhre and Gieger 2012). In ageing, specific metabolites vary significantly between young and old healthy subjects. A panel of 24 metabolites was observed to significantly vary with age in the serum of both Japanese men and women (Saito et al. 2016), while 52 metabolites were differentially found in urine (Thévenot et al. 2015). Studying >300 unique compounds, >100 were shown to correlate significantly with age and it was determined that many of them are specifically involved in oxidative stress, energy and protein metabolism. For example, metabolites like hippurate and oxoproline, increase with age, while carnitine, beta-hydroxybutyrate and cholesterol have lower concentrations (Lawton et al. 2008). In Italian centenarians, metabolites like arachidonic, 9-oxo-octadecadienoic and 9-hydroxyoctadecadienoic acids were proposed as markers of exceptional longevity among subjects aged 98 to 102 (Collino et al. 2013).

Complementarily, cross-species studies on mammals showed positive correlations with longevity, in several organs, for high urate:allantoin ratio and sphingomyelin levels. Negative correlations between triacylglycerols containing polyunsaturated fatty acid (PUFA) side chains and longevity were also found (Ma et al. 2015). Interestingly, this is supported by results from the Leiden Longevity cohort. By comparing middle-aged offspring of nonagenarians with their spouses, female longevity was shown to correlate with high plasma levels of sphingomyelin and low levels of PUFA-triacylglycerols (Gonzalez-Covarrubias et al. 2013).

In pathologies, thousands of metabolites show connections to hundreds of human disorders, including cancer, obesity, and neurological diseases (comprehensively reviewed by Miller et al. 2019), suggesting that a proper regulation of metabolomics is required for a healthy state. Moreover, the intestinal metabolome contains approximately 150 times more genes than the human genome and changes in its microbiome may lead to severe diseases (Ursell et al. 2014). Diets or xenobiotics can impact microbiota and modify metabolite concentrations in the gut, which may lead

to disorders like inflammatory bowel diseases, in which microbiota and their metabolites play pivotal roles in intestinal permeability and immune responses (Dong et al. 2019). Unfortunately, with age, more and more metabotype dysregulations accumulate, leading to higher disease susceptibility. Butyrate, propionate and acetate (SCFAs) are, for example, significantly reduced in old subjects compared to young (Parada Venegas et al. 2019). These decreased levels favor the entry of pathobionts into the intestinal mucosa (Biagi et al. 2010) and as metabolic health declines with age, it is possible that altered levels of SCFAs are, at least partly, responsible for the age-related degradation (Nagpal et al. 2018).

Recently, metabolomics activity screening was used in immunology, cardiovascular diseases or diabetes (Guijas et al. 2018). In this context, several key metabolites were found upregulated or downregulated comparatively to other metabolites, indicating a differential activation for phenotype modulation. Using mass spectrometry, it was found that L-arginine levels decrease in the activated naive T-cells (Geiger et al. 2016), and that protectin D1 promotes neuron differentiation of embryonic stem cells up to 15 times more than other metabolites (Yanes et al. 2010).

Finding biomarkers of health using metabolomic data is one of the hottest subjects today, with more than 1600 publications on the topic (Trivedi et al. 2017). It should, however, be noted that due to relatively few samples (generally less than 100 subjects per analysis), the results of many metabolomics studies should be weighed carefully with respect to statistics and generalization. In future years, the integration of omics, including metabolics, will give a broader understanding of health, but for now challenges still remain in achieving this (Karczewski and Snyder 2018).

## 5.4 Modelling Health with Biological Networks

Integration of multi-omics requires a holistic rather than reductionist view on health and diseases, evaluating the emerging properties of the entire system and not of individual components alone (Menche et al. 2015). This can be done by modelling biological entities (cells or organisms) as networks, in which molecular components like genes, proteins, drugs or other regulatory elements are nodes, and the interactions model diverse functional relationships between components (Barabási and Oltvai 2004), including protein-protein interactions (PPIs), co-expression, gene regulation, metabolic relationships, etc.

### *5.4.1 Network Stability and Robustness*

The main benefit of network representations is that system-level properties can be computed, allowing to assess entire systems and simplifying the understanding of combinatorially complex interactions. With most studies considering systems in

quasi-static states, the analyses generally focus on single time points and topological properties, such as node degree, centrality, shortest paths, clustering coefficient, etc. Even though this approximation disregards specific dynamics, it can still give insightful glimpses into the overall health of the network.

For example, biological networks usually have scale-free topologies, where the degree distribution follows a power law (Barabási and Oltvai 2004). This means that most nodes have low connectivity and only a few nodes, called hubs, are highly connected and hold the network together. Such nodes are mostly genes that are essential for development (Barabási et al. 2011), but also genes more likely to be associated with ageing (Promislow 2004). Hubs are extremely important to network integrity and stability, and their failure may severely impact systems, even disrupting their functionality completely (Albert et al. 2000).

Robustness is defined as the system's ability to respond and maintain relatively normal behaviour, despite changes in external conditions or internal organization (Barabási and Oltvai 2004). System perturbations include external, environmental factors (part of the exposome) but also internal ones, such as gene mutations (Stelling et al. 2004). Even if hub damage can critically affect network integrity, scale-free networks have higher topological robustness against random failures, as perturbations will most frequently affect small degree nodes (Barabási and Oltvai 2004). To put this into perspective, networks can remain compact clusters even if 80% of the nodes randomly fail (Barabási and Oltvai 2004).

The ageing process is associated with changes in the network topology, increases in network failures (Soltow et al. 2010) and noise, and an overall decrease in complexity (Promislow 2004). Random damage occurs in cellular networks, so the "Weak Link" theory proposes that the ageing decline is due to damage affecting mainly links between weakly connected nodes, thus leading to increased noise and instability in the system (Csermely and Soti 2006).

In an alternative approach, longevity genes have been associated with a limited number of network modules, both in human brain and fruit fly ageing networks, and it was shown that genes connecting these modules are more likely to affect ageing (experimentally supported by *C. elegans* assays). This was complemented by network simulations revealing that disabling longevity-associated genes affects the network stability much more than attacking random nodes (Xue et al. 2007). Thus, although scale-free biological networks are very robust to average events, they are sensitive to a small number of specific perturbations (Stelling et al. 2004). This topology also means that, during evolution, robustness improvements in some critical areas might have been achieved while sacrificing optimization in others. Moreover, the fitness function for long-lived animals is based on the reproductive healthspan (i.e. health up to reproduction) and on functions that ensure survival of the offspring. If so, ageing might be caused by tradeoffs—resilience to acute perturbations, at the cost of vulnerability to slowly accumulate damage, especially in the post-reproductive period. This "robust yet fragile" system is considered to be in a state of highly optimized tolerance (Kriete 2013).

So, while biological networks have high tolerance and robustness, specific signals can still trigger strong responses, further propagated by signaling and metabolic

pathways (Somvanshi and Venkatesh 2014). In this manner, large areas of the system can be disrupted, partly explaining why pathologies rarely affect only one component (Barabási et al. 2011).

### 5.4.2 *Networks Dynamics*

From a systems-perspective, environmental exposure is a time-varying signal, driving biological systems dynamics. A stable and healthy biological system does not implicitly mean inactivity. Keeping homeostasis requires that system parameters are within a range, not necessarily in a single equilibrium point, so transitions to other stable states may be physiological (Kriete 2013). Hormesis is a good example of beneficial system dynamics, when mild exposures to otherwise harmful agents, such as irradiation, food limitation, heat stress, hormetins, hypergravity, free radicals, and stress hormones stimulate and "shake" the system, increasing adaptability and robustness, and leading to positive hormetic effects (Rattan 2008; Gopi and Rattan 2019).

To analyze network dynamics, several approaches have been employed. For example, genes that are expressed differently in time can be superimposed on known PPI networks, yielding static subnetworks for each age group, and can be analyzed as time-series (Chatr-Aryamontri et al. 2017). While global topology is mostly unchanged, local topology features (e.g. average clustering coefficient, graphlet frequency distribution) do change and provide correlations with age, suggesting that ageing dynamics is encoded only locally (Faisal and Milenković 2014). Centrality correlations with age mean nodes become less or more connected (i.e. "hub-like"), and since most correlations are positive, it appears that ageing-related proteins become more central in general (Faisal and Milenković 2014), thus accumulating dysregulations in or around them poses system vulnerabilities.

Network dynamics can also be employed to investigate the mechanisms of disease deterioration by identifying dynamical network biomarkers (DNBs). DNBs represent a group of genes or proteins, usually from a common network module, whose pattern of activity in time is a biomarker. Briefly, signalling networks can be considered communication systems governed by rules from Shannon's information theory (Uda et al. 2013). Pairwise information flow between two nodes can be locally computed as mutual information (MI), while global information flow is the weighted sum of MIs along multiple network paths. Using this, network properties characterizing deterioration in four diseases, including type 2 diabetes, were identified. Interestingly, MI in symptomatic subjects was higher than in asymptomatic ones, while global information flow was higher in diseased subjects, compared to non-diseased. The association with increased flows might suggest that acute diseases trigger redundant cellular signalling pathways, increasing MI and "synchronizing" the network (Li et al. 2015). By contrast, it would be expected that during "healthy" ageing, the system slowly drifts towards decreased MI, more uncertainty and lack of correlation—which is consistent with increases in gene expression heterogeneity during ageing (Southworth et al. 2009).

Similarly to modeling molecular data, higher-order, non-molecular phenotypes can be structured into networks, with nodes representing phenotypes (e.g. BMI, arthritis, hypertension, MMSE results) and edges measuring the association intensity. Studying phenome dynamics can then determine a richer representation of the phenotype space, and thus a more rigorous description of ageing and its specific patterns (Freund 2019).

In summary, with the passing of time and due to continuous exposome interactions, systems transit through a dynamic space, reaching healthy or pathological phenotypes. These transitions are generally small and slow during ageing and more dynamic in disease emergence or progression. At the molecular level, the transitions are characterized by changes in the expression and function of nodes, but also by global, or more frequently, local modifications in topological features of the system. Overall, a healthy system can be described by efficient signalling and communication, decreased uncertainty, increased stability and, ultimately by increased robustness.

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# Chapter 6
# Health in Philosophy: Definitions Abound but a Theory Awaits


**Jonathan Sholl**

**Abstract** Philosophers of medicine have long debated the possibility of a/the definition of health, but they have yet to fully reflect on the intriguing observation that there is still no *theory* of health within the medical sciences similar to general theories in other sciences. In this chapter, I provide some reasons for why this lack persists and why philosophers have not been particularly helpful or even interested in filling it. After clarifying why such a theory could be useful, I discuss five general features of medical theories and how one could evaluate the utility of a given proposal. With these features in mind, I suggest that philosophers and scientists work together on analyzing actual medical research (experimental analysis), and the ways in which a theoretical construct of 'health' is being progressively identified and measured therein. I conclude by suggesting that research fields studying stress and aging might be particularly helpful in developing candidates for theory construction due to their broad scope, specificity, and potentially integrative explanations.

**Keywords** Health · Medical theories · Explanation · Theoretical constructs · Experimental analysis · Stress and aging

## 6.1 Introduction

It has likely gone unobserved by clinicians and medical researchers that philosophers of medicine who have been interested in the concepts of health and disease have largely been focusing on the problem of providing a *definition* of these concepts by stipulating, and then debating, necessary and sufficient criteria (individual X is healthy, if and only if …). This has given rise to a few main camps based around underlying intuitions about what is central to such definitions, and one can distinguish two general discussions. On the one hand, there is the debate over whether facts or values are more important to understand how to draw the line between health and disease (Boorse 1997; Cooper 2002; Wakefield 1992). There are those who believe

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that scientific descriptions of factual states alone provide the necessary and sufficient criteria with which to draw the line (naturalists), there are others for whom this line will always reflect human values and social, cultural, or personal preferences (normativists), and there are some who try to blend these two intuitions so as to build up a composite picture of objective facts and social values (hybridists). On the other hand, there is a debate over so-called negative and positive accounts of health, i.e. whether health is best understood as the absence of disease or as something *more* than this (Nordenfelt 2017). The positive account is often left vague, such as the notion of 'complete physical, mental and social well-being' famously suggested by the WHO. In both debates, the aim has largely been to clarify what doctors and the public mean when they use the concept 'health'. As these debates have proceeded without much reflection as to whether a clear definition is really what the medical sciences are lacking, it is perhaps no surprise that our philosophical efforts have not made much difference.[1]

More recently, philosophers have started pointing out the pitfalls of analyzing concepts and constructing armchair definitions (Fuller 2018; Kingma 2015; Lemoine 2013; Murphy 2005; Sadegh-Zadeh 2000; Schwartz 2007; Sholl 2015; Simon 2007), and have suggested that a more fruitful approach could involve a close examination of scientific descriptions, models, and theories and thereby investigating whether we can bring these different dimensions of medical knowledge together into a more general explanatory framework. Within the sciences, such a framework has a name: a scientific *theory*. What appears to have gone largely overlooked by philosophers is not whether there are theories in medicine, as there are clearly many theories and models describing specific physiological and pathological processes (Thagard 2005; Thompson 2011). Instead, what has gone overlooked is the very possibility of constructing a *theory of health*. This would raise the following questions. Can there be a general, theoretical framework that can explain what the medical sciences are after when they track 'health' in their labs, clinics, and observational studies? If so, would this imply that we conceive of 'health' as we do other concepts within the sciences, e.g. as a theoretical or hypothetical 'construct', much like 'intelligence' or 'personality' (Cronbach and Meehl 1955; Lovasz and Slaney 2013)? In other words, is 'health' more like a construct that is not directly observable, but is a property, or set of them, for which the medical sciences have a variety of scores and indicators that are used to explain and predict specific outcomes stemming from it?

To better understand what philosophy can add to these questions, I will first need to analyze a bit deeper the observation that there is still no theory of health within philosophy or the medical sciences (Sect. 6.1). I will then discuss five general features of medical theories and how one could evaluate the utility of a given proposal, focusing specifically on the value of explanatory integration that is both wide in scope and specific in detail (Sect. 6.2). With this in mind, I will suggest a different approach within philosophy of medicine based on an analysis of experimental constructs (Sect. 6.3), and will conclude by suggesting that fields such as stress research and

[1] One might see the philosopher Jerome Wakefield as an exception here, as his harmful dysfunction analysis of 'mental disorder' (1992) has frequently been discussed in specialized psychiatry journals.

biogerontology might be particularly helpful in developing candidates for theory construction in the medical sciences due to their integrative explanatory potential (Sect. 6.4). While I will not provide a full-fledged theory here, the overall aim is to outline the benefits of starting from actual experimental observations, research and localized theories in medicine, and then exploring whether these diverse aspects comprising medical knowledge might point towards a coherent and integrative theoretical framework.[2] It is my hope that this will also be well-suited to make sense of the different, and perhaps disparate, ways that 'health' is being explained and described throughout this volume.

## 6.2 On the Lack of a Theory of Health

Across the various sciences, it would seem that theories, be they local or general, are central to understanding the progress made in each of these sciences. For example, physics is now strongly supported by the theories of general and special relativity, as well as quantum mechanics and thermodynamics. Biology continues to build on the 'modern synthesis' of the theory of evolution by natural selection and population genetics, with fields like epigenetics or biochemistry only further expanding the explanatory reach of evolution. Ecology has guiding theories covering the notions of ecosystems and biogeography; geology is driven by the theory of plate tectonics; economics by theories of human nature and social dynamics; and modern psychology finds its support in modular theories of mind, learning theory and neuroscientific theories of brain function. Some theories, like systems theory or chaos theory, cross disciplinary boundaries and can found new subfields within a given science, such as systems biology, network medicine, or bioinformatics.

The situation with the medical sciences is similar, but with an interesting caveat. For example, there is certainly no shortage of theories to explain various physiological or pathological phenomena: specific theories about the role of autophagy, brain-derived neurotropic factor (BDNF), and heat-shock proteins in explaining the benefits of exercise; theories in microbiology and immunology concerning microbe-host dynamics; the seemingly universal role of inflammation or mitochondrial dysfunction in chronic diseases; broader theories of evolutionary and eco-developmental constraints and trade-offs in energy regulation and phenotypic patterns; and a whole host of theories about why we age. All of this, together with a few centuries of laboratory observations and experimentations has left us with immensely detailed, albeit incomplete, knowledge of the phenotypes characterizing human anatomy and physiology.

There does, however, appear to be one theory missing from such a list: a *general theory of health*—a theory that would describe, integrate and explain precisely what the medical sciences are after when investigating physiological capacities beyond

[2] A condensed version of the main arguments below first appeared in Sholl (2020), but with more focus on aging research.

the mere 'absence of disease'. If, as many doctors and researchers claim, future healthcare systems will have to shift or are already shifting from so-called 'sick-care' to 'health-care' practices (Kresser 2017; Marvasti and Stafford 2012), i.e. more effectively employing and inculcating preventative and personalized interventions/behaviors, or to analyzing factors of 'health' rather than just factors of disease (VanderWeele et al. 2020), then having a theory of what constitutes this 'health' would seem to be both useful and necessary.

So, similar to the notorious phrase that 'nothing in biology makes sense except in the light of evolution' (Dobzhansky 1973), we might ask: *what is it in light of that everything in medicine makes sense?* Can such a question even be answered? There have been various attempts to develop encompassing or integrative explanations of health and disease going all the way back to each of the ancient medical traditions (Fábrega 1997; Thagard 2005). These traditions generally shared the idea that some form of 'balance' was central to explaining health. This theory held sway over Western medical practice for over 2000 years and left its mark on the scientific theories to come with the birth of physiology as a science. It is not controversial, for example, to trace the conceptual lineages of Claude Bernard's 'milieu interieur' and Walter Cannon's 'homeostasis' back to the Greek idea of (humoral) balance or dynamic stability (Jackson 2013). While homeostasis is generally seen as being central to modern physiology (Cavagna 2019; Widmaier et al. 2019), the history of this field reveals a rather messy picture of not only homeostasis but a variety of other conceptual refinements made along the way (Schulkin 2003). At any rate, there has been no real attempt to generalize or unify these refinements so as to produce a theoretical explanation of health as such. If this project is even feasible, surely evolutionary biology will play some role in it, but this role remains unclear even if we look to the newer fields of evolutionary or Darwinian medicine (Gluckman et al. 2009; Nesse and Williams 1991; Stearns 2012) where it is claimed that evolutionary theory should be at the center of medical education (Nesse et al. 2010). While there has been much written about how to 'demystify' disease etiology and thereby explain *why* we get sick (Gluckman et al. 2011; Nesse and Williams 1994), there remain conceptual and epistemological gaps when it comes to concepts like health and disease (Cournoyea 2013; Gammelgaard 2000; Méthot 2015; Nesse 2001), and there is still no concerted effort to explain what health *is*. Why do these fields remain without such a theory?

Part of the reason is clearly historical. As mentioned above, nearly all ancient healing systems had a universal theory or at least a general explanatory framework for disease, e.g. as a form of imbalance (regardless of the differing views on what caused it and its nature) (Fábrega 1997). With modern medicine, and specifically microbial theory, driven by the many advances in medical technologies, there was a shift to localized and single or simple explanations for specific disease classes and etiology (Porter 2002; Thagard 2005). As such, modern medicine works on what Darrason (2013) calls a *Theory of diseases*, rather than a *Theory of Disease*. Advances in explanation have focused mainly on specific diseases or disease classes, but with little discussion about explaining 'disease' itself. Something similar seems to be the case with 'health'. Modern medicine and physiology have provided a host of

localized explanations for the role of specific parts or functions in so-called 'normal' or 'healthy' organisms, resulting in a seemingly endless and disorderly list of ways to realize this property of health. What has not been proposed, however, is an overarching *Theory of Health* that would unify explanations of most/all types of 'homeostatic', 'preferred', or 'optimal' functioning to better explain what health is beyond the mere absence of disease. (Perhaps the situation in modern physiology resembles the parable of the blind men and the elephant—each describing a different part without a vision of the whole.)

At the same time, I mentioned above that medical history has indeed been very productive of specific theories. This led Thompson (2011) to point out that despite what it might seem from looking at philosophy, theories and models abound within medical research. What he finds surprising is that few philosophers have given this wealth of resources much attention. He argues that the reasons are multiple. One reason comes from medicine itself: since clinical or practical applications are central to the very institution of medicine, this focus can obscure the sheer amount and epistemological value of medical theories. This is further supported by the fact that social and political interests more generally focus on developing clinical applications and experimental trials for testing the efficacy of pharmaceuticals or other localized interventions on specific diseases. Both of these reasons are easy to understand: the problem of treating disease is more pressing than that of explaining health.

There is yet another reason why little attention has been paid to medical theories and to a theory of health, and it comes from philosophers of medicine. Thompson (2011) lays the blame on the fact that, at least until rather recently, philosophers have focused mainly on ethical issues, witnessed by the growing field of bioethics, and there has not been much work on the nature and implications of these theories. While this is generally true, the problem would seem to run even deeper. As mentioned above, philosophers have been quite engaged with the problem of constructing a *definition* of health or disease for quite some time. Frustrated with this endless and seemingly fruitless debate, there are several positions that push against the idea that a more general definition, let alone a theory, could even be developed. The so-called 'eliminativists' claim that a notion like 'health' is simply too vague to do any explanatory work and that philosophers, scientists, and perhaps even clinicians, would be better off without it (Hesslow 1993; Ereshefsky 2009). There are those defending forms of 'normativism' or 'constructivism' who would claim that health can never be truly scientific since it is inescapably a folk or popular concept and, as a consequence, is bound up with the numerous values of a given society, culture, or individual (Cooper 2002; Sedgwick 1982). Finally, there are others who would perhaps concede that there is an objective difference between health and disease in general, but would argue that the line between them cannot be drawn without reference to the clinical encounter between doctors and individual patients (Canguilhem 1991). Health, in this view, is simply not a scientific concept (Canguilhem 2012). One could certainly conclude from such a seeming consensus that medical science progresses just fine without the need for an overarching concept or theory to organize its knowledge and practice and that philosophers are better off abandoning this issue (Kincaid 2008).

Despite these pessimistic conclusions about the definition of health, I maintain that there may actually be some hope for a theory of health. Put differently, the non-utility of such a theory is (1) actually yet to be shown (there is little reason to assume it to be useless a priori), and (2) is not supported by the history of science. It is one thing to point out that medical science has progressed by piecemeal descriptions without reference to a theory of health (Kincaid 2008), and it is another thing to claim that having a theory would be unhelpful. As discussed in the introduction, general theories abound in many sciences and, as was the case with biology, developing a general explanatory theory like evolution and genetic inheritance was quite fundamental in the ability of biology to integrate many observations and further solidify its scientific status. It is also doubtful that any of the above philosophers would argue that our understanding of physiology, and the models and theories it relies upon, has not greatly progressed since the nineteenth century. While there is much we do not fully understand, there is a lot that we do and it behooves philosophers to take this knowledge and the theories involved seriously. What's more, an analysis of medical models and theories reveals that the most robust of them are "deeply connected to the rest of science" and share the "theoretical depth, sophistication and explanatory power of those sciences" (Thompson 2011, 116–117). As such, there is an already functioning integration or consilience between medicine and the other life sciences that remains to be fully examined and its implications gleaned by philosophers and scientists alike. Consequently, rejections of the project of theorizing health appear to be unjustified and potentially short-sighted.

So, what if the problem, at least in philosophy, is that we have not been naturalistic enough? And have we even been using the right tool for the job? In various areas of philosophy, there are strong critiques of the focus on *definitions*, on searching for underlying meanings, and on analyzing folk concepts and intuitions through conceptual analysis (Ladyman and Ross 2007; Lemoine 2015; Machery 2009, 2017; Millikan 1989; Schwartz 2007; Quine 2013). Part of the problem here is that a focus on definitions involves the aim to provide descriptive or stipulative criteria for the *use* of a concept, whether this use is scientific or lay, but does not in itself provide the means by which to *explain* physiological observations or descriptions. Following the suggestion of Thompson (2011), perhaps what is needed is more direct inter- or cross-disciplinary analyses of the descriptions provided by physiological and biological concepts, models and theories. Philosophers and scientists interested in this lack of a theory of health could start from our most robustly verified theories and models—not to clarify classifications and intuitions, or to stipulate the criteria for yet another definition of health, but to understand *what* is being measured in the health sciences and to investigate whether these descriptions can be situated within a broader explanatory theory. As philosophers, our role is certainly not to design a whole theory of health by ourselves. Working together, we can at least remove some conceptual obstacles, take a broad view over the wide variety of our knowledge of health, and suggest or sketch the rough lines of a unifying theoretical framework for the most fruitful and consistent study of the physiological property of health.

## 6.3 Some Desiderata for a Theory of Health

If theory-construction is to be the aim of this new project, then the challenge becomes one of specifying what such a theory would look like, and perhaps providing some desirable features for evaluating various candidates. Building on philosophical work concerning the central features of medical theories, we can better determine how to evaluate the most useful of these features.

On the most general level, medicine works with specific models that describe the ontology and dynamics of a given system (Thompson 2011), e.g. models of lipid metabolism describe the types, components and specific ratios of lipoprotein particles carrying cholesterol and triglycerides, and track the complex coordinated dynamics of ingestion, intestinal absorption, microbiome regulation, hepatic clearance, endogenous synthesis, and excretion of these particles (Daniels et al. 2009). Such models become the basic components of medical theories, which exhibit four general features (Thompson 2011): integration, counterfactuals, interpretation/correction, and explanation, to which I add an overlooked one of operationalization (see Table 6.1).

I begin with the feature of *operationalization*, which plays a fundamental role in accounting for how a theory provides ways to identify and measure an object of interest, which may not lend itself to direct observation. A theory can provide formal, mathematical, or experimental criteria that help clarify what exactly is being studied and how to go about doing so. Researchers know, for example, that when they are studying 'lipid metabolism' there are standardized measures for identifying the specific kinds of lipoproteins, precise procedures for separating the lipids from the blood, for tracking their dynamics throughout the body, etc. As such, these measures together allow the construct of 'lipid metabolism' to be more precisely operationalized. This construct thereby plays an important role in studying, describing and, as we will see, explaining physiological phenomena. From these measures and clarifications of *what* is being studied, the question becomes one of organizing the data and knowledge produced.

The second feature of *integration* captures precisely this gathering and identification of the relevant bodies of knowledge, i.e. the currently accepted and robustly tested models and descriptions of the operationalized phenomena. Theories have

**Table 6.1** Five desirable features to assess in scientific theories

| Desiderata | Objectives |
|---|---|
| Operationalization | Identifying and measuring object, construct |
| Integration | Gathering of relevant knowledge |
| Counterfactual claims | Developing testable predictions, hypotheses |
| Interpretation/correction | Providing context and clarification |
| Explanation | Specifying causes, mechanisms (with scope, specificity, robustness, multidimensionality, invariance) |

a unique role here in terms of providing an overarching framework that organizes and codifies the descriptions and observations made in a given field into a coherent body of work. This body of work will then allow for the third feature, *counterfactual* claims. For instance, these could take the form of 'if the individual had X, she would present with symptoms A and B', or 'had the patient taken Y, she would have improved'. Such claims thereby involve making assumptions or testable predictions about system dynamics, at times without relying on specific observations or inductions, but simply based on current knowledge. On the one hand, this can produce new knowledge or hypotheses where experiments cannot be done, such as describing how a system or its parts would likely have functioned in the distant evolutionary past. On the other hand, this also allows for predictions about what will likely happen under specified conditions and can provide the basis for experimental manipulations of a system designed to test a given hypothesis, e.g. how a novel dietary component or lifestyle pattern might affect metabolism and overall physiology.

As past knowledge, novel claims and predictions are integrated, a theory provides a fourth aspect: the *interpretive* context for observations. In other words, observations and measurements, and the data they produce, take on meaning due to their roles in supporting, clarifying or falsifying hypotheses made by the theory. This can also take on a *corrective* role in that it helps to revise our perhaps intuitive and parochial understanding or assumptions, such as the misleading intuitions that all calories are equal, that the fats we consume are uniquely fattening in the body, or that consumed fats 'gunk up' our arteries just like grease accumulates in our drains (Guyenet 2018; Taubes 2008).

The final and perhaps key feature of theories is their ability to provide the 'why' answer for the observed system behavior and dynamics; they give *explanations*. These generally involve specifying the causal mechanisms purportedly responsible for producing an observed or manipulated outcome, e.g. explaining the importance of lipid metabolism in eukaryotic life, the role of this metabolism in physical and mental functioning (Morgan et al. 2016), and, ideally, when such metabolism can be considered 'healthy'. These explanations, and the evidence they entail, can of course be evaluated as better or worse in terms of whether they provide a satisfying mixture of *scope*, i.e. coving and integrating the knowledge discussed above, and *specificity*, i.e. doing so on the appropriate levels of granularity (Haack 2003). Similarly, explanations can be described as *robust* when they apply to both scientific idealizations and the real world, and *multidimensional* when they explain many, if not all, features of what is being studied, e.g. explaining the symptoms of a disorder (Murphy 2006, 109–110). When explanations have these features, they can become 'fundamental explanations' in that they have the ability to "explain a lot even in the face of messy, real-world detail" (Murphy 2006, 133). Consequently, the more encompassing in breadth and depth, and thus the harder an explanation is to vary (Deutsch 2011; Woodward 2000), the more robust the theory of which it is part. It is this feature, perhaps more so than the others, that provides the real pay-off of a theory since robust explanations form the basis of further experimentation and can allow for generalizations from one system, individual, or population to another. Explanations in medicine are thereby crucial for providing the reasons why some changes are more

beneficial to an organism than others, and subsequently, why and where we should intervene if we wish to promote such changes.

With these features in mind, we can be a bit more precise when it comes to developing a theory to explain 'health'. They entail, for example, that any such candidate for a theory be evaluated in terms of its ability to: (1) clearly and usefully operationalize a construct of 'health', (2) integrate, or at least be consistent with, as much of the existing physiological knowledge as possible, (3) provide counterfactual claims and make testable predictions about 'healthy' system dynamics, (4) situate our general knowledge and observations within an interpretative and potentially corrective framework, and (5) provide an explanation of the nature of 'health' that exhibits scope and specificity, or robustness and multidimensionality. Of course, any theory of health will exhibit these aspects to varying degrees, but at least having some clear desiderata in mind can help to know what to look for. Doing so, however, may require a different philosophical approach than what has been offered in traditional debates.

## 6.4 Reconceiving 'health' as an Experimental Construct

Returning for a moment to the diagnosis of why philosophers of medicine have failed to explore this possibility, one further reason could be that most discussions about 'health' have focused on how this concept is understood within the context of clinical medicine and reasoning. For example, some have emphasized how medical concepts emerge from specific *practices* within health communities (Jensen 1987). This nicely shows that when we look at the clinical focus of trying to identify and treat specific diseases, we come to understand why a 'negative' view of health as the absence of disease might best capture what is driving these practices. Diagnosing, treating, and if possible, curing disease—or at least alleviating suffering—are, after all, the central aims of clinical medicine and drive many of the clinical applications of medical research. And there is good reason to focus on these aims since they are surely of central importance to understanding (modern) medicine. However, the clinic involves only one set of practices, and it has a long and complicated relation to those practices found in medical research and laboratories, what Claude Bernard long ago deemed 'experimental medicine' (1865). Health *as described within the experimental context* would seem to capture something different than this negative view of health and so we need some tools to better understand this difference. One could argue that here too a negative view of health dominates in that medical research is also driven by the aim to identify and treat localized dysfunctions and diseases. However, as I will suggest, while this view is likely a result of the tight link between the clinic and the lab, this does not exhaust the practices of medical research where explanation, understanding, and prediction are key (cf. Broadbent 2019).

Within an experimental context, one can argue that perhaps the negative/positive distinction of health was on the right track, even if it alone cannot produce a theory or explanation of health. The most well-known 'positive' view of health is of course

the WHO's definition, but this was not initially developed so as to *explain* health, but instead to serve social and political ends (Valles 2018). Furthermore, this definition has long been criticized for rendering health unattainable and perhaps incapable of being quantified or operationalized (Huber et al. 2011). However, the basic idea that when the medical sciences are tracking 'health' there is something 'more' involved than the mere absence of disease may actually be closer to the practice of physiological research than it seems. This can be seen in how this research produces a rather different set of questions than those pertaining to how clinicians reason about signs and symptoms with an aim to relieve the suffering of the concrete individual in the clinic. For example, experimental medicine involves specifying what the methods are for studying 'healthy' physiology, how specific properties are individuated, how perturbations to a system or model are distinguished and how to make predictions concerning these perturbations, how results in one setting are translated to different groups, levels, species, etc. Understanding the theoretical import of these latter issues may be better achieved by shifting away from the traditional method of conceptually analyzing how we use concepts, and instead focusing on an *experimental analysis*—an analysis of the experimental methods and measures used to identify and explain this physiological construct called 'health'.

Now, concerning the project of theorizing health, experimental analyses may shed some light on the ever-growing number of ways to identify and track 'health' in the health sciences. In the context of the preferred features of a medical theory, the issue of *operationalizing* 'health' seems to be at stake when the physiological sciences employ their many health scores and indexes to determine the 'biomarkers of health' (Sholl & Rattan 2019; Rattan this volume) and overall physiological capacities: e.g. heart rate variability, $VO_2$ max, insulin sensitivity, metabolic flexibility, microbiota diversity, inflammatory load, Apgar scores, grip strength, flexibility and mobility tests, allostatic load, the frailty index, etc. The sheer quantity and quality of these measures would suggest that the health sciences have a wide variety of ways to identify, quantify and measure a *construct* (Lovasz & Slaney 2013) that is usually called 'health'. While not a directly observable entity, such a construct is nevertheless a quantifiable property ascribable to living systems. Although these various measures still lack an overarching theoretical framework to explain why and how they fit together, perhaps we could describe what the health sciences are doing in terms of composing a *health mosaic:* slowly weaving together disparate measures and indexes to form an ideally complete picture of 'health'. Even though there is no single measure of this property of overall 'health', the very compilation of these measures at least provides a more complete representation of what health consists of. The question becomes: can these different scores and operationalizations be unified into a coherent theoretical framework? What explains, for example, why seemingly disparate measures such as insulin sensitivity, heart rate variability, or Apgar scores track specifically *physiological* capacities?

The challenge when it comes to theorizing health would seem to be threefold. First, we would need to specify what the most relevant measures are when it comes to this health construct. Are *all* of the above measures (equally) relevant and, if not, what determines their relevance, e.g. alterations in risk factors, tolerance of specific

perturbations, or survival and fitness? Second, we need to investigate whether there are states/processes/properties etc. that are *specific to* the physiological sciences and which provide a description of this health construct. As will be discussed shortly, 'homeostasis' has been one possibility for providing a measurable and potentially explanatory property within physiology, but its utility as a more general theory remains to be seen. Third, we would need to determine whether the specified property can be situated within a theoretical framework that produces explanations that are robust enough in scope and specificity. In other words, we need to evaluate candidates based on the features discussed above in terms of their ability to not only integrate current knowledge, but to also make testable predictions and generalizations that allow for new knowledge and interpretations.

As mentioned, one way of clarifying what is specific to physiology, and thereby suggesting a general explanation of what health is beyond the mere absence of disease, dates all the way back to the origins of Western medicine in the theory that health could be explained by the 'balance' of bodily humors. While the basic theory of health as a form of balance, be it dynamic or static, persisted into the nineteenth and twentieth centuries, it was also thoroughly transformed by the rise of laboratory and experimental medicine. It was this science that produced the still-central concept of *homeostasis*, which relied on the basic idea of balance but sought to make it quantifiable and measurable. Like its predecessor, this concept is often seen to be a central and even unifying concept within contemporary physiology (Lemoine & Pradeu 2018). For example, in the 15th edition of a popular physiology textbook the authors write that "when homeostasis is maintained, we refer to physiology; when it is not, we refer to pathophysiology (from the Greek pathos, meaning "suffering" or "disease")" (Widmaier et al. 2019, 7). In this sense, homeostasis plays a role in demarcating the very discipline of physiology as well as its object of investigation. These authors go on to list eight general principles of physiology, with the first four all directly relating to homeostasis (Widmaier et al. 2019, 15; for a similar list, see Noble 2008):

- "Homeostasis is essential for health and survival."
- "The functions of organ systems are coordinated with each other."
- "Most physiological functions are controlled by multiple regulatory systems, often working in opposition."
- "Information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes."

It has been pointed out that homeostasis is not uniquely explanatory in physiology, in part because it can also be used to explain pathological conditions such as obesity, hypertension, or diabetes (Bernard-Weil et al. 1999). Furthermore, some have pointed out limitations with the concept itself (Boorse 1977), with one central limitation being that it is difficult to generalize homeostasis to the level of the whole organism. While there is also debate as to whether the traditional concept of homeostasis is sufficient to capture complex, dynamic and anticipatory biological processes (Rattan 2013; Schulkin 2003), it can nevertheless be argued that the central

*phenomenon* being tracked by the physiological sciences, i.e. the dynamic coordination of bodily functions and systems that support survival and optimal functioning, has remained relatively constant throughout physiology's recent history (Jackson 2013). As the health sciences have progressed with newer technologies and more complex modelling with the rise of 'omics' medicine, a host of newer concepts, such as allostasis, resilience, plasticity, robustness, homeodynamics, etc. (Kitano 2007; Rattan 2013; Sholl and Rattan 2019; Smirnova et al. 2015; Whitacre 2012), are now playing important roles in understanding the specificity of 'healthy' physiology, and are doing so within broader, and potentially integrative, theoretical frameworks such as dynamic systems theory. There have been recent attempts to use some of these latter concepts to provide a more integrative view on health. For example, the various measures and scores discussed above are what provide mechanistic descriptions of physiological functioning on various levels, and they appear to track the 'presence' of specific properties. In other words, they can be said to track different higher-level phenotypic 'parameters' (Sholl and Rattan 2019) or 'trajectories' (Lenart et al. 2019) of healthy functioning, such as robustness, resilience, or homeodynamics. Identifying and studying these parameters may provide a scientific and objective way to clarify a 'positive' view of health.

It remains an open question, however, as to whether one of these latter concepts, or perhaps a novel field such as dynamic systems theory or network medicine (Loscalzo et al. 2017), could provide an integrative framework within which to operationalize and explain this experimental construct of health that is being tracked by medical research. The success of a given proposal will ultimately have to be determined based on the ability to meet the criteria discussed above in terms of providing robust explanations, generalizations, and testable predictions.

## 6.5 Concluding Remarks: Where to Look and What is Gained from Doing so?

As mentioned at the outset, there has been much philosophical work on trying to provide a/the definition of health, but little attention has been paid to the question of whether a theory of health could be constructed within the health sciences. If such a theory were to be constructed, it would have to exhibit the same features that make scientific theories useful tools within science more generally: operationalization, integration, counterfactuals, interpretation/correction, and explanation. In order to construct and evaluate a theory on these grounds, however, requires a shift in focus, with more attention being paid to how research in the physiological sciences involves the identification, measurement and description of 'health' constructs (what I called experimental analysis). Now, all of this is still to speak rather generally, so in concluding I will just provide some brief remarks as to where one might look to begin such a project and the potential benefits of seeing it through.

Clearly, not all fields within the health sciences are equally amenable to theory construction. For example, cellular physiology provides great detail about cellular dynamics (cell signaling, growth, division, reproduction, metabolism, etc.), and applies throughout life, but it is not clear how such fine-grained descriptions could be generalized to explain the dynamics at higher levels of biological organization where the coordination of and interactions between systems are being tracked (Noble 2008). At the other extreme, fields like epidemiology or biodemography help explain health and disease patterns in populations and their determinants in space and time, but they often lack the specificity and mechanistic explanations required to help explain variations between and within individuals. Both ends of the spectrum clearly further our understanding of physiology, and newer subfields such as molecular epidemiology or environmental epigenetics do aim to bridge these gaps, but there are still trade-offs between specificity and generality for explaining health. As mentioned above, combining medicine with evolutionary biology, rich as it is for generating theories, may meet medicine's need for specificity and generality (Stearns 2012). However, given the long-standing debate in the philosophies of medicine and biology over how to use biological explanations to explain 'health', especially at the individual level (Schaffner 1993; Ereshefsky 2009; Matthewson and Griffiths 2017), it remains an open challenge to find the right balance.

Some fields do seem to be particularly promising in these regards and I only mention two here: the fields of stress and aging research. Both fields suggest a kind of consilience, or independent and converging agreement of explanations at various levels, that could support health theory construction. For example, stress research tracks stress responses from the levels of molecular interactions, genetics, and epigenetics, through sub-system levels and pathways, into the higher dynamics and complex interactions of bodily systems, as well as the intricate relations between all of the former levels and cognition, perception, and general psychology, all to be set within still broader accounts of social, environmental and evolutionary modulators of stress (Sapolsky 2004). Similarly, aging research has been tracking the ways in which the progressive loss of physical function on multiple bodily levels is driven by damage accumulating at the cellular and molecular levels (Jin 2010; Rattan 2018), ultimately providing an increasingly detailed picture of many of the pathways by which organisms lose their battles against entropy (Hayflick 2007) and exhibit the so-called 'hallmarks of aging' (López-Otín et al. 2013).[3]

In both of these fields, we find intriguing attempts to clarify and operationalize constructs such as 'stress tolerance/resistance', 'resilience', 'robustness', 'adaptability', 'physiologic reserve', 'healthy aging', and 'healthspan', and the related notions of health-promoting 'eustress' and 'hormesis', all of which directly implicate the broader construct of 'health'. Insofar as such fields aim to provide coherent and unifying explanations of the specific phenomena of interest— 'healthy' stress and aging across all physiological levels and across species—it would seem that they could be fruitful areas from which to consider the broader challenge of explaining the specificity of 'health' in physiology.

[3]For more details about the benefits of aging research for theorizing health see Sholl (2020).

Finally, what could be gained by having such a theory? First, a unifying theory could help to clarify what is being tracked by the different health scores and indexes discussed above. It would thus provide an interpretative context and integrative explanations that could organize the various health sciences around a common framework. In this sense, the worries about medicine's continued fragmentation into distinct subdisciplines might even be alleviated by a framework that can actually cash out the aims of developing and promoting so-called holistic medicine. Second, it could go some way towards providing a measurable and scientific notion of 'health'. Of course, normative questions of personal values, cultural norms, and statistical variability would still need to be addressed, but at least it would show us how far the sciences can go in explaining health and could even help inform these normative considerations. For example, the interesting notion of trade-offs that we find in aging discussions (Maklakov and Chapman 2019), e.g. how a given physiological change might be beneficial for one system and not another, or at one time but not later, helps to explain the well-known issue that what might be most beneficial for health in the long-term need not align with an individual's current behaviors or short-term concerns—such as the apparent divergence between high-level athletic performance and longevity (van de Vijver et al. 2016). Such divergences need not render the construct of health unscientific, but they show how health may not fully converge with our other values. Third, it could lead to posing better research questions if the target we are after is more clearly described, which could in turn allow for better use of resources and better design of interventions. If, for example, 'health' could be articulated in terms of of robustness or resilience, then we might perhaps focus less on manipulating individual biomarkers or single pathways, and instead focus on enhancing the system performance as a whole and its trajectory through time (see Lenart et al. this volume; Rattan 2019).

Ultimately, the actual benefits of having such a theory remain to be seen, and getting it wrong could cause harm, but that is exactly the challenge and the promise of an interdisciplinary project. We won't know before we try. At the very least, as physiological knowledge accumulates, it is worth considering whether our modern healthcare systems, with all their problems, might benefit from some clarity about what exactly they are caring for.

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# Chapter 7
# Mental Health and Well-Being in Philosophy


**Dominic Murphy, Caitrin Donovan, and Gemma Lucy Smart**

**Abstract** Mental health is philosophically understudied, especially compared to the growing interest in mental disorder among philosophers. In this chapter we survey the literature and discuss the relations between mental illness, well-being and mental health. Negative theories identify mental health with absence of disorder, whereas positive theories look to identify it with neither absence of disorder nor well-being, but something independent of either. We put the debate into context by introducing the existing literature on disease and discuss both negative and positive theories and the relation of mental health to well-being. We also discuss mental health in the light of recent externalist theories of mind.

**Keywords** Health · Well-being · Mental disorder · Function · Capabilities

## 7.1 Introduction: The Problem of Mental Health

An enormous amount of attention is paid to mental illness, but very little effort, in comparison, goes into trying to establish what we mean when we talk about mental health. The Australian government, for example, maintains a website on mental health as a public educational tool: (https://www.health.gov.au/health-topics/mental-health). It mostly discusses mental illness. Philosophically, too, there has until very recently been almost no treatment of mental health despite a growing literature on mental illness and psychiatry more generally. This is not atypical of policy initiatives, which sometimes seem to see mental health as the absence of psychiatric diagnoses. But other policy proposals look at mental health as a state of being that goes beyond the mere absence of mental disorder and involves human flourishing in important ways. This relation between absence of disease and well-lived lives is what this chapter is about, and the conceptual dispute over mental health exists in the spaces in between these two visions. In arriving at a concept of mental health, we might also dispute the extent to which we should preserve the way the term is currently

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used, particularly among medical practitioners, researchers and other allied experts. It seems doubtful that doctors think of health in terms of total well-being. While the boundaries of health contract and expand, medicine recognises a distinction, for example, between therapy and augmentation.

It is very hard to define mental health in a satisfactory way. In part, this is because it is hard to define health, but there are added problems with respect to mental health. These stem from the especially intimate relation mental health has with well-being, and the lack of any very clear descriptive understanding of what normality looks like when we talk about the mind. There is controversy over what a normal body looks like, especially in connection with disability, and there is controversy about the relation of physical health to well-being. But these controversies are less acute than their counterparts in psychiatry and psychology, where every bit of the terrain is contested. In this essay we will first briefly lay out the conceptual debates relevant to health more generally as we see it, and then ask how that framework applies to mental health (for philosophical accounts of well-being with roots in philosophy of science see Bishop 2015; Alexandrova 2017).

A very elementary view of health maintains that to be healthy is to have a correctly functioning biology, in which one's anatomy and physiology are doing whatever it is that they are supposed to do. This picture of health is derivative of a simple view of disease as the absence of bodily malfunction, disorder or other failure: it sees the body as a collection of systems that aim at maintaining homeostasis. Wren-Lewis and Alexandrova (forthcoming) call this is the minimalist view. They reject it for reasons we will address soon, but, like them, we find it a useful place to begin. A corollary of the minimalist position is the negative definition of heath as the absence of disease; health is the absence of disease and disease is absent if one's bodily systems are functioning as they should. Of course, what counts as "functioning as they should" is open to interpretation. For mental health, the corresponding negative definition is that one's mind is functioning as it should. This is again a disputed idea; a reductionist will tend to think of the mind as a set of neuropsychological systems that collectively enable intelligent behaviour. Less reductively inclined theorists will think of mental capacities considered in themselves, regardless of their basis. But a negative definition of mental health just says: it is the absence of mental disorder.

A theory of mental health, then, can be derived from a naturalistic theory of disease if we think of psychology as working like physiology. The dominant approach in the cognitive neurosciences provides a natural way to cash out such an idea. The approach says that human behaviour consists of capacities that can be broken down into their component processes and these processes can be understood, typically in representational terms, as the outputs of neurological systems that perform tasks like assigning a meaning to a phonological representation or compute visual edges. Capacities are realized by mechanisms, and mechanisms have component parts; so we could, in principle, assess the function of your auditory transducers just as we could assess the function of the chambers of your heart.

The positive definition of health is more encompassing: health isn't merely absence of disease. Most thinkers who write about health will insist on additional factors relating to quality of life. On this view, we need a threefold distinction between

disease, normality and health, where health involves some properties of a person's life that enable us to evaluate how well it is going for them.

The positive states of the healthy person are part of a good life; they are studied by positive psychologists and specialists in recovery. This picture is 'state based', insofar as an agent is mentally healthy to the extent that she manifests certain states, be they positive psychological states (happiness, a sense of fulfilment) or the occupancy of a social role. The problem with the positive view is that it is very demanding and is in danger of becoming a theory of well-being. The WHO, for example, defines health in terms of total well-being. It is this connection to well-being that bedevils positive conceptions of health. The worry is that positive conceptions of mental health just *are* conceptions of well-being, and therefore redundant or misplaced.

So we have three constructs to juggle: absence of disorder, well-being and mental health. Negative theorists identify mental health with absence of disorder, whereas positive theorists look to identify it with neither absence of disorder nor well-being, but to carve out a separate conceptual zone for it. In this paper we will first discuss negative views of health, by introducing the relevant concept of disease and then showing how it applies to mental health. Then we will discuss positive views. Then we look at the relation between mental health and well-being, which is the main sticking point for positive views. We will briefly survey the philosophical terrain with respect to well-being and then ask what the relationship between positive mental health and well-being amounts to. We will look in more detail at a recent proposal for an undemanding positive account by Wren-Lewis and Alexandrova.

Before we move on, a couple of notes. We have spoken of juggling three constructs, but there are arguably more that we should consider. First, there is recovery. A generation of theorists have stipulated that recovery is the goal that all treatment of mental illness aspires towards, but there is very little agreement about what constitutes recovery, or whether indeed it should be seen as an end state, or a process, or a guide for researchers, or something else (Roberts and Wolfson 2004; Davidson and Roe 2007). Philosophically, though, recovery raises many of the same question as well-being and mental health more generally—the question of the sort of life we should aim at as the goal of treatment, and most of the issues we will discuss later will recur in a discussion of recovery (Thornton 2017 is a useful philosophical review). So we will treat recovery as a question in the philosophy of well-being, and not discuss it explicitly.

Second, our concerns in this essay relate to intellectual or cognitive disabilities as well as mental disorders like anxiety or depression. DSM 5 (American Psychiatric Association 2013) relabelled mental retardation—the label previously in use—as "Intellectual Disability" (pp. 33–41). It is diagnosed on the basis of scoring two standard deviations below the mean for IQ, although the DSM-5 (p. 37) also notes the limitations of IQ as a measure of intellectual function, especially at the extremes. Cognitive disability includes deficits in the practical and social domains; roughly, the practical domain encompasses self-care and capacity for independent living, whilst the social domain is a matter of how well you can navigate social life (including the regulation of your own emotions). Although cognitive disabilities feature in DSM-5,

they would not normally be considered a mental disorder. We will not treat them explicitly here, but as with recovery, a comprehensive theory of mental health ought to have something to say about them.

## 7.2 The Negative View of Health, Part 1. What is Disease?

The negative definition of health is that it is the absence of disease. What is disease? The modern debate stems from the very influential work of Christopher Boorse. His "biostatistical conception" of disease (Boorse 1975, 1976, 1997) distinguished "disease" from "illness". He understood illness to depend on value judgments about suffering or deviance in addition to the presence of disease. For Boorse, it is a perfectly objective matter whether one is diseased, to be determined by which he saw as the perfectly objective matter of whether one's physiology is dysfunctional relative to a species-typical inventory of bodily systems, appropriately indexed to reference classes such as age or biological sex. The species-typical design specifies, at various levels of analysis, what systems compose the physiological structure of the body and what functions they perform, where "function" refers to a contribution made by the system to survival and reproduction (1976, pp. 62–63).

Boorse argued that a disease only counts as illness if it is undesirable, entitles one to special treatment, or excuses bad behavior. This is the two-stage picture; scientific judgments that a destructive or abnormal bodily or psychological process has occurred, plus, at the second stage, judgments about the extent and manner of its impact.

The typical way of setting up the debate in the wake of Boorse's work distinguishes naturalists and normativists. Naturalists, like Boorse, see our concepts of disease as involving, at least in part, the idea of a destructive process that prevents bodily systems from performing their customary function. The difficulty for such views is establishing an objective notion of bodily function. Normativists think of disease ascriptions as a matter of value-judgements about how a life is going, although specifying the particular type of value judgement that is distinctively health-related is very difficult. That is the main difficulty faced by normativists. We will not attempt to resolve the dispute, because, as will become clear, we think both conceptions of disease have very similar implications for negative and positive views of health.

There are ways in which these two perspectives could be combined. One might, for instance, embrace naturalism about bodily disease but be a normativist about mental disorder: you might be sceptical, for instance, about the prospects of assembling an inventory of mental systems with functions along the lines of our physiological inventory of the body. Typically, a naturalist will acknowledge a role for values as part of our concept of disease or disorder, in addition to the role played by bodily (or psychological) dysfunction. A standard naturalist response is to argue that both dysfunction and impairments in well-being are part of our concepts of disease, in both the physical and mental realms. This introduces a normative element into the

naturalistic account; such accounts are sometimes called ‘mixed’ or ‘hybrid’ views. Murphy (2006) referred to such views in psychiatry as ‘two-stage views’.

Certainly, ascriptions of disorder are usually made without waiting for findings about physical or mental dysfunction. Rashed and Bingham argue that this reflects the diagnostic importance of “consequences of the syndrome as they manifest for the subject” (Rashed and Bingham 2014: 245). This is true, but what is in dispute is the conclusion they draw from this, which is that therefore depression is nothing over and above a collection of impairments in a person’s mood, well-being and daily functioning and not a malfunction of underlying systems. They think of dysfunction as a cause, but not a necessary condition, of depression, but the order of discovery is not the same as the order of nature. Our diagnostic practices and our concern for intervention and guidance might mean that values play a role in diagnosis and in conceptions of health and disease, but they do not show that there is no role in disease concepts for functional deficits. However, the role of values in ascribing and thinking about disease has persuaded most naturalists that although malfunction is an objective matter, disease involves normative as well as objective criteria—both how a life goes and how a body is working. This is especially true in psychiatry.

## 7.3 The Negative View of Health, Part 2. Psychiatry

The upshot of Boorse’s view of disease is a simple negative view of mental health. An organism is healthy to the extent that it is not diseased (Boorse 1976: 197). The corresponding picture of mental health is straightforward. Human beings are mentally healthy in so far as they are not mentally ill or disordered. This depends on whether we can find the relevant psychological analogues of the physiological systems whose normal functioning determines bodily health. Boorse raised the possibility that psychoanalysis might provide the needed analogous theory of mental functioning, but although that idea has not aged well, there is a research program in psychiatry that has boomed in recent decades that does aim to fit the bill, namely the medical model. The medical model in psychiatry can be seen as having adopted the dominant approach in the cognitive neurosciences, which is that human behaviour consists of capacities that can be analysed into component processes and these processes can be understood, typically in representational terms, as the outputs of sub-personal, neurocomputational systems that do things like assign a meaning to a phonological representation or computing visual edges. This decomposition of the task and the allocation of the subtasks to interacting physical entities gives the general form of a mechanistic explanation.

Not all psychiatry can be read in this way, but a Boorsian approach is consistent with the assignment of psychological processes as the output of mechanisms—interacting systems of biological components. The problem, with psychology as with physiology, is whether a notion of function can be defended that is both scientifically

useful and value-free in the way Boorse wants. In addition, although Boorse originally made room for evaluative practices in his conception of illness, few subsequent theorists have endorsed the sharp distinction he made between illness and disease.

The most influential Boorsian treatment of mental health in psychiatry is Jerome Wakefield's Harmful Dysfunction Analysis or HDA (Wakefield 1992, 1993, 1999, 2006). Wakefield has argued that there are two individually necessary and jointly sufficient conditions for disorder. First, there is a biological dysfunction. Unlike Boorse, Wakefield sees this as specifically a failure by a bodily system to perform its naturally selected function: "the failure of a mechanism in the person to perform a natural function for which the mechanism was designed by natural selection" (Wakefield 1993, p. 165).

Second, the dysfunction must result in harm to the individual. "Harm" is generally recognised to be a normative notion, and Wakefield thinks we follow a simple rule when judging that someone is harmed. It is judged by prevailing social norms: "defined by social values and meanings" (1993, p. 373). The fact that this is a simple rule does not mean that it is a simple matter to tell where it applies. Whether somebody is harmed may be difficult to assess, and although judgements can be uncontroversial (a terminal disease or a serious injury is obviously harmful) they often won't be. But harm is assessed relative to the prevailing norms of the society, not the views of the individual concerned, who may not feel as though they are badly off at all. In sum, we have the two components of the HDA (Wakefield 2006, p. 157), which state that for a condition to count as a mental disorder:

(1) it is negative or harmful according to cultural values; and
(2) it is caused by a dysfunction (i.e., by a failure of some psychological mechanism to perform a natural function for which it was evolutionarily designed).

We count Wakefield's view as a species of naturalism despite its concessions to norms, because it involves the assumption that there is an objective scientific inventory of functional components of the human mind. Other thinkers will cavil at this label, but little turns on it. Our point here is that the most straightforward way to translate a negative picture of health from general medicine into psychiatry is to adopt a medical model that sees the human mind as a collection of neurocomputational structures.

However, there are other answers to the question, how do we know what human psychology comprises? Graham (2010) suggests that this is not to be resolved through scientific inquiry, but by reflecting on the ends or purposes that all human beings share—normal psychology is the psychology that you need to live a decent life (p. 139). Graham puts philosophical psychopathology squarely in the philosophy of mind and moral psychology. The aspects of the mind we care about are the ones that help us flourish. It is deliberation on the ends of life, not the science of the mind, which tells us what is psychologically important. So Graham's list of basic psychological faculties does not include working memory, theory of mind or perception, but phenomena like emotional commitment, the ability to act in the world, to form goals and shape our behaviour to fit them, make choices, and so on (pp. 147–150).

This is a normative conception of the mind's capacities. One such capacity is rationality: though the concept is quite fundamental to our projects, because it is a highly normative concept it is notoriously difficult to naturalise without revision or loss. Nonetheless, some theorists argue that these are precisely the capacities that should feature in our explanation of psychiatric disorder. Like Boorse's account, though, it furnishes a simple negative concept of mental health; mental health, in both cases, is the absence of the phenomena that constitute mental disorder, however they are understood. Graham's basic idea is that mental illnesses are "capacity-tethered rationality impairments" (p. 137). This means that in mental disorder fundamental human mental faculties are, in his words, "gummed-up" through a mixture of intentional causes and brute ones; both mental and non-mental states interfere with the normal operation of our basic human psychology. In the absence of these interfering causes, we have a normal, healthy mind, able to do the things that human minds are supposed to do. For Graham, as for Rashed and Bingham, a healthy mind is one that enables us to navigate the world as we are supposed to; for Wakefield, it also involves an assessment of structures that are the neuropsychological equivalent of our anatomy and physiology. But a negative view is that mental health is the absence of mental symptoms or deficits, whatever your theory of the mind might be.

## 7.4 The Positive View of Health

We have discussed negative views of health that say health is just the absence of disease. We now turn to positive accounts of health. The positive conception of mental health is what the World Health Organization has in mind: (https://www.who.int/en/news-room/fact-sheets/detail/mental-health-strengthening-our-response).

Mental health is an integral and essential component of health. The WHO constitution states: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." An important implication of this definition is that mental health is more than just the absence of mental disorders or disabilities. So, as the WHO specifies: "Mental health is a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community."

Clearly the WHO definition is very demanding. It sets a standard for mental health that few will reach. Wren-Lewis and Alexandrova worry also about the conception of human well-being animating this definition: the stress on working productively is uncomfortably akin to the distinctively modern idea that the function of human life is to serve the economy. On the other hand, some psychologists have challenged the WHO definition on the grounds that it overemphasizes positive affect; Galderisi et al. (2015) suggest that we might regard you as mentally healthy even if you're unhappy because you've just lost your job, and we should view somebody as unhealthy if they enjoy positive mental states while committing an atrocity. They offer the following definition (pp. 231–2):

> Mental health is a dynamic state of internal equilibrium which enables individuals to use their abilities in harmony with universal values of society. Basic cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as empathize with others; flexibility and ability to cope with adverse life events and function in social roles; and harmonious relationship between body and mind represent important components of mental health which contribute, to varying degrees, to the state of internal equilibrium.

This goes beyond any simple conception of mental health as the mere absence of illness and sees it as a collection of positive states. But it is not quite a theory of well-being either. There is a gap between what we might call the enhanced theory of mental health—that mental health is more than the absence of mental illness—and well-being.

Wren-Lewis and Alexandrova refer to such definitions as "demanding" positive accounts (pp. 14–15). They reject these accounts on several grounds. First, demanding accounts represent an encroachment of the medical into the rest of life. By bringing more and more aspects of human flourishing under a medical lens, they expand the medicalization of ordinary life. Wren-Lewis and Alexandrova want to resist this encroachment of the medical on our views of human flourishing because of the dangers associated with medical technologies as forms of social control. At the borders of health-ascriptions are legitimate worries of over-medicalisation. In some cases, the behaviours we call unhealthy might only be tenuously connected with disease (if at all) and might instead be inflected with moral or aesthetic judgments. In these cases, there are worries that medicine has the power to condone or veto lifestyle choices for medically arbitrary reasons. Second, well-being is such a heavily contested construct, both as a philosophical matter and as a policy instrument, that we have reason to shy away from involving concepts of health with it, since we will simply be analysing the obscure with reference to the even more obscure.

Despite these problems with demanding positive accounts, Wren-Lewis and Alexandrova still hold out hope for a positive account that is less demanding. Why think positive accounts are desirable? Their argument turns on a desire for criteria of health that are independent of the categories of psychiatry and provide an alternative source of legitimacy and guidance for assessments of health. Provided, of course, they can avoid the problems besetting expansive positive accounts.

Solving the relation between mental health and well-being is the chief difficulty a positive account faces. We will now look at two positive accounts that tackle this problem. The first is advanced by Keller (2019) who denies that well-being and mental health are more than contingently related. Then we will discuss Wren-Lewis and Alexandrova's own positive account.

## 7.5 Mental Health and Well-Being

We have distinguished positive and negative concepts of mental health and introduced well-being. As we noted, the relationship between mental-health and well-being is a difficult question, especially for positive theories. In this section we ask what the

relation should be between the two, assuming that we have good reason not to treat them as identical.

In a recent paper Keller (2019) has argued strongly for keeping mental health and well-being separate although he does think they have 'some connection' (p. 230). It is not obvious how two things that have a connection can be kept separate, but Keller seems to mean that conceptually the two constructs are distinct even though they sometimes coincide, and perhaps one makes the other more likely. You might think this about the relationship between intelligence and success for instance. It might be that the cleverer you are the more likely you are to be successful in diverse activities or walks of life; nonetheless, you can become successful even if you lack high intelligence, and fail to do so even if you're unusually bright. It could also be that different sorts of intelligence enable success in different spheres. The sort of academic potential measured by IQ tests might help you in a career that depends on book-learning skills, but a soccer player or pastry chef might need different sorts of intellectual acumen.

We will discuss Keller's account of the terrain and then wonder what the connection might be between mental health and well-being. Keller agrees that mental health is not just the absence of disorder but the presence of something positive: however, he thinks that the positive features that make up mental health are different from those that comprise well-being. Intuitively, he thinks, we believe that well-being is a matter of how a person feels and how their life is going for them. Mental health, on the other hand, is a condition of the mind. There are various circumstances, then, in which one's mind might instantiate the properties needed for mental health but in which one's pursuit of well-being is frustrated by the wider world. Keller's examples are people who suffer from various kinds of social exclusion like an immigrant without work papers, or simply people who are the victims of circumstances; someone who is in jail or who is caring for a sick relative may see their quality of life decline with corresponding adverse effects on well-being. All of these people, Keller thinks, are deficient in well-being but can still have positive mental health. Conversely, one can have a life that is going well but a mind that is disordered; an alcoholic can organise their life around goods other than booze, or a socially phobic person might live an enriched and fulfilling life despite very few human contacts. (One might also imagine high-functioning sociopaths, who might be very happy and successful).

Keller disputes the connection between mental health and well-being because of the differences in their assessment. Someone's mental health is a matter of states of mind, whereas their well-being depends on circumstances. Even if both well-being and mental health feel very similar, or cause the same states, they are empirically distinct.

First, Keller notes (p. 232) that when "well-being and positive mental health are construed as the same thing, it is more likely that any form of unhappiness, or anything that sets back the quality of a person's life, will be viewed as a mental health issue." This blurs the line that we might want to retain, between genuine mental health issues or mental disorders on the one hand, and what psychiatrists sometimes call 'problems in living' which are genuine sources of mental distress that fall short of being pathological. If the line is blurred, we run the risk of over-medicalizing

everyday life. This can have consequences for how a person views her own situation and for what kinds of interventions she seeks and is offered. If any setback to well-being is construed as a mental health problem, then it is easy to think that the fault for low well-being lies within the person's mind, or that interventions should focus upon the person's feelings and attitudes, rather than upon—for example—the ways in which she is treated.

Now, one might ask whether mental health and well-being are really as distinct as Keller contends. For example, although Keller thinks they can vary independently, mental health is not in fact likely to endure in circumstances that are seriously detrimental to well-being. One's mental health might survive a blow such as unemployment or social exclusion, since these might be initially neutral with respect to mental health even if they reduce well-being. However, somebody who thinks that the connection between mental health and well-being is tighter than Keller affirms might argue in response that such circumstances are likely to go on to deprive one of good mental health. To take an extreme example, John Doris (2015, pp. 113–14) reviews evidence that solitary confinement in the prison system has profound ill-effects on mental health, including chronic depression, confused thought processes and hallucinations. (Solitary confinement also has a number of adverse effects on physical health). There might be numerous and various states of affairs in which one at first enjoys good mental health as well-being drops but cannot sustain or maintain it if adverse circumstances persist. Prolonged unemployment or discrimination, for example, are likely to see mental health drop over time as the sources of well-being dry up.

To be sure, this is not a conceptual point; Keller's contention that mental health and well-being are conceptually distinct might still go through. But it does raise the question of their connection—what might it be if it is not conceptual? We turn now to the positive account offered by Wren-Lewis and Alexandrova, which attempts to answer this question.

## 7.6 Wren-Lewis and Alexandrova's Positive Account

Wren-Lewis and Alexandrova also use the language of capacities, as we did earlier when talking about negative theories, but they have something different in mind. They have in mind those capacities of a person, which enable one to engage in life and to value pursuing their own version of human flourishing. They break these down into further capacities: valuing life is seen as caring about states of affairs that are important to both oneself and others; engaging in life involves enough psychological flexibility and resilience to deal with setbacks and losses and keep on going through life. This set of capacities is necessary but not sufficient for well-being; someone might be disposed to value life in ways that promote false or self-undermining conceptions of the good, for example—such a person would be mentally healthy, but not enjoy well-being because their mental health is serving goals in life that are not good for them.

Wren-Lewis and Alexandrova regard their theory of mental health as a stripped-down version of current positive accounts that captures what is valuable about them but does not load the theory down with the excessive demands that can make positive accounts too demanding or utopian. They are keen to distinguish personal effectiveness, which they see as the core of mental health, from subjective well-being or happiness. Indeed, on Wren-Lewis and Alexandrova's view, it seems that one could de desperately miserable and also in excellent mental health—the ability to value and engage in life might make the difference between dying in a concentration camp and surviving it, for example, but you wouldn't expect a camp inmate to be happy, no matter how personally effective they might be. Like Keller, Wren-Lewis and Alexandrova want to distinguish mental health and well-being, but unlike Keller, they think the former is necessary for the latter.

Wren-Lewis and Alexandrova offer an account that situates health at the intersection of two traditions of thought, one that sees health in terms of openness to the world, and one that sees it as a relation to the self. Other theorists have opted for different facets. Carel (2007, 2008), for example, thinks that the important thing about health is one's lived experience of one's own body. One should be at home in one's body, rather than alienated from it or feeling at odds with it. The analogous experience to Carel's might be a sense of one's psychic life as something that one is in control of and not alienated from, unlike the experience of enacting severe mental illness, in which it can seem that one's mind is acting in ways that are outside one's power to prevent or modify. This is an experience of agency, which we see as akin to the ability to value life and engage in it that Wren-Lewis and Alexandrova emphasise. But the other aspect of their view is resilience, adaptability and effective coping, which has a long history as the marker of health.

Canguilhem (1991, 2012) thinks of health as flexibility, in the sense that a healthy organism can tolerate environmental impacts, adapts to new situations and possesses a store of energy and audacity. However, he claims that this cannot be captured in a physiological model (2012, p. 49). Gadamer's (1996, 113) healthy person is someone who is in harmony with their social and natural environment, and disease is a disturbance of this harmony: "it is a condition of being involved, of being in the world, of being together with one's fellow human beings, of active and rewarding engagement in one's everyday tasks".

As we noted above, the understanding of capacities in Wren-Lewis and Alexandrova is not the same as what we meant by capacities when we referred to them earlier. We were thinking of the inventory of sub-personal effects of computational systems, such as semantic memory or varieties of visual cognition. It seems clear that such systems need to be, by and large, in working order in order to enable one to value life and engage in it. The question is, what else is needed.

The objection can be put like this: a naturalistic negative account gets the extra stuff for free. If one's network of sub-personal capacities is functioning appropriately then one will be able to engage in life effectively, because engaging in life effectively is what those systems are for. So a negative theorist can say that the positive theory is confused—mental health can't be 'correct functioning plus capacities' because those personal level capacities just are the operation of the sub-personal systems. It is like

saying that physical health involves functioning leg musculature plus the ability to walk.

So, the concern is that Wren-Lewis and Alexandrova have weakened the positive conception of mental health so far that there is no space between their view and a negative one. The traits they see as constitutive of positive mental health are not something over and above the absence of symptoms, they just are the absence of symptoms, because when symptoms are absent people value life and engage in it.

The problem is also present if we look at a more normative conception of the mind, like that of Graham which we mentioned earlier. Graham, recall, contended that mental disorders are "capacity-tethered rationality impairments" (p. 137) in which fundamental human mental faculties are, as he says, "gummed-up". A negative view of heath derived from this view would state that a person's mental life is de-gummed. That would mean the smooth operation of our rational and affective abilities to engage in the world, as Graham suggests. But that sounds very much like the positive account of mental health that Wren-Lewis and Alexandrova have in mind.

In sum, then, the objection is that the absence of symptoms just is the presence of whatever it is that the symptoms interfere with. The absence of symptoms is not just a neutral state in which nothing bad is happening but it is the healthy state of a human being in which engages with the world. Wren-Lewis and Alexandrova need there to be "extra psychology" over and above the smooth functioning of deficit or symptom-free psychology, in order to turn negative mental health into positive mental health. It is not clear where this is to be found.

A response to this objection might concede the point that there is no extra psychology beyond the functioning of normal capacities but still insist there is a difference between health and absence of symptoms. Let's call a *capacitarian* definition of positive mental health any definition that doesn't identify mental health with the attainment or exercise of certain goods—be they social, physical, or psychological. Rather, it sees mental health as resting on the psychological capacities that either secure or promote their attainment. For example, the kinds of capacities that help a person acquire a job are not limited to, but include, a range of general-purpose psychological capacities that are probably instrumental for a number of diverse conceptions of the good life. While it is by no means straightforward exactly which capacities are health-constituting, this view attempts to identify them in a way that is neutral with respect to the goals and values that are relevant.

However, we can also draw attention to the difference between the presence of a function and the extent to which it is realized. So on a purely negative view of mental health, being mentally healthy is a matter of being free from conditions such as dementia which involves (among other things) a severe impairment in memory. We know, however, that even when a person is unaffected by psychopathology, the functioning of their memory can vary greatly. It is also a capacity that can depreciate with age and, while this might not constitute disease per se, it nonetheless rises to the level of medical significance. It does so, plausibly, because the capacity to encode, store and retrieve information across different moments in time is instrumental for a person's well-being. We have seen that the connection between capacities such as memory and well-being isn't one of identity, or even strict entailment. They are conceptually

dissociable. Having an excellent memory won't increase your well-being if it means you are beleaguered by vivid flashbacks. Conversely, even a devastating condition such as dementia can enhance well-being if it relieves the sufferer from otherwise ineradicable grief caused by persistent memories of great loss.

However, it may be that even a level of memory performance that puts you into the "absence of symptoms" class is not enough to count as mental healthy—to be mentally healthy you would need a level of memory performance that is enough to enable you to live what Wren-Lewis and Alexandrova think of as the kind of life a mentally healthy person lives. The extent to which memory is important to different individuals, moreover, might vary across contexts in ways which require different levels of memory over and above the minimum represented by the mere absence of deficit. It is possible that health is a capacity that is cross-culturally variant, or relative to the particular psychologies of individuals (Washington 2015).

Our objection to the modest positive view of Wren-Lewis and Alexandrova was that there was no gap between "well-being" and "absence of symptoms" into which even a modest positive theory could be inserted. The response we have considered is that absence of symptoms might secure a minimal level of functioning, but that is not enough for health. Perhaps different lives make different demands and what counts as healthy should be indexed to a life. Wren-Lewis and Alexandrova appeal to Sen's (1999) notion of capabilities. For Sen (1993, p. 31) capabilities secure "functionings" which are alternative suites of things that different human beings are able to do. Different people will have different potentials and goals, which will place different demands on underlying capacities, in our sense.

The issue confronting modest positive accounts, then, is the extent to which capacities can be specified in ways that are not just specifications of deficit- or symptom-free functioning, but which represent the basis for a chosen type of life. Reductionist accounts of capacities, rather than views like Graham's, might have an advantage here, in so far as they can be couched in ways that do not have norms of well-being embedded within them, and so provide a more neutral starting point.

It remains an open question, however, exactly how we should understand the capacities that subserve mental health, as well as how clinicians should intervene to promote them. An answer to these questions will partly depend on the way we understand the relationship between cognition (broadly construed here, to include affective states) and the environment in which agents are embedded.

## 7.7 Agent, Environment and Health

Over the last few decades, there has been a debate among philosophers of psychology, and theoretically oriented cognitive scientists, between advocates of internalism, on the one hand, and externalism on the other (Wilson 1994; Clark and Chalmers 1998; Rowlands 2003; Menary 2007, 2010). Internalists are attributed the view that the mind is confined to the 'skin and skull' of individual agents. They assent to the intuitive idea that psychological processes are achieved by the brain and central

nervous system. On this view, the architecture responsible for cognition is wholly internal to the agent, and thus can be studied while 'bracketing off' an agent's social and material environment. Arguably, this way of thinking about the mind and its breakdowns has both driven, and been reinforced by, approaches to psychiatry that are very brain-centred (Sneddon 2002; Roberts et al. 2019).

Externalists share an alternative view of the mind and how it ought to be studied. Their central criticism of internalism is that it assigns too much explanatory weight to neurological processes, neglecting the role that external resources contribute to the performance of cognitive tasks.

Consider, again, the case of memory, a capacity that is general-purpose enough to be relevant to an agent's mental health. Externalists claim that the remembering is often heavily dependent on, or 'scaffolded' by, material culture and socio-environmental resources. Tribble describes, for example, the way in which Shakespearean performance relies on contextual cues to enable actors to remember their lines, rather than committing them to 'internal' memory (Tribble 2005; see also Sutton et al. 2010). More mundanely and ubiquitously, we use a variety of props and prompts, including post-its, napkins, landmarks, keepsakes and digital devices, as well as relying on others to help us construct a coherent and action-guiding account of the past.

Sometimes our capacity to remember is deeply contingent upon the interpersonal relationships we have cultivated. Sutton and colleagues have studied memory in the context of long-term couples (Sutton et al. 2010; Barnier et al. 2014). Usually, groups do worse than individuals at memory tasks. But when the couples they studied recollected together, memory improved dramatically: perhaps some aspects of psychic health depend on positive social relations? This idea that we use the environment to scaffold our memories is sometimes displaced by a much stronger claim. According to the extended mind thesis (Clark and Chalmers 1998; Menary 2010), psychological processes are not merely dependent upon external resources but constituted by them. On this view, psychological capacities should sometimes be attributed to an agent-environment system.

Clark and Chalmers (1998) motivated the extended mind thesis using a thought experiment centring upon memory. Its protagonists, Otto and Inga, each need to remember how to get to MOMA for an exhibition. Inga, who has been to MOMA many times, is able to make her way there via introspective recall. Otto, who suffers from Alzheimer' diseases, has an impaired capacity to produce, store and retrieve memories using his 'naked brain'. To cope with this, he uses a notebook containing important information. Otto routinely consults and updates his notebook, he always carries it with him, and he endorses its contents.

The purpose of the Otto/Inga example is to challenge the widely held assumption that only processes that take place "in the head" are psychological. When Otto consults his diary, he has the occurrent belief that MOMA is located on Fifty-third street. What the authors claim, in addition to this, is that, like Inga, Otto also had the dispositional belief that MOMA is located on Fifty-third street before he consulted his notebook, and this explains why he takes this route to the museum. Otto's capacity for storage and retrieval of memories extends beyond the brain, and encompasses the

notebook as a resource, in the same way that Inga's storage and retrieval depends on neural resources.

What implications does this have for our understanding of mental health? According to an internalist or scaffolded/situated approach, external artefacts (such as notebooks) and other agents (such as life partners) can only be props that compensate for an incapacity, rather than co-constitute or even rehabilitate it (Drayson and Clark 2019). On this view, Otto suffers from a deficit Inga does not have, and is thus less healthy than she is. However, if we think, as externalists do, that Otto's notebook is a part of his cognitive architecture, we should attribute him the same capacity to remember as Inga, for the only difference between Otto and Inga, in this respect, is that Otto's psychological capacity is realised by an agent-environment system of which he is part.

Hoffman (2016) argues that the extended mind thesis thus has implications for how we judge the mental health status of an agent, including whether or not they meet diagnostic criteria for particular disorders, which—owing to such factors as social stigma—has consequences for their self-understanding. The ethical implications are further spelled out by Drayson and Clark (2019), who discuss cases in which sufferers of Alzheimer's disease perform poorly in standard tests but live alone successfully. In such cases it was found that their homes were carefully scaffolded by personalised mnemonic props—post-its, labelled pictures, strategically placed items, messaging centres. Insofar as we are interested in an accurate assessment of an agent's mental health, we must strive for ecological validity: standard capacity tests must account for the integral role of an agent's environment in their cognitive functioning. Further, the role of the environment must also be considered in therapeutic contexts: decisions to relocate subjects from their homes to residential care facilities, for example, are typically accompanied by decline in cognitive health.

Based on this discussion, we can draw a distinction between narrow, situated and wide theories of mental health. The narrow construal is strongly internalist: only psychological capacities that are produced by cognitive architecture that is internal to the agent are genuine capacities. The situated view construes psychological capacities as intimately dependent upon environmental states of affairs, and in doing so prohibits methodological solipsism. A full understanding of the capacities exercised require an understanding of agent-world dynamics.

A wide account tells a different story. With respect to memory, Otto's mental health is equivalent to Inga's, insofar as (ex hypothesi) both agents can store and retrieve memories in a functionally equivalent manner. It does not matter, for the purposes of determining whether and to what degree someone is healthy, that it is achieved by reciprocally coupling to an artefact or agent.

These accounts of mental health should not be seen as competitors to the views we have looked at in earlier sections. Rather, they are based on the idea that our existing accounts are too narrowly focussed on the individual person, and they suggest that the system which we evaluate as healthy or diseased should be seen as much wider, perhaps including families, physical structures or other aspects of the social and material world. They would represent, though, especially the wide account, a much

more radical re-orienting of clinical thought about mental health. With that in mind, let's try to conclude.

## 7.8 Conclusion

As we have seen, many theorists have understood health in terms of capacities. For negative theorists, mental health just is a state in which certain psychological capacities are not compromised by disorder. How these capacities are construed, however, depends on what theory of disease one assents to. Those taking a neurocognitive approach think of the capacities as those that are implemented by subpersonal mechanisms. The breakdown of these mechanisms is responsible for symptoms. To be healthy, on the negative view, is to be free of the breakdowns that disrupt self-monitoring and that typically cause a great deal of suffering and impairment for those who suffer from psychotic disorders. Not all accounts understand the incapacities that constitute psychopathology in these terms. Rather, they refer to "personal-level" capacities, which may not feature in the project of functional composition that cognitive neuroscientists are engaged in. So that is one difference among approaches. The other main difference we have identified is that between negative approaches that identify health with the absence of disease and positive approaches that seem to equate health with well-being. A key criticism of positive accounts is their demandingness. The WHO is a demanding positive account insofar as it defines health as a state of total mental and physical well-being.

Wren-Lewis and Alexandrova aim to strike a workable middle ground between a demanding positive account, that identifies health with well-being, and a negative account, that identifies it with the absence of disease. They argue that we should think of mental health as a suite of psychological capacities that are a precondition for well-being and living a good life, rather than its constituents. The psychological preconditions are, the authors argue, a capacity to value life, and a capacity to engage in it.

We have suggested that this "goldilocks solution" might not be so much a middle ground as a redescription of the negative account. This is the case if the psychological capacities that are undermined by disease are, in the end, identical to those that allow agents to value and engage in life. In other words, if a functioning organism (i.e. one that is non-disordered) is one that can value and engage in life, then there are no extra capacities for a positive account of health to posit that would distinguish itself from a negative account. Being able to value and engage in life is equivalent to being free of disease. If this is correct, the philosophical terrain is quite simple: there is the absence of disease, and there is well-being. Whether this is correct is a matter for discussion in what we may hope will be a much bigger literature in the near future.

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# Chapter 8
# Health Concepts at Work in Interdisciplinary Fields


**Jan Pieter Konsman**

**Abstract** Much of the debates surrounding the concept of health in philosophy of medicine has been between 'naturalism' and 'normativism'. Here, the aim is to apply the revisionist naturalists' recommendation and to look for definitions of health in the biomedical literature. Based on our own research experience with neuroendocrinology, neuroimmunology, psychoneuroendocrinology, psychoneuroimmunology and microbiota-gut-brain research, we speculated that these interdisciplinary fields mobilize notions of health including: (1) health as constancy of internal milieu or homeostasis, (2) health as absence of or due to specific interoception, (3) health as absence of stress or as the result of eustress or hormesis, and (4) health as result of (immune) defense. To assess which health concepts interdisciplinary research fields studying interacting biological systems mobilize, the PubMed database was interrogated with search strings linking (1) proposed health concepts-related terms and biological systems, (2) health and health concepts-related terms, and (3) health and interdisciplinary research fields. Health was mostly encountered in the context of "health and disease" without being further specified. The terms stress, homeostasis and immune were most frequently used in relationship to health, but health was only clearly defined, referring to homeostasis, in two articles. More articles, however, evoked the biopsychosocial model of medicine in which "overall health reflects a high level of intra- and intersystemic harmony" (Engel, Ann N Y Acad Sci 310:169–187, 1978, p. 175). In conclusion, applying the revisionist naturalists' recommendation to scrutinize the theoretical sense of 'health' throughout the biomedical literature will need to go beyond the level of definitions and may therefore not be that straightforward.

**Keywords** Bibliometrics · Empirical philosophy of medicine and science · Homeostasis · Interdisciplinary biomedical research

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## 8.1 Concepts of Health in Philosophy of Medicine

According to the WHO, health is "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". Much of the debates surrounding the concepts of health and disease in philosophy of medicine has been between two poles that can be qualified as 'objectivism' or 'naturalism' and 'constructivism' or 'normativism'. In this debate, the former stipulates that health and disease can be objectively defined based on natural functioning of a body and the latter opposes that these notions depend primarily on values that social groups hold. Christopher Boorse, as the major proponent of naturalistic accounts, stated in 1977 that: "Health as freedom from disease is then statistical normality of function", which corresponds to "the ability to perform all typical physiological functions with at least typical efficiency" (Boorse 1997, p. 542, 562). Twenty years later, he persistently argued that: "Theoretical health is the absence of disease" (Boorse 1997, p. 1). Lennart Nordenfelt, instead, proposed a normative "holistic welfare" account of health according to which a person "P is healthy, if and only if P is able, given standard circumstances, to realise all his or her vital goals, i.e. to realise all those states of affairs which are necessary and together sufficient for his or her minimal happiness" (Nordenfelt 1993, p. 172). If Boorse's naturalistic concept of health does not respect the spirit of the WHO definition of health, "Nordenfelt's definition of health is [just] less extensive than the WHO's conception" (Schramme 2007, p. 14).

It may well be that, in spite of the still-ongoing debate between the two camps, "philosophy of medicine has reached an impasse over how to define the concepts of health and disease" (Sholl 2015, pp. 395–396). Several paths forward have been indicated, ranging from calls for stronger holism considering "the individual as an integrated whole of organs and organ parts" as "an absolute condition for health in scientific medicine" (Taljedal 2004, p. 145), or that "health and disease are best understood as systemic or organismic properties" (Sholl 2015, p. 412), to a defense of a naturalist theory of health "taking account of the point of view of medical science" in addition to an individual's evaluation of his or her condition (Schramme 2007, p. 15). In an effort to put, at least, a temporary hold on the debate around the notion of disease, revisionist naturalists have proposed to look "for perspicuous and coherent accounts of different disease types" and to finally come to "an overall picture of the role disease thinking plays" (Murphy 2015). Maël Lemoine, another proponent of this stance, suggested that "[t]he philosopher's job is to scrutinize the theoretical sense of 'disease' throughout medical science and decide whether a consistent, specific, and operational concept of disease exists therein" (Lemoine 2013, p. 324). In the present chapter, the aim is to try and apply Murphy's and Lemoine's recommendations to health and to look for definitions of health in the biomedical literature.

Even though the WHO is very clear on what health is not, it is not easy to conceive how "a state of complete physical, mental, and social well-being" can be addressed by biomedical science. In addition, if one would like to follow the plea for holistic approaches in trying to understand health as 'systemic properties', one is faced with the problem that most medical and biological disciplines employ reductionist

strategies. One may therefore be more likely to encounter health concepts that go beyond the absence of dysfunction or disease in interdisciplinary research fields that propose to span different biological systems and/or disciplines.

Over the past decades, some more holistic definitions of health have been put forward in medicine. In an article on medical education in 1950, John Romano, defined health as "the capacity of the organism to maintain a balance in which it may be reasonably free of undue pain, discomfort, disability or limitation of action, including social capacity" (Romano 1950, p. 409). The internist and psychiatrist George Engel used this definition as a starting point but judged it too broad (Engel 1960, p. 48). In the 1970s, Engel expressed the hope that "a general-systems approach becomes part of the basic scientific and philosophic education of future physicians and medical scientists" (Engel 1977, p. 135) and proposed the biopsychosocial model of medicine. In addition, Engel specified that his model is based on Von Bertalanffy's general systems theory and stipulated that "overall health reflects a high level of intra- and intersystemic harmony" and that restoration of health "is not the former state of health but represents a different intersystemic harmony than existed before the illness" (Engel 1978, pp. 175–176).

Recently, several authors have presented psychoneuroendocrinology, psychoneuroimmunology, and microbiota-gut-brain research as fields relevant to, or as validations of, the biopsychosocial model (Gaab 2019; Havelka et al. 2009; Maier and Al'Absi 2017; Morgan et al. 2014; Trilling 2000). Here, the interdisciplinary research fields of neuroendocrinology, neuroimmunology, psychoneuroendocrinology, psychoneuroimmunology and microbiota-gut-brain research, which address in varying ways interactions between biological systems, including the nervous system, will be analyzed and compared for the concepts of health they mobilize. Based on our own research experience in and with these different fields of research, we speculate that they mobilize notions of health including: (1) health as constancy of internal milieu or homeostasis, (2) health as absence of or due to specific interoception, (3) health as absence of stress or as the result of eustress or hormesis, and (4) health as result of (immune) defense. Considering the assumptions and histories of these fields, we hypothesize in particular that neuroendocrinology would preferentially mobilize notion (1) and neuroimmunology and psychoneuroimmunology notion (4), while psychoneuroimmunology and psychoneuroimmunology may apply notion (3) more.

## 8.2 Health Concepts that May Be at Work in Interdisciplinary Basic and Medical Research

(1) Constancy internal milieu-homeostasis → health as a disposition to maintain vital parameters fixed or within normal range?

Claude Bernard proposed the stability of the internal milieu as the condition for life. With regard to health and disease, he pointed out in his *Introduction to Experimental Medicine* that "[b]y normal activity of its organic units, life exhibits a state of health; by abnormal manifestation of the same units, diseases are characterized" (Bernard 1949, p. 65) and that "it is in the study of inner organic conditions that direct and true explanations are to be found for the phenomena of the life, health, sickness and death of the organism" (Bernard 1949, p. 98). Walter Cannon was inspired by Bernard's work when he introduced the notion of homeostasis, but did not necessarily equate homeostasis to health. For example, he wrote regarding plasma proteins that: "The very existence of the fluid matrix of the body is dependent, therefore, on constancy of the proteins in the plasma-and usually they are remarkably constant in various conditions of health and disease" (Cannon 1929, p. 412).

Even though Christopher Boorse considered that "the notion of homeostasis has wide … influence as a clinical concept of health" (Boorse 1977, p. 549) and that "[c]ountless biological variables like blood temperature, acidity, speed of flow, … must be kept within narrow limits in a state of health" (Boorse 1977, p. 549), he did not consider homeostasis "as a general model of biological function". Indeed, for Boorse "[m]any life functions", such as "[p]erception, locomotion, growth and reproduction upset an equilibrium" and can therefore not be qualified as "homeostatic unless one stretches the concept" (Boorse 1977, p. 550).

More recently, Masseh Annath presented a philosophical account of health using homeostasis as a starting point. Indeed, his account includes "elements of homeostasis [that] are relevant to the various organs and organ systems of the body" as well as a notion of "organism homeostasis" (Ananth 2008, pp. 191–193).

(2) "Life lived in the silence of the organs" → health as result of specific interoception?

In the 1930s, the French surgeon Réné Leriche stipulated that "[h]ealth is life lived in the silence of the organs" (Leriche 1936, p. 16). Recent research, in particular by Bud Craig, has identified neural afferents that have been proposed to convey the physiological condition of the body, a phenomenon called interoception (Craig 2002). It is, however, important to point out that, in spite of the initial formulation of Leriche and the fact that an important part of interoception-related research is on pain and/or inflammation, some authors have also emphasized the importance of internal health signals and feelings of wellness (Fantuzzi 2014; Mayer 2011). For example, Emeran Mayer proposed that a feeling of wellness may occur in response to the gut sensation or state of satiation (Mayer 2011). In addition, Giamila Fantuzzi suggested

that "we can approach biomedical research from the point of view of studying what improves health" and "define messages of health as molecules produced and released by healthy, unstressed cells and whose presence contributes to support a healthy organism" (Fantuzzi 2014, p. 1).

(3) Stress response → health as lack of distress, or result of eustress or hormesis?

In the mid-twentieth century, Hans Selye raised the possibility that "many individuals who carry the pathogens (whatever these may be) of rheumatoid arthritis, allergies, lupus erythematosus, and so forth can remain in perfect health throughout life" because "they have rendered these potential pathogens quite innocuous" through "the general adaptation syndrome", which was later to become the stress response (Selye 1950, p. 1388). In addition, he wondered what aspects of the stress response "are useful for the maintenance of health and which are merely signs of damage" (Selye 1955, p. 626). Later in his career Selye proposed to distinguish "between 'eustress' and 'distress'—the former being agreeable or healthy, and the latter, disagreeable or pathogenic" depending on the "intensity [of a certain stimulus] and the particular receptiveness of the affected person" (Selye 1976, p. 54).

Edward Calabrese and others have recently positioned hormesis as adaptive and protective responses to stressors and "defined [it] as a dose–response phenomenon characterized by a low dose stimulatory response and a high dose inhibition" (Calabrese 2008, p. 9). In addition to its purely descriptive definition, "hormesis may [also] be defined on the basis of evolutionarily conserved biological responses to stress" (Hoffmann 2009, p. 5) with the idea "that biological systems must routinely experience mild stress for optimization of health" (Hoffmann 2009, p. 27).

(4) Guardians of health → health as a result of (immune) defense?

Elie Metchnikoff reported at the end of the nineteenth century that he has "succeeded … in isolating infected *Daphniae* [water flea] and keeping them till they were fully restored to health, thanks to the destruction of the spores by their phagocytes" (Metchnikoff 1893, p. 85). Later, he mentioned "recent discoveries" showing that "blood-serum of animals which have been subjected to the action either of microbes or of the soluble products of microbes … is capable … of protecting those in good health from diphtheria" (Metchnikoff 1908, p. 211). Several decades later, Frank Macfarlane Burnet still considered that: "the phagocytic cells … are the final defenders of the body" (Burnet 1940, p. 36). Even in the early 1960s when humoral-specific immunity in the form of antibodies had eclipsed cellular immunity somewhat, Burnet made it clear again that "there are … a variety of phenomena for which antibody plays no part" (Burnet 1962, p. 42).

In the past decades, some scientists have proposed to move "from an antigen-centered, clonal perspective of immune responses to an organism-centered, network perspective of autonomous activity in a self-referential immune system (Coutinho et al. 1984, p. 151). Others have suggested that "the immune system [i]s but one component of a larger, integrated system of defenses serving the adaptive interests of the individual" (Ader 2000). Most recently, the view that "the immune response

[i]s an integral and dynamic part of how animals optimize their fitness in challenging, competitive environments" even has become the cornerstone of the emerging field of research of eco-immunology (Viney and Riley 2014, p. 1).

## 8.3 Methodology

To assess which health concepts interdisciplinary research fields studying interacting biological systems mobilize, the biomedical literature database PubMed (https://www.ncbi.nlm.nih.gov/pubmed) was interrogated with search strings linking (1) proposed health concepts-related terms (homeostasis, interoception, stress, defense) and biological systems, (2) health and health concepts-related terms, and (3) health and interdisciplinary research fields. For searches undertaken to evaluate the penetration of health concepts-related terms in relation to biological systems, the relative (compared to the total amount of PubMed articles) numbers of publications per year were analyzed. In contrast, analyses pertaining to health and health concepts-related terms and to health and interdisciplinary research fields were more aimed at contents. Therefore, searches yielding more than 500 hits were repeated by adding more specific terms or "review" to the search string until the number of hits fell below 500. In this case, titles and abstracts were scrutinized and publications that were, at least, in part, conceptual were selected. In these articles, it was determined to what health and health-related terms refer.

## 8.4 Results

### *8.4.1 PubMed Search Strings Associating Proposed Health Concepts-Related Terms and Biological Systems*

Among the terms that may be employed in relation to health in articles found on PubMed, 'stress', 'homeostasis' and 'defense' were the most frequently encountered with 'stress' making up for 4% of the recently indexed articles and 'homeostasis' and 'defense' for respectively 1.15–1.20% and 0.6%. The percentage of PubMed articles obtained with the search string "((nervous and endocrine) or neuroendocrine) and homeostasis" was found to increase fourfold between 1953 and 2000–2018, while that for "((nervous and immune) or neuroimmune) and homeostasis" rose tenfold from 1980 to 2018 (Fig. 8.1a). Similarly, a tenfold increase in the percentage of PubMed articles in which 'stress' was associated with the adjectives nervous and endocrine or the compound adjective neuroendocrine was observed between 1961 and 2000–2018 (Fig. 8.1b). Regarding 'defense', steady increases in the percentage of PubMed articles between the 1970s and 2018 were found for the search strings "((nervous and endocrine) or neuroendocrine) and defense" and "((nervous and

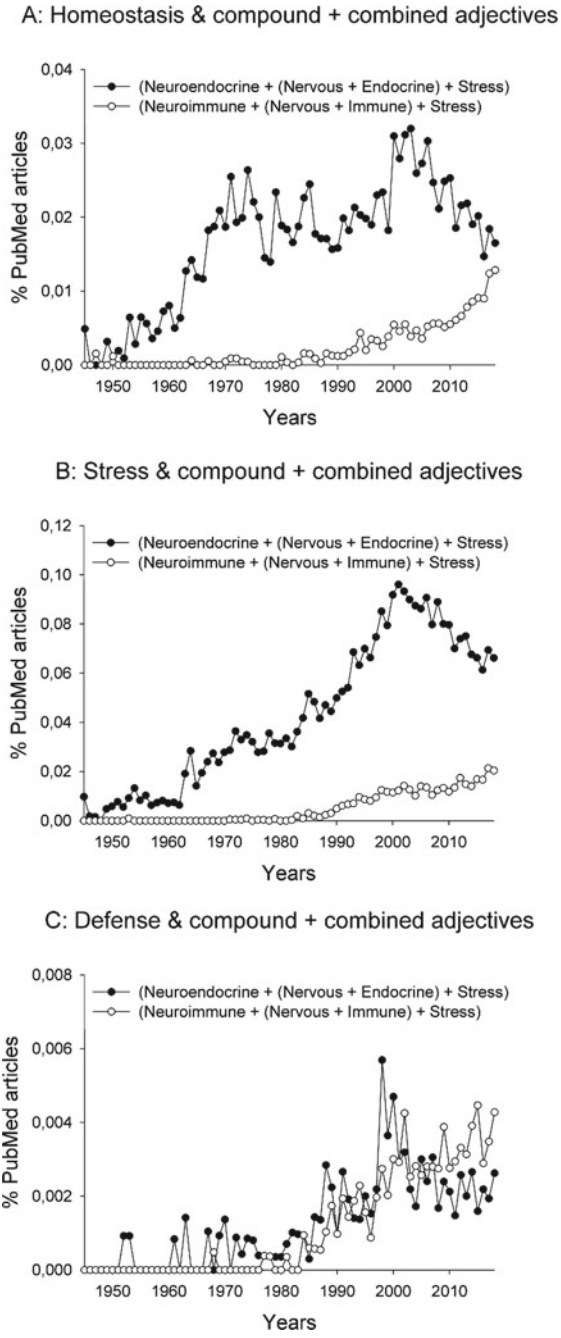


**Fig. 8.1** Konsman

immune) or neuroimmune) and defense", fluctuating around 0.02 and 0.0035% in the past years, respectively (Fig. 8.1c). Finally, search strings combining 'intero-cept*' with the adjectives nervous, immune and immune or compound adjectives like neuroendocrine or neuroimmune yielded too few hits to do any meaningful quantitative analyses on.

### *8.4.2 PubMed Search Strings Linking Health and Proposed Health Concepts-Related Terms*

The majority of the articles obtained with the search strings combining health and health concepts-related terms in their titles referred to "health and disease".

#### 8.4.2.1 Homeostasis and Health

Several of 137 PubMed articles with homeostasis and health in their titles did not concern the organism, system, or tissue level and were therefore not considered. Two conceptual articles were found (Table 8.1). G. N. Kryzhanovsky's judged that "satisfactory definitions of … health and disease, have not been found for a long time" and proposed that "[f]or comprehensive consideration of the problem and definition of the notions 'health' and 'disease', it is necessary to dwell on … homeostasis" (Kryzhanovsky 2004, p. 135). Concerning homeostasis, he emphasized that "it is reasonable to consider dynamic, functional homeostasis rather than a strictly rigid one" (Kryzhanovsky 2004, p. 136). This then brought Kryzhanovsky to define health as "the state of an organism with undisturbed functional dynamic homeostasis providing optimum performance of organism functions to the extent necessary for productive relations of the organism with the environment" (Kryzhanovsky 2004, p. 137).

Antoine Dussault and Anne-Marie Gagné-Julien suggested "that an organism's health is linked to its ability to homeostatically maintain the functions of its organs and its whole body" (Dussault and Gagne-Julien 2015, p. 69). However, they considered that "homeostatic maintenance, although necessary, is not sufficient for health" and "that an account of health should include a reference to a design", which is grounded "in ontogeny rather than phylogeny" (Dussault and Gagne-Julien 2015, p. 72). Thus, Dussault and Gagné-Julien proposed their "homeostatic maintenance of design (HHMD)" definition of health according to which "[a]n organism is healthy if and only if it is intrinsically disposed to homeostatically maintain or restore its intrinsic disposition to perform its designed functions in relevant situations" (Dussault and Gagne-Julien 2015, p. 75).

**Table 8.1** Pubmed articles addressing conceptual issues regarding health and proposed health-related terms or health and interdisciplinary research fields (searches done during the first half of December 2019)

| Search string | Hits | References addressing conceptual issues |
|---|---|---|
| Homeosta* [TI] and health [TI] | 137 | Dussault and Gagne-Julien (2015); Kryzhanovsky (2004) |
| Interocept* [TI] and health [TI] | 9 | Farb et al. (2015); Khalsa et al. (2018); Quadt et al. (2018); Tsakiris and Critchley (2016) |
| Stress [TI] and health [TI] and review | 427 | Brosschot et al. (2006); Cohen (2000); Edwards and Cooper (1988); Eriksen et al. (1999); Glaser and Kiecolt-Glaser (2005); Kasl (1984); Korte et al. (2005); McEwen (2008); Roger (1998); Schneiderman et al. (2005); Taylor et al. (2004); Ursin and Eriksen (2007); Vitetta et al. (2005 |
| Hormesis [TI] and health [TI] | 25 | Calabrese et al. (2013); Li et al. (2019); Yashin (2009) |
| Defense [TI] and health [TI] | 307 | |
| Immun* [TI] and health [TI] and review | 371 | Netea et al. (2016); Schwarz (2019); Stapelberg et al. (2019, 2018) |
| Health [TI] and neuroendocrinology | 40 | Beerse et al. (2019); DeVries et al. (2007); McEwen (2003, 2008); McEwen et al. (1997); McEwen and Gianaros (2010) |
| Health [TI] and neuroimmunology | 29 | Anisman et al. (1996); Schwartz et al. (2013) |
| Health [TI] and psychoneuroendocrinology | 68 | Juster et al. (2010); Kelly et al. (1997); Money (1983); Vitetta et al. (2005) |
| Health [TI] and psychoneuroimmunology | 105 | Adler and Matthews (1994); Briones (2007); Cohen and Herbert (1996); Glaser and Kiecolt-Glaser (2005); Havelka et al. (2009); Kiecolt-Glaser and Glaser (1995); Lambert (2005); Langley et al. (2006); Lutgendorf and Costanzo (2003); McCain et al. (2005); Miller et al. (2009); Zachariae (2009) |
| Health [TI] and "microbiome gut brain" | 8 | Lucas (2018) |

#### 8.4.2.2 Interoception and Health

Several of the 9 PubMed articles with interocept* and health in their titles addressed conceptual issues (Table 8.1). Depending on the authors, interoception was proposed to include "the process of receiving, accessing and appraising internal bodily signals" (Farb et al. 2015, p. 1), "reflexes, urges, feelings, drives, adaptive responses, and cognitive and emotional experiences" (Khalsa et al. 2018, p. 501) and "(1) the afferent (body-to-brain) [neural and humoral] signaling …; (2) the neural encoding, representation, and integration of this information …; (3) the influence of such information on

other perceptions, cognitions, and behaviors; (4) and the psychological expression of these representations" (Quadt et al. 2018, p. 112).

Well-being was often encountered with statements like "interoception is critical for our sense of embodiment, motivation, and wellbeing" (Farb et al. 2015, p. 1 or "[a] comprehensive understanding of cognition, emotion, and overall well-being must incorporate an understanding of interoception" (Quadt et al. 2018, p. 112). However, well-being was not described beyond "physical and mental well-being" (Quadt et al. 2018, p. 112). Likewise, health was also not further specified other than that "[h]ealth and disease have distinct … profiles that can be characterized by the presence or absence of reported symptoms and changes in behavior" (Quadt et al. 2018, p. 119). Although the majority of PubMed articles with interocept* and health in their titles referred to mental health, a closer inspection revealed that these articles dealt with mental health problems and disorders (Farb et al. 2015; Khalsa et al. 2018; Tsakiris and Preester 2018).

#### 8.4.2.3 Stress or Hormesis and Health

Some of the 427 PubMed review articles with stress and health in their titles referred to health professionals, economics or heat stress and were not considered. Several conceptual articles on stress and health were found (Table 8.1) of which many spent some ink on the problem of the definition of stress (Edwards and Cooper 1988; Kasl 1984; Korte et al. 2005; McEwen 2008). This naturally led to calls "to define stress cleanly" (Kasl 1984, p. 320), to "separately assess individuals' perceptions of events … appraisal … health-related outcomes, and coping efforts" (Edwards and Cooper 1988, p. 15) or to adopt "a new stress concept" such as allostasis or allostatic load (Korte et al. 2005; McEwen 2008).

With regard to health, the vast majority of these articles contained formulations like "stress-related changes have broad implications for health" (Glaser and Kiecolt-Glaser 2005, p. 248) or "[s]tress … can take its toll on physical and mental health" (Korte et al. 2005, p. 4), but none provided a definition of health. Some authors also discussed the notion "that some stress may be seen as 'good', with corresponding health status benefits" before criticizing the idea "that some levels (or types) of stress are associated with health benefits" and recommending that "such issues need to be argued out on an empirical basis and with more specific and precise concepts" (Kasl 1984, p. 321, pp. 322–323). Others have argued that "certain aspects of the stress and coping process may actually improve health" (Edwards and Cooper 1988, p. 18).

Some of the 25 PubMed review articles with hormesis and health in their titles were more conceptual in nature (Table 8.1). The basic idea behind the so-called "hormesis hypothesis" would be the "existence of hidden defense capacities which become activated in response to 'mild' stresses", which, in turn, "enhance [the] organisms' robustness and resilience properties" (Yashin 2009, p. 41). Accordingly, some authors stated that some naturally occurring "stressors … are required for healthy growth or homeostasis" and claimed that this "exemplifies how 'illness is the doorway to health'" (Li et al. 2019, p. 944). But like for stress, none of these

more conceptual reviews containing health and hormesis in their titles provided a definition or description of health.

#### 8.4.2.4 Immune and Health

Many of the 307 articles with defense and health in their titles referred to national or department of defense, psychological defense, defense of some point of view or policy or public health. None of them seemed to address conceptual issues regarding defense and health. Many of the 371 PubMed review articles with immun* and health in their titles were on immunization, immunizing or immuno(histo)chem*, health care or health professionals and were excluded. Some articles linked immun* and mental health and these also made up the majority of the more conceptual articles (Table 8.1).

Among the conceptual articles, only one dealt with the immune system as such and concerned the description of "the properties of trained immunity", and proposed to discuss "its important role in health and disease" (Netea et al. 2016, p. aaf1098-1, p. aaf1098-7). The other three publications addressed the role of the immune system as part of a network of interacting biological systems in mental health. Thus, Jaclyn Schwarz "hypothesize[d] that interactions between the endocrine, immune and nervous system of mother and infant have an important impact on the risk of … psychiatric disorders" and expressed her motivation "to … prevent the onset of mental health disorders in the mother" (Schwarz 2019, pp. 1–2, 4). The two articles by Chris Stapelberg and colleagues dealt with changes in "the psycho-immunoneuroendocrine [PNIE] network" relevant to the transition "from health to major depression" (Stapelberg et al. 2019, 2018). Thus, these papers proposed hypotheses "constructed around a model of disease progression wherein the stable healthy state of the PINE network undergoes progressive but reversible pathophysiological changes to an unstable pre-disease state", but also explored how the "PINE network may then undergo critical transition to a stable, possibly irreversible disease state of [major depressive disorder] MDD" (Stapelberg et al. 2019, p. 108). However, none of these more conceptual articles provided a definition or a description of (mental) health.

### *8.4.3 PubMed Search Strings Associating Health and Interdisciplinary Research Fields*

#### 8.4.3.1 Neuroendocrinology and Health

Several of the 40 publications obtained with the search string "health [TI] AND neuroendocrinology" were already encountered under stress and health. A relatively high proportion of conceptual articles was found, with several being written by Bruce McEwen's group (Table 8.1).

The first of the selected articles by McEwen proposed to "summarize our current knowledge of glucocorticoid physiology in relation to immune function in health and disease" (McEwen et al. 1997, p. 80). Subsequent publications by this group put forward the concepts of allostasis and allostatic load. These concepts were introduced with regard to "physical and mental health" considering the "profound effects" of the "stability of a child's early life" (McEwen 2003, p. 149). Allostatic load can be "defined as the 'cost' or 'wear and tear' on the body produced by repeated activation of stress-responsive biological mediators such as glucocorticoids and catecholamines" (McEwen 2003, p. 149). "These stress processes impacting health can be heuristically labeled as 'good', 'tolerable', and 'toxic'— depending on the degree to which an individual has control over a given stressor and has support systems and resources in place for handling a given stressor over the lifespan" (McEwen and Gianaros 2010, p. 190).

Other authors also tried to differentiate between the detrimental and beneficial effects of stressful situations on health. For example, Courtney DeVries writes that "[i]n contrast to social stress and social isolation, positive social interactions are beneficial to health" (DeVries et al. 2007, p. 588). Still other authors pointed out that "the association between chronic daily stress and anxiety and poor physical health" may be mediated through "neuroimmune and neuro-endocrine responses" and that "[m]indfulness-based interventions exert positive impacts on an individual's mental health in addition to physical health" (Beerse et al. 2019, p. 2). But despite the fact physical and mental health are regularly mentioned, these terms are never defined.

#### 8.4.3.2 Neuroimmunology and Health

Two articles of the 29 obtained with health as a title word and neuroimmunology dealt with more conceptual issues (Table 8.1).

In 1996, Hymie Anisman and colleagues claimed that "[a] novel scientific discipline that examines the complex interdependence of the neural, endocrine and immune systems in health and disease has emerged in recent years" (Anisman et al. 1996, p. 867). Thus, it was hypothesized that "[t]he immune system is constantly interacting with the neuroendocrine system " and that "[t]his interaction assures that immune and inflammatory responses are in homeostasis and in harmony with other bodily functions, in order to maintain health" (Anisman et al. 1996, pp. 868–869).

A more recent article by Michal Schwartz and colleagues focused on "[h]ow … immune cells support and shape the brain in health" (Schwartz et al. 2013, p. 17, 587). Besides, the role of "[m]icroglia and infiltrating monocyte-derived macrophages … in maintenance of brain plasticity in health" (Schwartz et al. 2013, p. 17, 587), these authors indicated that "CNS-specific T cells are involved in the maintenance of the functional plasticity of the healthy brain" (Schwartz et al. 2013, pp. 17, 588–17, 589). Accordingly, neuroimmunology "is a field in which the two systems not only interact but also have a mutual dependency" (Schwartz et al. 2013, p. 17, 593). However, and in spite of describing in some detail what neuroimmunology is in the context of health, health is never defined in these publications.

#### 8.4.3.3 Psychoneuroendocrinology and Health

Of the 68 articles obtained with health as a title word and psychoneuroendocrinology, several were more conceptual (Table 8.1). Some of these publications were already encountered under stress and health.

In 1983, John Money argued that "[a] psychoendocrine rapprochement began to appear in the 1950s" when "Geoffrey W. Harris (1913–71) moved toward psychology and behavior" and the author "moved psychology and behavior toward endocrinology" (Money 1983, p. 394). Several authors discussed the links between stress, health and psychoneuroendocrinology as well as psychoneuroimmunology (Kelly et al. 1997; Vitetta et al. 2005, p. 494). For example, Vitetta and colleagues concluded, based on "evidence … accumulate[d] within the field of psychoneuroendocrinology and psychoneuroimmunology", that "the brain has truly an overarching role in health and disease" (Vitetta et al. 2005, p. 502).

The paper from Bruce McEwen's group reviewed "theoretical and empirical work using the allostatic load model vis-à-vis the effects of chronic stress on physical and mental health" (Juster et al. 2010, p. 2). Thus, Robert-Paul Juster and colleagues stated that "[h]ealth and successful aging can … be conceptualized as one's ability to adapt and effectively respond to the dynamic challenges of being alive" (Juster et al. 2010, p. 2). In contrast to the "[t]raditional homeostatic models [that] define health as a state in which all physiological parameters operate within normal values", "allostasis defines health as a state of responsiveness and optimal predictive fluctuation to adapt to the demands of the environment" (Juster et al. 2010, pp. 2–3). Accordingly, "[a]llostasis differs from homeostasis vis-à-vis its emphasis on dynamic rather than static biological set-points, considerations of the brain's role in feedback regulation, and view of health as a whole-body adaptation to contexts" (Juster et al. 2010, p. 3).

So, among the more conceptual/theoretic articles found here, several described what psychoneuroendocrinology is about and one article even provided a definition of health that does not refer to homeostasis.

#### 8.4.3.4 Psychoneuroimmunology and Health

Searching PubMed for health as a title word and psychoneuroimmunology yielded 105 articles, of which numerous were more conceptual (Table 8.1). Several articles were already encountered under stress and health.

Many of these conceptual articles addressed the health psychology question of "why do some people get sick and others stay well". Thus, in 1994, Nancy Adler and Karen Matthews noted that "the psychology community has increasingly embraced questions of essential importance to physical health" (Adler and Matthews 1994, p. 230) and hypothesized regarding the health outcomes of stress, that "appraisal of stress appears to play a more important role … than simple exposure to life events" (Adler and Matthews 1994, p. 251). A year later, Janice Kiecolt-Glaser and Ronald Glaser suggested "that immune modulation by psychosocial stressors and/or

interventions may importantly influence health status," in particular in "those whose immune system function is already compromised to some degree" (Kiecolt-Glaser and Glaser 1995, p. 269). Sheldon Cohen and Tracy Herbert argued that "[m]uch of psychoneuroimmunology's popularity … derives from its promise to explore and explain the common belief that our personalities and emotions influence our health" (Cohen and Herbert 1996, p. 114), but also warned that "immune … outcomes … do not necessarily indicate changes in resistance to disease" (Cohen and Herbert 1996, p. 117).

In the early 2000s, Susan Lutgendorf and Erin Constanzo considered that "[p]sychoneuroimmunology provides an understanding of some of the fundamental mechanisms involved in the biopsychosocial model" (Lutgendorf and Costanzo 2003, p. 225), but also pointed out that "[i]t cannot be assumed that because there is an effect on the immune response there is also an effect on disease processes" (Lutgendorf and Costanzo 2003, p. 231). Mladen Havelka and colleagues agreed that "[t]he biopsychosocial model" has given rise to "the fields of health psychology and psychoneuroimmunology" (Havelka et al. 2009, p. 303), but added that "[Engel] also claims that the borderline between disease and health has never been clear" (Havelka et al. 2009, p. 305). Robert Zachariae put forward a slightly different story in suggesting that "[b]y challenging the biomedical concept of the immune system as an 'autonomous' defense system, psychoneuroimmunology represents a shift from a predominantly biomedical paradigm of health and disease towards an interdisciplinary bio-psychosocial approach" (Zachariae 2009, p. 645). He did, however, agree that "the critical question of whether behavioral manipulation, e.g. stressors or intervention, can affect immunity so as to influence health and survival, still remained to be answered" (Zachariae 2009, p. 650).

In spite of the regular reference to health, only one of the more conceptual articles mentioning psychoneuroimmunology proposes a definition. Thus, Nancy McCain and colleagues "broadly define *health* to include the entire spectrum of wellness-illness phenomena" and considered that "the [PNI] model incorporates a variety of health outcomes, termed 'adaptational outcomes' includ[ing] psychosocial functioning, quality of life, and physical health" (McCain et al. 2005, p. 323).

#### 8.4.3.5 Microbiota Gut Brain Research and Health

Of the 8 articles obtained with the search string "health [TI] AND "microbiome gut brain"", one more conceptual article dealing with mental health was found (Table 8.1). In this article, Grace Lucas argued that "if … the gut is 'an organ of mind'" this raised the questions of "[w]hat and where exactly is our 'mental' health?" (Lucas 2018, p. 2). She referred to a definition of "[m]ental health … framed within a biopsychosocial paradigm", but judged that "despite its emphasis on an integration of perspectives, [this paradigm] speaks to disciplinary boundaries of biology, psychology, and social sciences" with "each taking a vertical disciplinary cut through the mental health conundrum" (Lucas 2018, pp. 4–5). Lucas also related

how "[p]roponents of alternative models of health may reach to microbiome-gut-brain research to validate why it is necessary to think holistically about health", but warned that "data connecting the gut to mood, behaviour and mental health does not provide a neat answer" (Lucas 2018, p. 6). Nevertheless, she acknowledged as an upshot of this research that "it does call attention to the possibilities for a model of 'embodied mental health' …, one that recognises that mental health is not a separate entity from physical health and explores the entanglements within a horizontal bio-psychosocial framework" (Lucas 2018, p. 6) without providing an explicit definition of health.

## 8.5 Discussion

The overall conclusion of our investigations on how "health" is employed in articles available on the biomedical literature database PubMed is that in the vast majority of cases the term is encountered in the context of "health and disease" without being further specified. In these cases, the disease part is often developed whereas health is not. Among the terms that we proposed may be employed in relation to health in articles found on PubMed, stress, homeostasis and defense were the most frequently encountered with stress recently making up for 4% of the indexed articles. When using these terms and health as title words, by far the most hits were obtained for "health and stress" and "health and immun*", even when limited to reviews. However, many reviews containing health and immun* in their titles concerned immunization, immunizing or immuno(histo)chem*, health care or health professionals. Three of the four more conceptual articles found with "health and immun*" were on mental health (Schwarz 2019; Stapelberg et al. 2019, 2018), but none provided a definition or a description of (mental) health. Comparatively, more reviews with health and stress in their titles dealt with conceptual issues. These issues often concerned the problem of the definition of stress or the nature of the effects of stress on health, but none provide a definition or description of health.

Using homeostasis and health as title words resulted in more than a hundred publications on PubMed, of which two were judged more conceptual. Interestingly, these did not only contain further specifications of the concept of homeostasis, but also proposed definitions of health that both referred to an organism's function. Thus, Kryzhanovsky defined health as "the state of an organism with undisturbed functional dynamic homeostasis providing optimum performance of organism functions to the extent necessary for productive relations of the organism with the environment" (Kryzhanovsky 2004, p. 137). Dussault and Gagné-Julien proposed their "homeostatic maintenance of design (HHMD)" definition of health according to which "[a]n organism is healthy if and only if it is intrinsically disposed to homeostatically maintain or restore its intrinsic disposition to perform its designed functions in relevant situations" (Dussault and Gagne-Julien 2015, p. 75). The differences in style of formulation between these two definitions may be related to the fact that Kryzhanovsky is a scientist and Dussault and Gagné-Julien are philosophers. Even

though interocept* and health as title words only rendered 9 articles, many of these were conceptual in nature. Moreover, it is noteworthy in light of the WHO definition of health, which refers to well-being, that interoception in these articles was often linked to well-being. For example, statements like "interoception is critical for our sense of embodiment, motivation, and wellbeing" (Farb et al. 2015, p. 1) and "[a] comprehensive understanding of cognition, emotion, and overall well-being must incorporate an understanding of interoception" (Quadt et al. 2018, p. 112) were found. However, in none of these instances were well-being and health described beyond physical and mental well-being or health.

We speculated that one may be more likely to encounter concepts that go beyond the absence of or disease in studies that propose to span different biological shealthystems, including the nervous system, or different biomedical disciplines. We therefore also investigated the occurrence of the terms mentioned above in the context of possible interactions between biological systems. Interestingly, the percentages of PubMed articles obtained with the search strings associating homeostasis, stress or defense on the one hand, and (nervous and endocrine) or neuroendocrine) or (nervous and immune) or neuroimmune) on the other, all increased 4–10 fold between 1946 and 2018. To address the question of how interdisciplinary research fields studying interacting biological systems use the term health, we did searches employing "health" as a title word in association with neuroendocrinology, neuroimmunology, psychoneuroendocrinology, psychoneuroimmunology or microbiota-gut-brain research. Although very few of the conceptual articles thus found defined health, an important proportion referred to the biopsychosocial model, stress and interacting biological systems. In particular, Robert-Paul Juster and colleagues proposed that in contrast to "[t]raditional homeostatic models defin[ing] health as a state in which all physiological parameters operate within normal values", "allostasis defines health as a state of responsiveness and optimal predictive fluctuation to adapt to the demands of the environment" (Juster et al. 2010, pp. 2–3).

We postulated that neuroendocrinology would preferentially mobilize notions of health involving homeostasis, neuroimmunology and psychoneuroimmunology would rely on notions of health referring to defense, while psychoneuroendocrinology and psychoneuroimmunology would apply stress-related notions. Based on our analysis of the relevant biomedical literature, it appeared that homeostatic health accounts were found in all of these domains if only as a starting point to criticize. Referring to stress in the context of health was also not limited to psychoneuroendocrinology and psychoneuroimmunology, but also found in neuroendocrinology. Alternatively, this raises the question of how tight the borders are between neuroendocrinology and neuroimmunology, on the one hand, and psychoneuroendocrinology and psychoneuroimmunology, on the other.

Taken together, our findings indicate that, even though health was rarely explicitly defined in the publications identified with our search strings, the few that did so all use homeostasis as a starting point. Many more articles referred to the biopsychosocial model of medicine in the context of which George Engel stated that "overall health reflects a high level of intra- and intersystemic harmony" (Engel 1978, p. 175). Still more publications seemed to establish links between health and stress. However,

while the vagueness of the concept may have facilitated more integrative models, it has the potential to render the links between stress and health more complicated between some forms of stress having negative health consequences and other forms of stress promoting health.

So, if one would like to apply the recommendation to base a concept of disease on "accounts of different disease types" (Murphy 2015); https://plato.stanford.edu/entries/health-disease/) or "to scrutinize the theoretical sense of 'disease' throughout medical science and decide whether a consistent, specific, and operational concept of disease exists" (Lemoine 2013, p. 324) to the notion of health, this is likely not going to be straightforward. First, and possibly in contrast to disease, which covers different types, and for which it may therefore be conceivable to come up with a common theoretical sense, the notion of health is not supposed to exist in different forms, except for the broad division into mental and physical health. This being said, notions of health referring to parts of the organism, such as "brain health" or "healthy microbiota", are increasingly being encountered in the biomedical literature. But in these cases it still concerns one health state and many more possible disease states for the same part. Second, the different disease types have at least rather precise diagnostic criteria to start with, whereas notions of health seem to lack such criteria. Beyond diagnostic criteria, there is an increased interest in biomarkers. Even though most of the literature concerns biomarkers of disease, the idea of biomarkers of health is getting some traction. Related to the notions of health discussed, Giamila Fantuzzi seemed to allude to biomarkers of health when she "define[d] messages of health as molecules produced and released by healthy, unstressed cells and whose presence contributes to support a healthy organism" (Fantuzzi 2014, p. 1). However, it is not straightforward to imagine a marker of something like health that is not clearly defined to start with. In addition, and like for biomarkers of disease, there will also be the question of specificity of a biomarker of health. Finally, based on our investigation of part of the biomedical literature, it appears that health is most often considered as the opposite of disease and that even when some notions of health are hypothesized to be linked to defense, homeostasis or stress, few clear descriptions are encountered. While the lack of conceptual clarity may be problematic for philosophy of biology and medicine, that does not seem to be the case for science, for which it may even allow for establishing new links and working hypotheses.

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# Chapter 9
# Health, Ageing, Authenticity and Art


**Desmond O'Neill**

**Abstract** Our conceptions of health and well-being in later have been unduly coloured by ageist and failure models of decay along with negative socio-cultural framing of the ageing experience, agnostic of not only the opportunities for personal growth and mastery but also of the priorities and understanding of older people and well-being in later life. Understanding health and well-being in later life requires a reconceptualization of later life which is deeper and more balanced than that of common perceptions in society and much of generalist healthcare, as well as an interrogation of what older people themselves perceive as the key elements of health and well-being in later life, and in particular resilience, flourishing and environmental mastery. Cultural gerontology, seeking to gain a more insightful and meaningful perspective of ageing through scholarship in the arts and humanities, provides powerful tools for breaking free of traditional methodologies and providing the possibility for a more authentic and meaningful responsiveness to supporting health and well-being in later life.

**Keywords** Ageing · Health · Arts · Humanities · Flourishing · Authenticity

## 9.1 Starting on the Back Foot

In many ways, the very focus of research and debate about later life in terms of successful, healthy, positive, or happy ageing raises challenging questions as to the status of ageing in society. We do not see a similar degree of impetus for defining successful, healthy, positive, or happy childhood, adolescence or mid-adult life, as generally these appear to be well enough understood and accepted to not need such a depth of inquiry. Indeed, the witty aphorism of René Leriche that health was "the silence of the organs" reflected the societal acceptance that health was understood for younger cohorts, even if definitions of health for them have progressed considerably in sophistication in the intervening years.

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This means that the challenge of defining how life, and in particular health, might be optimal in later life starts defensively on the back foot and emphasises that the sociocultural constructs of ageing and well-being remain enmeshed in negativity, reflecting both the persistence of the failure model of ageing in the public domain, as well as structural lag in professional, media and governmental circles. By structural lag is meant the failure of society and its agencies to catch up with the ever-increasing knowledgebase on ageing into later life (Alkema and Alley 2006), and in particular to recognize the benefits accrued both personally and to society from our longevity dividend (O'Neill 2011).

It always seems almost demeaning to not only have to defend the equality, human rights, personhood and citizenship of older people, but also to need to lay out the benefits of ageing into an extended later life. This is particularly the case for me personally as a geriatrician and gerontologist, now past the age of sixty and enjoying the benefits and insights of being older, and as well as one who has benefited immensely from the company and relationships with my older parents, grandparents, extended family and indeed the very many older people I have had the privilege to serve in over three decades of working as a geriatrician.

However, necessary it remains. The COVID-19 crisis of 2020 has revealed a breadth and depth of negative sentiment and prejudice against older people that is quite astounding at a political level in terms of an insouciance that an excess of older people might die in political discourse in the United States and United Kingdom. This was reflected in healthcare, from professional support for age-based restrictions on access to care (Vergano et al. 2020) to the *British Medical Journal* hosting a poll as to whether it was wrong to prioritize younger patients with COVID-19. It would have been inconceivable that such a poll would be hosted for prioritization on the basis of other socio-demographic characteristics with an impact on outcome such as ethnicity, gender, body habitus or socio-economic group, but ageing into older age has clearly become the last bastion of widely tolerated overt prejudicial attitudes and behaviour in medicine and society. Compounding the undermining by this poll of the rights of older people was a gerontologically illiterate commentary by the author in favour of prioritizing younger people (Archard and Caplan 2020), and as an indicator of the size of the problem, over 40% of respondents to the poll were in agreement with him.

## 9.2 How Do Gerontologists Portray Their Own Ageing?

It is important to recognise that we as geriatricians and gerontologists may also have had a part to play in the unfurling and reinforcing of failure and negative models of ageing (Kalish 1979). It is recognised that geriatricians themselves are likely to be ambivalent about ageing and our existential vulnerability (O'Neill 2016). Notwithstanding, this may also be an issue of articulacy, as geriatricians in the United States, despite being among the lowest paid specialties report high job satisfaction (Leigh et al. 2009), suggesting that they understand implicitly the richness and rewards

of engaging with older people. In addition, although geriatricians are the group of gerontologists most likely to be in everyday contact with older people, this is by and large contact with older people suffering from illness, frailty and disability, and freeing themselves to be able to step backwards and see the bigger picture of ageing is challenging (O'Neill 2012). Even in gerontology, usually defined as the collective sciences of the study of normal ageing, the preponderance of studies relating to a range of the downsides of ageing is notable in the contents pages of journals dedicated to the sociology and psychology of ageing.

This was quite markedly in evidence in a special issue of *The Gerontologist* journal dedicated to gerontologists writing about ageing as a personal experience (Pruchno 2017). The outcome was disappointing: one might have expected that the gerontologists would talk about their own individual ageing and how it had enhanced their ability to master their subject, stripping out the inessentials, and learning to develop a more meaningful prioritisation of life and activities would feature strongly. Instead the issue was full of stories of the challenges of looking after older parents with illness and disability, further reinforcing this sense of ageing viewed through the lens of disability, dependence and disease rather than positivities.

Gerontologists and geriatricians have also contributed to a problematic conceptualization of health and ageing through the uncritical embrace of the concept of 'successful ageing' (Rowe and Kahn 1997). Although well-intentioned as a waystation in reclaiming the possibilities of a healthier old age, the very term 'success' implied an antonymous group of older people with 'failed ageing', those who did not meet the parameters outlined in the brief. This has been rejected eloquently in a Canadian paper aptly titled: "I may be frail but I ain't no failure" (Richardson et al. 2011).

## 9.3 Redefining Health on the Terms of Older People

Given that the socio-cultural constructs of well-being and health in later life are so coloured not only by negative socio-cultural constructs but also often measured in parameters not chosen by older people, it is really important that we redefine our concept of health on their terms. This can be done in a manner that recognizes the apparent paradox to outsiders of the quite constant finding of high levels of life-satisfaction among older people co-existing with increased levels of 'objectively' measured diseases and disabilities, as well as the fact that self-related health is consistently a better guide of longevity than most 'objective' measures. Despite the increased health problems and disability, most seniors subjectively rate their health positively, and view aging as a positive period of life evaluation, increased wisdom and maturity, albeit increasingly constricted by socio-economic factors in later years (Clarke et al. 2000). The somewhat paradoxical nature of these findings suggests that later life well-being is multidimensional and variable.

It is clear that understanding health and well-being in later life requires an understanding of later life which is deeper and more balanced than that of common

perceptions in society and much of general medicine, as well as an interrogation of what older people themselves perceive as the key elements of health and well-being in later life. These perceptions of health show consistently a sense of multi-dimensionality across psychological, social and physical domains, consistent with a realism among older people of adaptation to existential vulnerability and moving beyond a simplistic tally of diagnostic labels (Fernández-Ballesteros et al. 2008). In addition, there is a move to begin to recognize the salutogenic aspects of health in later life, and in particular the importance of understanding the opportunities arising from conceptualizing the concepts of resilience and flourishing in the face of physical and societal challenges (Tomás et al. 2012). There is an increasing recognition of the centrality of eudaimonia—flourishing—in later life through an emphasis on meaning-making, self-realisation and growth, quality connections to others, self-knowledge and managing life (Ryff 2014). Nurturing and sustaining the possibility of growth in self-mastery and awareness represents a key goal for health and well-being in later life through promoting an increasing sense of authenticity and ownership of the human experience as a key factor in resilience and autonomy (Ryff and Singer 2008).

## 9.4 Finding New Portals to Understand Ageing, Health and Flourishing

Just as the philosopher Michel Foucault helped us to understand how healthcare workers' vision of the real experience of people with illness was blinkered by what he termed the 'medical gaze', or as the historian Roy Porter radically altered our review of the history of medicine by changing the perspective to that of the patient rather than of the doctor, all professionals and scholars of ageing are impeded to a certain extent in understanding the true nature of ageing by the extent to which their training, methodologies, ethos and discourse create barriers between them and those experiencing ageing. So to speak, the 'social gerontologist gaze', the 'psychologist of ageing gaze' and the 'biology of ageing gaze' are companions to the medical gaze.

This is not in any way to diminish the standing or importance of these important areas of development of scholarship and understanding, but rather to point out that they are not sufficient in themselves to give us the bigger picture of what it means to age and the complex interplay between us as we age and the societies and cultures within which we live. An emerging area of scholarship which holds much promise to provide enlightenment as to how we might better understand ageing arises from recourse to the arts and humanities. This should not come as a surprise to those acquainted with the philosophy of knowledge in science. Immanuel Kant wrote in his *Critique of Pure Reason* (1781) that: "Reason.. must approach nature in order to be taught by it: but not in the character of a pupil who agrees to everything the master likes, but as an appointed judge who compels the witnesses to answer the questions he himself proposes". These thoughts were mirrored two centuries later by Jürgen

Habermas who raised concerns over the apparent hegemony of scientific methods in his *Knowledge and Human Inquiry* (1968), referring to scientism, science's belief in itself: that is, the conviction that we can no longer understand science as one form of knowledge, but rather must identify knowledge with science.

## 9.5 Humanities and Ageing, Cultural Gerontology

Into this breach has developed an innovative and exciting movement in gerontology to provide a deeper and more comprehensive insight into the meaning of ageing. Largely encompassed by the terms of cultural, humanistic and narrative gerontology, their intent and methodologies in many ways mirror the relationship in another arena where arts and humanities are seen as an important element of epistemology, that of the contribution of the medical humanities to medicine and healthcare (O'Neill 2015). The terminologies seem to represent a transatlantic linguistic divide, with humanities and ageing more common in the USA, and cultural gerontology in Europe (Twigg and Martin 2015): recently the Gerontological Society of America has recognized this by renaming their advisory panel on the topic as "Humanities, Arts and Cultural Gerontology" (HACG) in 2020.

As tellingly introduced by one of the pioneers of HACG, Thomas Cole, the opportunity arising from the humanities approach to ageing is to more fully respond to the second of TS Eliot's proposed questions for every issue (Cole et al. 1992). Eliot had proposed that there were two sorts of problems in life, one prompting the question, 'What are we going to do about it?' and the other provoking the questions, 'What does it mean? How does one relate to it?'. Responding to this deeper question generally arises from an impetus in mid-career, as many of us spend the first decade or so of our professional or academic careers in preparing the techniques and methodologies to answering the first question. Indeed by this stage in their careers many gerontologists of all persuasions are pleased to learn of HACG as they feel increasingly limited by the boundaries and parameters of their traditional methods, many overtly or covertly carrying much baggage relating to the failure models of ageing, and mainstream gerontology generally tends to leave questions of meaning unanswered (Baars 2012).

While 'culture' as a term is open to broad and conflicting usage, HACG can be described as a tendency, or a field, with a central focus on meaning, a desire to transcend old paradigms, and to bring a fuller, richer account of later years than heretofore presented in gerontology and geriatric medicine (Twigg and Martin 2015). An increasing focus of the humanities in recent decades has been critical to the development of the field, including literature, film (Chivers 2011), music (Bennett 2013), philosophy (Baars 2012), fashion (Lewis et al. 2011), and history (Thane 2005): there have also been important contributions from social and psychological themes such as the body and embodiment (Gilleard and Higgs 2013), identity and subjectivity (Biggs 1997), visual imagery of ageing (Martin 2012), consumption (Drolet et al. 2010) and perceptions of time and space (Angus et al. 2005). Gerontology

journals carry increasing space for HACG scholarship, including a regular rubric in *The Gerontologist* (Kivnick and Pruchno 2011) and *European Geriatric Medicine* (O'Neill 2019).

## 9.6 Illuminating the Grandeur and Richness of Ageing

One of the most powerful contributions of HACG has been to help illuminate the opportunities for the human condition arising from our collective ageing. This has found a potent metaphor in the scholarship exploring late-life creativity: as expressed by one of the pioneers of the field, Gene Cohen, the art of later life is great not in spite of old age, but because of it (Cohen 1998). Through a range of artforms, we can increasingly recognise that for the majority of major artists their greatest creativity, and often most radical creations, occur in later life. Often occurring during times of significant physical and other hardships, we begin to see patterns of the gains of ageing which in turn help us reflect on the drivers of this mastery.

A typical example is the radically new découpage style of Henri Matisse, as typified by *The Snail* (1953) hanging in the Tate Modern in London: radical, vibrant, and witty, it was created when the 83-year-old Matisse was bed- and wheelchair-bound. Matisse's response to illness illustrates not just his resourcefulness, but also the role of adversity in sparking personal growth (O'Neill 2011). This was most notable in his late development of the technique of découpage, cutting out the shapes and applying gouache with the assistance of his students, to create an unforgettable series of large art works into his ninth decade, and belying the image of older people as conservative or prisoners of tradition. The message of the gifts of ageing is all the stronger for being delivered metaphorically, transcending supplication and the usually worthy tone of advocacy by harnessing the emotional, aesthetic, and transformative power of great art.

Equally impressive are the late paintings of Emil Nolde: banned by the Nazis from painting as a degenerate artist, he developed a series of unpainted paintings that are masterpieces of stripped down simplicity and impact (O'Neill 2018). These small and hugely expressive watercolours are a subtle yet often wild distillation of a lifetime of exploring and mastering colour as a primary medium of expression. Once this avenue of scholarship is opened to our eyes, the art of the longevity dividend is the gift that keeps on giving, from the great late art of Renoir, who due to his severe arthritis had had to paint his last paintings with a paintbrush strapped to his hand, to the late paintings of Claude Monet, with very impressive scale and ambition matched by a lifetime's mastery of the essence of Impressionism. The dividend extends into virtually all other artforms, from the late songs of Leonard Coen, through the movies of eight and ninth decades of Clint Eastwood, the late poetry of poets such as Thomas

Kinsella and Czesław Miłosz, the novels and writing of George Bernard Shaw and PG Woodhouse in their 10th decade (Cotter et al. 2011), and sculptures of Louise Bourgeois.

## 9.7 Illuminating the Inner Life

What is equally powerful in studying the great art of later life is that it affords us the possibility for an authentic vision of the inner life, the complexity and magnificence of life as an older person that effectively bars us from retreating to a vision defined by their disability. Every stage of life has its downsides, challenges and negativities, but as previously noted there is a societal tendency to lose the sense of equipoise between growth and loss in later life. Great artists allow us to see that they engage with, learn from, and manage to rise above the vicissitudes of later life. The classic example is *Self-Portrait with Clock* by the Norwegian expressionist artist Edvard Munch. The multi-layered messaging of art allows us to simultaneously see not only the thin solitary figure, the single bed with utilitarian bedstead but also the vibrant colours, the clever placing of past conquests and art in the background, the witty joke of the clock without hands suggesting timelessness, and the clear message that Edvard Munch in his old age matters, contributes, and sustains in the face of his existential vulnerabilities.

Another powerful example is the music of Leos Janácek, only becoming a composer of note from the age of 50 and entertaining his greatest achievements in his 70s. His work gives us insights into his own ageing in at least three ways, including the subject matter of his late operas, the composer's own extensive correspondence during this period, and the shape of his musical structures (Beckerman 1990). One of the most extraordinary gifts is the parallel between his romance with a younger women, and the portrayal of love and ageing in his late operas. In *The Makropolous Case*, the central prima donna has the dubious gift of living 337 years thanks to an elixir of life but finds life less meaningful than those whose span has finitude. Janácek saves his most heartfelt, lyrical and radiant music for the final scene for her own bodily transformation into someone who looks 337 years old, underlining the meaning of life with a lifespan (Wainwright and Williams 2005). More personally, the relationship between the old forester and the vixen in the *Cunning Little Vixen* portrays movingly the strains yet joys of renewal of relationships and love in later life. An added bonus of this approach to ageing is that it affords us pathways to understanding that rise above and outside the written word so central to much scholarship: as the composer Mendelsohn said, "it is not that music is too imprecise for words but that it is too precise."

## 9.8 Illuminating Theories of Ageing

An added benefit of the late life creativity approach is that the work of great artists in later life also provides insights into theoretical aspects of ageing. For example, Arthur Rubinstein, active as a concert pianist into his nineties, is an embodiment of one of the most significant theories of successful ageing, Baltes' theory of Selection, Optimization and Compensation. As Rubinstein grew older, he reduced his repertoire (Selection), practiced these pieces more intensely (Optimization) and played the slow passages ahead of fast passages more slowly so as to give an impression of speed in the fast movement (Compensation) (Baltes and Singer 2001). There is good evidence that older workers compensate for age-related changes very well through mechanisms such as reducing the physical load (while maintaining productivity), adopting safer practices, and changing prioritization: in sophisticated practice such as surgery, such strategic measures almost certainly explain the safer record of older surgeons (Satkunasivam et al. 2020).

Another confluence with late life creativity is the socioemotional selectivity theory of Carstensen which proposes that the nearer we come to the limits of our existential vulnerability, whether through sickness, disability, or the proximity of death, the more we search for meaningful experiences and expression (Carstensen et al. 1999). It is not difficult to see this reflected in the progressive stripping down and emphasis on the essentials in late art that reflects this trend, from the sparse and rigorous late nocturnes of Gabriel Fauré (Sobaskie 2003), to the pared down and sombre style of late Titian (Freundlich and Shively 2006).

There are also resonances of the mastery of later life creativity with the theories of gerotranscendence and life review whereby we gain mastery and insight into the course and meaning of our lives. These assist us in understanding old age as the apogee of human experience. The "life review", as originally described by the late pioneer of geriatric medicine Robert Butler, was a radical rethink that viewed the process as a normal developmental task of the later years, characterised by the return of memories and past conflicts. Life review can result in resolution, reconciliation, atonement, integration, and serenity. It can occur spontaneously or it can be structured, and an ideal exemplar is *Metamorphosen* by Richard Strauss, composed at age 81. Embedded are echoes and palimpsests of Strauss's earlier work—*Also Sprach Zarathrusta*, *Ariadne auf Naxos*, and *Arabella*—and cryptic references to Wagner, Brahms, and Beethoven: the many layers of memory, remembrance, regret, and transformation fuse in wisdom, regret, and artistry. The background elements—destruction, tyranny, mistakes, and compromise—are a metaphor for the regrets of later life, but the music is a testament to the power of life review and an affirmation of what we have gained from increased longevity (O'Neill 2010).

In a different but complementary vein, his *Four Last Songs* elevate us to a serenity, peace and beauty that are aural and musical exemplars of gerotranscendence, a sense not only of complete mastery but also of reaching a higher plane of experience and insight (Canton et al. 2009).

## 9.9 Authenticity, Ageing and Well-Being

These various inputs from HACG are enormously valuable windows from different perspectives into a more authentic vision and understanding of the experience, meaning, challenges and opportunities of ageing into later life. A particularly useful contribution from the philosophy of ageing resonates with this sense of authenticity of experience, and in particular the ability to combine generativity and existential vulnerability without succumbing to simplistic dichotomy of either failure or older super-performers. Leaders in the field such as Jan Baars and Hanne Laceulle have developed counter-narratives which point to a framework that facilitates reconciliation of continued growth with our existential vulnerability and finitude (Baars 2012; Laceulle 2017).

Authenticity—the possibility of becoming ever more who you are as you age—is a social and moral concept which resonates with my practice and experience with older people. It is not a purely individualistic and inward-looking process but one which recognizes our social embeddedness and that all autonomy is exercised in the embrace of others. As described by Laceulle, it offers an opportunity to consider life-long development as a continuum into old age. Of particular interest is the consideration that there may be greatness and dignity in facing and even embracing existential vulnerability and anxiety with an attitude of courage, openness, and vitality. If existential vulnerability can be seen as something that can be integrated into life in a meaningful way, then the experiences in which we confront this vulnerability need no longer be perceived as failures that so many older people fear. Instead, the framework provided by this authenticity discourse can help us as a society to support people confronted with existential vulnerability in regaining the experience of life as meaningful, by focusing on their strength and potential for resilience in the face of adversity (Laceulle 2017).

As so often such concepts can often be also succinctly conveyed by great artists in later life, and this flux of vulnerability, resilience and growth was expressed by Samuel Becket when he said: "I always thought old age would be a writer's best chance. Whenever I read the late work of Goethe or W. B. Yeats I had the impertinence to identify with it. Now, my memory's gone, all the old fluency's disappeared. I don't write a single sentence without saying to myself, 'It's a lie!' So I know I was right. It's the best chance I've ever had" (Shainberg 1987).

In an equally striking examples, we have remarkable art arising from such challenging late-life diagnoses as severe stroke and dementia illustrating this growth in the face of adversity. Tomas Tranströmer, the Swedish poet, accomplished pianist and Nobel laureate, was left with severe speech deficits and hemiplegia after a stroke at the age of 59. Following a gradual but partial physical recovery, he began to play the piano with the left hand, and produced a remarkable collection of poetry fourteen years later, *The Great Enigma.* These elegant poems and haikus are notable for a bright energy, humour, wisdom as well as a familiarity—without being cowed—with death: "Death stoops over me./I'm a problem in chess./He has the solution." (Tranströmer 2015). Similarily, we are granted iconographic parallels in the remarkable self-portraits of

William Utermohlen that documented his journey with dementia, the diminishing technical skills counter-pointed by self-expression, artistic coherence and emotional impact (Crutch et al. 2001).

## 9.10 Mainstreaming HACG into Gerontological Scholarship and Practice

Further developing HACG into the main body of gerontology represents an important addition to our repertoire and articulacy, facilitating participation in important trends such as reframing aging, an initiative to emphasize the positivities and worth of later life (Lundebjerg et al. 2017). It is also a valuable tool for teaching gerontology and geriatric medicine at undergraduate and postgraduate levels. However, as with many interdisciplinary fields, there are many challenges to be faced, from sourcing open-minded reviewers, grant bodies, and establishing cross-disciplinary links and funding with colleagues who are blessed with the relatively scarce combination of academic security and academic humility (Callard and Fitzgerald 2015). Nonetheless it remains an exciting development that has the possibility of both intense scholarly achievement as well as the opportunity to significantly improve the lives of older people through a more authentic framing of the richness, possibilities and societal benefits of our collective ageing into later life. In addition, it can develop a deeper understanding of how a reconceptualization of health and well-being of older people on their terms can expand our horizons in healthcare to recognize those determinants and supports that maximize the potential for flourishing and authenticity of the human experience for all of us as we age into later life.

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# Part II
# Health Across Systems

# Chapter 10
# Healthy Mouth: An Odontological Perspective


**Tine Hjorth**

**Abstract** The face and the mouth are often considered to be the windows to our general health. Screening and monitoring of young children for healthy growth and development of the jaws and teeth is becoming a standard practice in more and more countries with a national health system/strategy. Such screenings are based on certain formal and informal notions of what a healthy mouth is. Making the ageing population more aware of their mouth and teeth status, and how oral health is connected to a healthy life is being realized increasingly. This article provides a brief overview of what characteristics are used while screening and evaluating the growth and development of a healthy mouth. The article describes the structural aspects of the healthy bony skeleton, temporomandibular joints, masticatory muscles, lips, palate, dental arches, occlusion, teeth, gingiva, periodontal ligament, oral mucosa, tongue, saliva and microbiome. This is followed by discussing the functional aspects of a healthy mouth, and finally commenting on the relation between a healthy mouth and a healthy body.

**Keywords** Beauty · Chewing · Dentistry · Face · Oral health

## 10.1 Introduction

We are often familiar with the problems that arise when our mouth is not healthy. This inherently implies that we do have certain formal or informal notions and ideas about what a healthy mouth is or should be. The basis for this understanding of what makes a mouth healthy lies mainly in the description of the structural components of the mouth in the context of their respective functions. Thus, a combined structural and functional description of the mouth creates a framework for defining what is a normal healthy mouth. Deviations from such a normality are then generally considered to be the cross-over threshold to one or more oral pathologies. Therefore, oral health is usually described in the context of oral diseases. Even the definition of oral health

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by the WHO is mainly derived from the diseases that may occur in the oral region: "Oral health is a key indicator of overall health, well-being and quality of life. It encompasses a range of diseases and conditions that include dental caries, periodontal disease, tooth loss, oral cancer, oral manifestations of HIV infection, oro-dental trauma, noma disease and birth defects such as cleft lip and palate" (https://www.who.int/health-topics/oral-health/#tab=tab_1).

The aim of this article is to provide a brief overview of what criteria are used while evaluating the growth and development of a healthy mouth. From a public health point of view, the case of my country, Denmark, is very interesting. In 1971, the Danish government decided by law that all children should have free access to dental checking and treatment. The law developed into a public program for the screening of all children between the ages of 1 and 18 years, monitoring the normal development of the mouth. The long-term aim of such a screening was prevention and treatment of oral diseases, and keeping functional teeth, mouth and jaws throughout life. The law resulted in the practice of calling all children regularly (at least once in 18 months) in order to check the health of their mouths. The law is still in practice and encompasses not only the checking and treatment of dental decay, periodontitis, oral mucosa and sequelae of trauma, but also the treatment of malformations and malocclusions.

This article is an attempt to highlight the characteristics of a healthy mouth, and does not aim to describe the methods and criteria used in oral health surveys on large populations, such as the WHO oral health surveys (https://www.who.int/oral_health/publications/9789241548649/en/). The article is organized into first describing the structural aspects of a healthy mouth, followed by discussing its functional aspects, and finally exploring the relation between a healthy mouth and a healthy body.

## 10.2 Structural Aspects of the Healthy Mouth

In a clinical setting, the components of the mouth are checked and evaluated for their health and normality status, using various criteria and methods, as described for each component below. It should be pointed out that in this article only the characteristics are mentioned without providing exact numerical values and ranges used as reference points.

### *10.2.1 The Bony Skeleton*

The bony skeleton of the mouth is comprised of the upper and lower jaws, and the palatine bone. The upper jaw is divided into two parts by the median palatal suture, and is surrounded by sutures towards the frontal bone, nasal bone, zygomatic bone, pterygoid bone, sphenoid bone, lacrimal bone, ethmoid bone, and palatine bone. The lower jaw is connected to the cranial base through the temporomandibular joint

and, in an intact mouth, is supported by the teeth, and "hanging" in the masticatory muscles (Berkowitz et al. 2017). A normal healthy bony skeleton of the mouth is identified by:

- symmetrical growth of both jaws
- symmetrical surrounding bony structures
- proportionate growth
- unbroken bony structure.

The normal structure of the bony skeleton is the basis for symmetric development of the mouth and the appearance of the face.

### *10.2.2 Temporomandibular Joints*

Temporomandibular joints are the connection between the cranial base and the lower jaw. A healthy joint is:

- surrounded by an intact capsule
- covered with cartilage on both surfaces
- has an intermediate articular disc, moving smoothly
- able to rotate and translate forward smoothly
- not sore on palpation.

The smooth movement of the temporomandibular joints facilitates normal chewing, swallowing, talking and other movements of the mouth (Okeson 2020).

### *10.2.3 Masticatory Muscles*

The masticatory muscles are crucial for the normal movement and the chewing action of the lower jaw. These muscles are categorized as elevators, depressors, protractors and retractors. Functionally connected to the masticatory muscles are the muscles of the neck, being part of the postural muscles of the head. The muscles of the cheeks, lips and tongue shape the oral cavity during chewing, swallowing and talking. The superficial masticatory muscles are often palpated for soreness during screenings (Berkowitz et al. 2017; Okeson 2020). The characteristics of healthy muscles are:

- no soreness
- symmetric development
- proportionate size
- ability to contract
- ability to stretch.

The structural and functional balance of the masticatory muscles is essential for giving shape to the face in terms of filling out the cheeks and temples.

### 10.2.4 The Lips

The upper and lower lips are muscles and connective tissue, covered on the outside of the mouth with skin and on the inside with mucosa. The vermillion border connects the skin and mucosa. The lips are evaluated to be healthy by the following characteristics:

- clear distinction between the three parts of the lips
- different color of the vermillion border than the skin and mucosa, all three having an evenly distributed color
- vermillion border is soft, adaptable and able to seal the mouth when closed.

The muscles of the lips (the orbicularis oris, the lip-lifting and lip-depressing muscles as well as the mentalis and the other mimical muscles) work together with the tongue, forming sounds and placing food between the teeth during eating and keeping the mouth closed during these activities (Berkowitz et al. 2017).

### 10.2.5 The Palate

The palate is the ceiling of the mouth, divided into the hard 2/3 and soft 1/3 of the palate. The palate creates a division between the nose and the mouth. The characteristics of the healthy palate are:

- hard palate with a continuous bony structure
- moveable, continuous soft palate
- presence of an uvula
- palatoglossal folds on both lateral sides, just anteriorly to the uvula
- palatopharyngeal folds on both lateral sides, dorsally to the uvula.

A healthy palate facilitates swallowing and clear speech in coordination with the tongue (Berkowitz et al. 2017).

### 10.2.6 Dental Arches

The dental arches are the two rows of teeth emerging from the upper and lower jaw, and a healthy arch is defined by the following characteristics:

- correct number of teeth (20 primary or temporary teeth; 32 permanent teeth)
- eruption in a standard sequence
- no teeth that block the eruption of other teeth
- no unerupted (retained) teeth
- optimal space in the arch for all teeth
- continuous bone structure.

Of the above characteristics of the normal, healthy dental arches, the presence of blocked or retained teeth is generally diagnosed using X-ray-based methods (i.e. radiographs and CBCT scans) and the optimal space in the arches is measured by comparing the width of the teeth and the width of the dental arch (Proffit 2018).

### *10.2.7 Occlusion*

The way the upper and the lower dental arches meet each other in the closed mouth position constitutes a "bite", termed the occlusion. The ideal occlusion is described according to certain criteria, the most common being: angle classification reporting the sagittal discrepancies. In addition, the vertical and transverse occlusion is evaluated as well as space conditions such as crowding and spacing of the teeth (Proffit 2018). The criteria for an ideal occlusion are:

- overjet 1–2 mm (discrepancy in the bite in the horizontal plane)
- overbite 2–3 mm (discrepancy in the bite in the vertical plane)
- no posterior crossbite (discrepancy in the bite in the transverse plane)
- no crowding of the front teeth.

### *10.2.8 The Teeth*

A healthy tooth is defined by having all or the majority of the following characteristics:

- presence at the correct place in the dental arch
- standard shape, size, and structure
- normal enamel structure
- normal dentine structure
- normal root cement
- normal pulp
- intact root area.

Whereas several of the above characteristics can be visually evaluated, others, for example dentine structure, pulp and root cement, and root area require X-ray-based evaluation. Furthermore, the pulp can be tested with electrometric or thermic sensibility testing (Proffit 2018; Berkowitz et al. 2017; Makdissi 2016; Reit et al. 2003).

### 10.2.9 Gingiva

Gingiva is divided in two parts: the keratinized part attached to the bone and closest to the teeth, surrounded by the free gingiva which can be moved in relation to the bone. The attached gingiva is considered to be healthy when it meets the following criteria:

- pale pink appearance even in cases where the gingiva is pigmented
- stippling (orange peel appearance)
- uninflamed state.

The healthy free gingiva is separated from the attached gingiva by the mucogingival line, and is darker in color (Berkowitz et al. 2017).

### 10.2.10 Periodontal Ligament

Teeth are attached to their alveolar sockets through a periodontal ligament which is a dense fibrous connective tissue. The periodontal ligament also includes proprioceptive nerve endings, giving information about pain and overload of the tooth in different directions, regulating the chewing force (Papanou & Lindhe 1998; Nyman & Lindhe 1997; Thilander et al. 2005). The characteristics of a healthy periodontal ligament are:

- collagen fibers embedded in a gel-like matrix, stretching in all directions and fastening on surrounding structures
- probing depth of periodontal pockets of 1–4 mm.

The periodontal ligament cannot be observed directly, but can be probed using appropriate instruments, and visualized using X-rays.

### 10.2.11 Oral Mucosa

Oral mucosa is the mucous membrane lining the inside of the mouth (Berkowitz et al. 2017). The buccal and labial mucosa is the lining inside the cheeks and lips, and is considered healthy according to the following characteristics:

- coral pink in appearance
- uninflamed
- intact surface
- moist surface.

Regular excessive consumption of, for example, burning hot food, tobacco and other irritants affect the oral mucosa negatively, resulting in reddening or hyperkeratinization of the affected mucosa.

### *10.2.12 Tongue*

The tongue is a muscular structure in the mouth facilitating speech, taste, and placement of food between the dental arches during mastication and swallowing. The characteristics of a healthy tongue are:

- smooth upper surface (dorsum) covered with taste buds (papillae)
- a midline groove dividing the tongue in two symmetrical parts
- ability to taste sour, salty, sweet, bitter and umami
- large papillae arranged in a V-shape at the back
- undersurface with large vessels
- optimally sized frenulum for connecting to the sublingual area
- ability to move in all directions
- tactile sense.

The tongue is examined and used extensively for determining the general health of the individual in the Chinese and Ayurvedic systems of medicine (Berkowitz et al. 2017; Wu et al. 2005; Lo et al. 2012).

### *10.2.13 Saliva*

Saliva keeps the mouth hydrated and creates a thin and viscous surface on the structures. It has cleaning, lubricating, buffering, tooth-mineralizing, antibacterial, digestive and analgesic properties. A healthy mouth produces up to one liter of saliva per day from the three large glands, the parotid which secretes only serous saliva (thin fluid), the submandibular which secretes a mixture of serous and mucus saliva (slimy fluid), and the sublingual which secretes mucus saliva. These glands secrete about 90% of the saliva. The remaining 10% of saliva is secreted by numerous small glands situated in the surface of mucosa of the palate, lips, cheeks, tongue and retromolar area (Nauntofte et al. 2003; Wisner et al. 2006) The characteristics of healthy saliva are:

- mucous or serous or mixed fluid
- sufficient volume
- colorless appearance
- no foul smell
- uninflamed salivary glands.

During screening, the lubrication of the mouth is visually observed, and the examination mirror should slide smoothly when moved over the mucosa without sticking to it.

The above brief description of the structural components of the mouth gives an idea of the complexity of the normal healthy mouth. This complexity increases when the bacterial fauna is also included in the description of a healthy mouth. There is still much to be understood of the variety of the microbiome in the mouth and its interaction with the genetics, epigenetics and the lifestyle of the individual.

## 10.3 Functional Aspects of the Healthy Mouth

The primary functions of the mouth are chewing, swallowing, and speaking. There is a large amount of information available about the parameters constituting normal healthy chewing, swallowing and speech (Helkimo & Ingervall 1976; Ingervall & Helkimo 1978). These parameters include the strength, length and pattern of activity of the muscles, the quantities of different muscle fibers (Hunt et al. 2006), and the amount and composition of saliva (Nauntofte et al. 2003), which are all required for healthy function.

It must be pointed out that the above structural and functional norms of a healthy mouth are idealistic. In reality, there are large inter-individual variations, and the mouth can perform its functions to varying extents despite imperfections of the structural components. For example, even when a person is missing several teeth, or the bite is incomplete, or the jaws are asymmetric, or the muscles are weak, or there is a repaired cleft, the mouth can still perform its basic functions to a large extent. Although such a mouth can perform its functions to an acceptable degree, do we still consider such a mouth as a healthy mouth? In my opinion such a structurally imperfect, but functionally adequate mouth, should be considered healthy.

Conversely, a mouth with chronic infections, in my opinion, cannot/should not be considered healthy even if it is able to perform its function adequately. This is because chronic bacterial infections of the mouth are very well reported to correlate with numerous diseases, including rheumatoid arthritis, Alzheimer's disease, type 2 diabetes and cardiovascular diseases (Acharya et al. 2019; Kubota et al. 2014; Sochocka et al. 2017; Sfyocras et al. 2012; Söder & Yakob 2005). Furthermore, infections of the mouth have been reported to correlate with a reduction of lifespan in the elderly, possibly by aggravating other pathological conditions in the body (Söder et al. 2007).

The health status of the mouth is also strongly affected by the health of the rest of the body and the life style of the individual. For example, the temporomandibular joints can be affected in general rheumatoid diseases (Stoustrup & Twilt 2019), several skin diseases can be seen in the oral mucosa as well as the skin, and the vascularization of the oral tissues is affected in diabetes reducing the resistance of the tissues to local infections (Papanou & Lindhe 1998). General muscular dystrophies can severely affect the bite (van Bruggen et al. 2015). A smoking habit is also known to

affect the health status of the mouth by inducing and/or worsening diseases of the oral mucosa, gingiva and periodontium. Additionally, smoking alters the oral microflora, and affects the quantity, quality and contents of the saliva towards a harmful profile, and reduces the healing capacity of the oral tissues (Rodriguez-Rabassa et al. 2018; Grine et al. 2019). Other habits such as tobacco and betel nut chewing, use of snuff, alcohol, narcotics and medications can lead to the loss of health of the oral tissues (Johnson & Bain 2000). In these situations, even if there is an apparently adequate functioning, the mouth cannot be considered healthy.

## 10.4 Healthy Mouth and Social Factors

Whatever the medical criteria for a healthy mouth may be, ultimately it is the individual experience, and the boundaries of tolerance and adaptability of the individual that determine whether one "feels" that one has a healthy mouth or not. These individual boundaries are affected by cultural norms, economy, age, and general physical and mental health. Furthermore, political decisions about public health can set a standard for what a healthy mouth is. For example, the 1971 decision of the Danish government to implement public dentistry for all children and adolescents has changed the social definition of a healthy mouth in Denmark. As a result, persons with severely decayed teeth and major malocclusions are a rarity, and are often not appreciated socially.

A structurally and functionally healthy mouth is also associated with the ideas of the beauty of the face and overall health. Historically, artistic depictions of faces in paintings, sculptures and photographs have almost never been shown with visible teeth and distortions of the mouth. This may be because malocclusions, missing or infected teeth, and untreated disfigurations were often associated with lower socio-economic status, and possibly a low moral character. Various evil and villainous characters in visual arts, theatre and cinema are often presented as having a distorted face and expression. Interestingly, the fictional character Dracula is almost always caricatured by protruding teeth!

Finally, recent developments in the availability and affordability of corrective technologies within facial aesthetics and dentistry have made them increasingly popular. These technologies do help people with severely distorted faces to achieve a certain level of functional and social normality. A healthy-looking mouth adds to the overall beauty and social acceptance of the face. New technologies may also lead to setting up new social and medical norms of what defines a healthy mouth.

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# Chapter 11
# Cardiovascular Health


**Ole Faergeman**

**Abstract** The concept of "cardiovascular health" is a practical idea promoted by health organisations such as the American Heart Association. It identifies a set of risk factors for common diseases such as myocardial infarction and stroke that allows monitoring of risk in populations. It deserves support, but it does not, as the term might suggest, have anything to do with physiological function of the heart and blood vessels, and it subverts classical and etymologically faithful ideas of health. Because of the complexity of the genetics of common diseases, moreover, precision medicine is unlikely to be of use in the promotion of population-scale cardiovascular health, however defined.

**Keywords** Cardiovascular health · Cardiovascular risk · Cholesterol · Hypertension · Smoking · Precision medicine · Personalized medicine · Genomics · Risk factors · Systems biology · Pharmacogenetics

Who would not want to be in excellent cardiovascular health? With any luck, that could be the verdict passed by your cardiologist or your general practioner, or by the app on your smart phone and supported, perhaps, by a profiling of your genes. But what does it mean, exactly?

Cardiovascular health is an idea promoted by organisations including heart foundations such as the American Heart Association (AHA) (Lloyd-Jones et al. 2010). We promoted the same idea when I was president of the Danish Heart Foundation a quarter of a century ago. It is not as straightforward as it might appear, however, and in this chapter I shall try to examine and perhaps clarify the concept in terms of fairly standard methodology. Half of the chapter, however, will be about cardiovascular health in the light of current interest in genomics and precision medicine.

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## 11.1 The AHA Concept of Cardiovascular Health

The AHA concept of cardiovascular health makes less sense in semantic terms than it does in practical terms. Like the Holy Roman Empire, which was in no way holy, nor Roman, nor an empire, "cardiovascular health" is not cardiovascular, since it refers to both much more and much less than the heart and blood vessels. It also refers to something much less than "health" in the biologically meaningful and etymologically faithful sense of the word.

As formulated by the AHA and other organisations, the idea is not that the heart and blood vessels right now are intact and well functioning, an understanding that might otherwise be the most straightforward. It is, instead, a strategy to monitor and reduce the risk of the most common forms of cardiovascular disease in the population. The term is used more or less in the same way in the USA, France, Germany and in my own country, Denmark, cf. santé cardiovasculaire, herz-kreislauf gesundheit, hjertekarsundhed, etc.

The AHA strategy is to measure your blood cholesterol, blood pressure and blood glucose, to calculate your body mass index from your height and weight, and to question you about your dietary habits, your smoking habits and how physically active you are. Knowing all that allows the physician or nurse, and perhaps you, to appreciate and perhaps calculate your risk of a myocardial infarction or a stroke further down the line. More importantly, though, the measurements can be used in public health research to follow trends in population risk of myocardial infarction and stroke in the USA as well as in other countries (Konig et al. 2018).

It is a practical strategy, and it is well supported by clinical science. Measurements are easily made and questions easily posed in a routine clinical setting, and there is good evidence from epidemiology and clinical trials to support the strategy. There are, nevertheless, fundamental limitations and semantic difficulties.

### *11.1.1 Temporality*

An obvious difficulty is temporal. Good cardiovascular health now, as determined by your personal history and the measurements just mentioned, means only that you are unlikely to suffer disease of the cardiovascular system sometime later on. So, the idea involves the past, the present and the future, i.e. it involves thinking about time, a philosophical problem in itself.[1] In any case, since the future cannot be known, the ascertainment of an individual's good or poor "cardiovascular health" now is a statement about something that also cannot be known. It is about risk of future disease, not about the state of your heart and blood vessels now.

[1] St. Augustine understood time when he didn't think about it, but he couldn't understand time when he did think about it. Same here.

### 11.1.2 Risk

What do we understand about risk and about the uncertainties inherent in the concept and calculation of risk? It is a tautology to say that it is unhealthy to be at increased risk of ill health. We can live with tautologies (the bench in the garden is and is likely to remain a garden bench), but what does risk mean? In particular, how do we go about understanding risk as it applies to ourselves? It is easy enough to deal with risk in mathematical and statistical terms. It is a measure of uncertainty of something bad happening to you sometime in the future, but it fits better into mathematical notation than into our minds.

To calculate your risk of something bad happening, we must know how often that something already has happened to as many individuals as possible belonging to a population to which you also could belong. Let's say it happened to 10 of 1000 individuals during the course of a year. We would then say that your own annual risk is 1%. All kinds of assumptions are necessary in thinking about what this means for other people some time in their future, and those assumptions are well described in books on statistics. Risk, however conceived or calculated, is obviously a certainty only for the non-existent, mathematically average individual of the population we just talked about.

Although we cannot know the future for any individual, we can use risk calculations based on the past experience of the group to which he or she belongs to decide how to reduce average risk. If risk is changing with time, the value of the past risk information is reduced considerably. Risk is part of a package of tools that we use in medicine to make an informed decision, knowing that it is a best guess and in most cases an improvement over simply tossing a coin to decide what to do.

Personalized medicine is presented as a solution to some of these problems, and we'll return to that possibility later in this chapter.

### 11.1.3 Which Organs Are Included?

A third difficulty is the selection of organs and diseases that are included in or excluded from the term, "cardiovascular." As used in medicine and by heart foundations, and indeed as used by most people, "cardiovascular" is taken to mean not only the heart and the blood vessels, but also the brain. There are good reasons for expanding the concept to include the brain, because various forms of stroke share pathogenetic mechanisms with some of the diseases of the heart (coronary atherosclerosis and hypertensive damage to heart muscle).

Still, it is misleading, because various diseases that also share chains of causation with coronary atherosclerosis are not included in the term. An example is intestinal ischaemia and perhaps gangrene due to atherosclerosis or thrombosis of the mesenteric arteries that channel blood to the gut. Indeed, all organs are served by the

cardiovascular system, but "cardiovascular health" is a term reserved for a select few of them.

Confusion is due also to the exclusion of diseases that are obviously cardiovascular. The AHA document makes fleeting references to congenital heart diseases, but it does not include them in the strategy to promote cardiovascular health, and it makes no references at all to the many cardiovascular diseases directly and indirectly due to infections (e.g. endocarditis, rheumatic heart disease, Chagas heart disease), non-coronary cardiomyopathies, as well as diseases of heart rhythm, diseases of vasculature such as aneurysms, arteritis, etc. Cardiovascular health is limited to avoidance of the subset of common diseases of the heart and brain that are due to atherosclerosis, thrombosis and hypertension.

We endorsed much the same narrow focus when I was president of the Danish Heart Association.

### *11.1.4 What is Normal?*

A fourth difficulty is the problem of what is normal and abnormal. At any particular level of inquiry, it makes sense to establish a range of the functions necessary to sustain the integrity of the whole. This is easily appreciated at the level of physiology, the regular contraction and relaxation of the heart as an example, but it also applies to levels of cellular and molecular function. The microbiome and immunology, respectively, come easily to mind.

Normality is a problematical idea, however, especially when physiological and societal levels of understanding are considered at the same time. If everybody smoked, it would be sociologically normal to smoke. It wouldn't even be risky, if risk is calculated with a smoking reference population in mind. Yet it would remain physiologically abnormal, and it would again be risky, if risk were to be calculated with a non-smoking population in mind.

This two-sided nature of the concept has confounded medical and sometimes public debates about treatment with drugs to lower blood pressure, glucose and especially cholesterol. In affluent countries such as Denmark, average concentrations of total cholesterol in blood plasma are around 6 mmoles/l, which therefore is normal in the sense of being common. We know from studies of animals, of human new-borns, and of cell function, however, that physiological concentrations are much lower. They are probably around 3 mmoles/l (Brown and Goldstein 1986). So opponents of drug treatment to lower cholesterol promote the sociological understanding of normality, and proponents promote the physiological understanding, which happens also to be supported by trial data (Sabatine et al. 2017).

The AHA statement takes a middle road: total cholesterol should be less than 200 mg/dl (5.2 mmoles/l). The Danish Heart Foundation avoids the question.

### *11.1.5 A Better Measurement*

A fifth limitation, or advantage according to one's view, is the eclectic nature of the AHA definition. Two of the variables are molecular (cholesterol and glucose), two are physiological (blood pressure and height and weight), and three are answers to questionnaires (smoking, diet and physical activity). That combination of variables makes sense from a practical, clinical and epidemiological point of view, since they all contribute to calculation of risk of forms of stroke and a particular form of heart disease, but, with the exception of blood pressure, they are not measures of physiological function of the cardiovascular system.

A better measurement would be the result of a cardiac stress test, i.e. measurements of pulse, blood pressure, and work performed on a stationary bicycle ergometer or a treadmill. Results of the test, even in its simplest form, which includes an electrocardiogram, really do reflect the state of the heart and blood vessels, and the test can be refined by adding echocardiography and scintigraphy.

Even the simple cardiac stress test takes time to do, however, and without more measurements, it doesn't tell us all that is worth knowing about heart function. A particularly relevant measurement is how much the heart can increase the work it does when it is asked to do so. That is measured as increase in cardiac output, which is the volume of blood the heart can pump per time unit. During rest, cardiac output can be 5 liters per minute, and in normal but untrained people it can be increased to 20–25 l/min during exercise. If you are physically well trained, your heart can pump up to 35 l/min when you exercise. That's impressive for a little organ the size of your fist. Cardiac ouput is not part of the AHA definition of cardiovscular health, however. There are several non-invasive ways to measure cardiac output, also during exercise, but they take time, require expensive instrumentation and are not immediately available for routine clinical practice or epidemiological research.

## 11.2 Genes

There is much enthusiasm and money for personalized medicine for the prevention and treatment of disease (All of Us Research Program, Denny et al. 2019). In its simplest form, it is a strategy to collect information about your environmental history, life style, a selection of clinical measurements and variations in relevant genes or genomic markers.[2] All of that information could, in theory at least, enable a physician to acertain your state of health, to estimate your risk of future ill health, and not least to tailor your treatment with drugs, if you should need them. Tailoring drug treatment to your combination of genomic variations could mean that you will be treated with

[2]Variations can be in a structural gene that codes for a protein. More often they are in non-coding regions of the genome, but they are somehow linked to, or "markers" for, structural genes that we don't necessarily know or understand.

a drug that works and not with one that doesn't. That would be good for you, and it might save money, hence the support for personalized medicine by funding agencies.

Support for the idea of personalized medicine is understandable, moreover, in the age of industrialized medicine, which in principle, and largely also in practice, has become more impersonal. Personalized medicine is also called precision medicine.[3]

### *11.2.1 Detecting Pathology*

A discipline called transcriptomics could offer a way to detect and perhaps rule out the presence of disease. The term requires a few words of explanation.

The information in the stretches of DNA we call structural genes are "transcribed" (written once again) into RNA, and that transcribed information is then "translated" into the sequence of amino acids that make up a protein.[4] Transcriptomics is the study of the RNA that indicate which genes are currently being used ("expressed") to tell the cell what proteins to make. For example, if you have an infection, certain cells in the blood will be making proteins to combat that infection, and measurements of RNA in those cells can tell us which genes are being read and which proteins are being made. Analyses of this kind, "gene expression profiling", can, for example, tell the physician a little about obstruction of the coronary arteries, risk of serious disturbances of heart rhythm, etc. (Musunuru et al. 2017).

At present, no one claims that looking at your genes can replace a physical examination, an echocardiogram or a stress test. Transcriptomics can at best supplement but not replace older methods in cardiovascular research and clinical routine to make a ruling about the state of your heart and blood vessels.

### *11.2.2 Discovering Gene Variants Involved in Disease*

Scientists study patients and families to find the single gene variant that is linked to serious inheritable dissease. An example is the discovery by direct DNA sequencing of one of the structural gene variants that can be responsible for familial hypercholesterolemia, a disease in which very high cholesterol concentrations in blood can cause coronary atherosclerosis and myocardial infarction in young adults and even in childhood. Another example is a structural gene variant responsible for a serious disease of heart muscle (hypertrophic obstructive cardiomyopathy), which

[3]The choice to write "precision" medicine rather than "accuracy" medicine is curious. "Precision" means how close results of several measurements are to each other, whereas "accuracy" means how close the results of a measurement are to the true value of what is being measured. Measurements can therefore be very precise even though they are completely off the target.

[4]Structural genes encode protein sequences, but non-coding regions of the genome are important. Some non-coding DNAs are transcribed, for example, into non-coding RNAs that control the products of the structural genes.

was discovered by linkage analysis (Kathiresan and Srivastava 2012). In both cases, these variants are mutations in genes with very large effects on blood cholesterol and cells of heart muscle, respectively. Inheritance patterns within families accord well with classical Mendelian genetics.

Most of the serious Mendelian diseases are fairly rare, but there are so many of them that there is much work to do for clinical geneticists. It is a very different story when it comes to type 2 diabetes and common forms of coronary atherosclerosis. The genetic problem here is not in one structural gene situated in a well-defined place in the genome. Instead, the problem is a combination of many genomic variants, each with very small effects on risk of disease, situated in many different places in the genome. Joe and Jack may look much the same in the cardiology ward, but the combinations of genomic variants that have contributed to their disease will not be the same. In other words, different genotypes can lead to the same phenotype.

Much effort and money have been spent on whole genome approaches to understand the complicated genetics of common forms of cardiovascular disease for which many, small-effect genomic variants share responsibility for disease with many different environmental effects. Data from whole genome sequencing are combined with data from public health registries to see whether any of a huge number of variants, distributed across the genome, are associated with disease. Association does not mean (but does not exclude) causation, and in genome-wide association studies there is not necessarily any attempt to look for variants that already are known, or at least hypothesized, to be involved in the development of disease. Once disparaged as fishing expeditions, this kind of study is now mainstream research, and it has led to understanding of previously unknown mechanisms of disease on the different levels of biological organisation (DNA, RNA, proteins, metabolites, etc.).

### *11.2.3 Estimating and Reducing of Risk*

A classical form of population epidemiology is to follow a number of people to see whether those who happen to smoke or those who happen to have high blood pressure are more likely to get a disease like stroke than those who don't smoke and those who have normal blood pressure. Such studies can establish association, but, as said, not causation, between a trait like blood pressure and occurrence of disease like stoke.

You can also do association studies to see whether people with genomic variants, discovered for example by genome wide association studies, in another population (external testing) get more disease than people without such variants. The authors of a study of this kind concluded that, although a combination of genomic variants was associated to disease, it did not improve risk estimation by adding it to the estimates already provided by conventional measurements of cholesterol, blood pressure, etc. (Krarup et al. 2015).

The largest study of this kind (Inouye et al. 2018) showed that a "meta-score" consisting of 1.7 million genomic variants was significantly related to occurrence of coronary artery disease in almost a half million men and women registered in

the United Kingdom Biobank. The authors claimed that their results substantially advance the concept that genomic analyses can identify people more or less destined for coronary artery disease.

In that study, the ability of the genomic score to discriminate between people with and without coronary artery disease (C index 0.62) was actually slightly lower than a score based on conventional risk factors (C index 0.67). Indeed, in noting that a C index in the 0.60–0.65 range indicates very modest predictive ability, Greenland and Hassan wrote that the claims on behalf of genomic analyses, made in this and other papers, "create an expectation of a level of precision medicine that cannot be delivered at present" (Greenland and Hassan 2019). Two later studies lend support this understanding (Elliott et al. 2020; Mosley et al. 2020).

These difficulties are due to the enormous and forever evolving heterogeneity of the genetics of common diseases. The number of genomic variations is so large "that complex human disease is in fact a large collection of individually rare, even private, conditions" (McClellan and King 2010). Such genomic variants and combinations of variants are not evenly distributed througout populations, moreover. They tend to cluster (Frikke-Schmidt et al. 2015).

Most of the many genomic variants that associate with disease are not in structural genes that actually code for proteins. They can nevertheless be linked in some way to such coding regions, but it takes time, money and careful research to work out the mechanism by which even one variant in a structural gene is part of the chain of biochemical and physiological events that really do cause human disease.

We surely do not have a reasonably full understanding of the contribution of genomic variations to the etiology of any the common diseases like coronary artery disease. Whether it is possible to get one is the subject of important debates in academic medicine.

### *11.2.4 Tailoring Drug Treatment*

The selection of drugs or drug dosage to suit the patient's genetic makeup is a discipline known as pharmacogenetics, an older and less evocative term than personalized or precision medicine. Pharmacogenetics has typically been focused on regions of the genome that code for proteins/enzymes that metabolize drugs. In recognition of important limitations and complexities, however, pharmacogenetic testing is used very selectively in clinical practice. That makes good sense. Direct-to-consumer genetic testing, including pharmacogenetic testing ("drug-gene testing"), on the other hand, is widely promoted. Lay-persons can be seriously misled by results of such tests, which even professionals find difficult or impossible to interpret.

Furthermore, precision medicine in its various forms, including the versions of entrepreneurial business, has a much larger focus than the classical genetics of drug metabolism. A major commercial provider of such tests, for example, recently expanded them to include common diseases such as heart disease and type 2 diabetes, which the provider recognizes as being polygenic, meaning that variation in many

genes contributes to the etiology of these diseases (https://blog.myheritage.com/2019/10/what-is-a-polygenic-risk-score/). A polygenic background for disease is only one level of complexity, however. Another, already emphasized in this chapter, is interindividual differences in polygenic background. The polygenic background for type 2 diabetes in one patient is not necessarily the same as the polygenic background for type 2 diabetes in another patient (McClellan and King 2010).

Selecting the right drug for the right person at the right time, the mantra of precision medicine, relies on strong data from association studies or, better in my view, identification of a mechanism linking one or more structural gene variants to disease. However plaubsible the link is, there must be trial evidence of benefit because there have been too many examples of treatment that should, from epidemiological, physiological or other reasoning, have conferred benefit but did the reverse (Echt et al. 1991; Rossouw et al. 2002).

From a look at the epidemiology or molecular biology, we might expect that a variant in a gene or a combination of variants in many genes will make the drug work better. But what if it doesn't? What if it makes the patient more susceptible to side effects? Proof of benefit must ultimately be based on clinical observation, e.g. as obtained by some kind of trial, preferably a randomized clinical trial (Sørensen 2018). With exceptions to be discussed below, persons or patients with a particular gene variant or a particular combination of genomic variants have not been randomized to treatment or control, be it with diet or drugs, and followed for the necessary period of time.

The exceptions are trials of reasonably "precise" medicine, particularly in treatment of leukemias, but also in cardiovasclular medicine. In a study of this kind, Lars Ulrik Gerdes and colleagues (Gerdes et al. 2000) exploited Danish and Finnish samples and data from the Scandinavian Simvastatin Survival Study (Scandinavian Simvastatin Survival Study 1994). That randomized clinical trial had shown that, on average, treatment with a cholesterol lowering drug, simvastatin, lowered rates of death in patients with coronary aretery disease. Approximately 15% of patients in both the treatment and control groups had the epsilon 4 variant in the gene for apolipoprotein E, which is an important protein in the metabolism of cholesterol. The epsilon 4 variant is therefore not rare, but it increases the risk of coronary disease. It happens also to increase the risk of Alzheimer's disease.

As expected from other studies, death rates were higher in the control patients with the epsilon 4 variant than in control patients without it. The new observation was that simvastatin, in lowering death rates, abolished the excess of deaths in the treated patients with the variant. The epsilon 4 gene variant was the first example of a common variant that identfies a subgroup of patients with coronary artery disease that is simultaneously at higher risk of death and particularly likely to benefit from preventive treatment. With data from another trial of statins, Pradeep Natarajan et al. recently published similar findings. They used a score based on 57 genomic variants rather than just one (Natarajan et al. 2017).

This kind of evidence is hard to come by. The number of patients with a particular variant, or a particular combination of genomic variants, is often too small to permit

a randomized trial, not to speak of the difficulties of getting money for a drug trial with limited market potential.[5]

More fundamentally, Kenneth M. Weiss argues that precision medicine for most patients with a common disease like myocardial infarction is likely to be impossible (Weiss 2017). That is because the genomic background for such diseases, apart from being very complex, differs so much from patient to patient. We therefore "have no way to know how imprecise our predictions are. And that in turn shows why the basis for the promised genomic precision medicine simply does not exist, no matter how much we might wish otherwise" (Weiss 2017).

## 11.3 Genes and Other Levels of Biology

Central to this discussion is our understanding of the role of genes. We tend to misrepresent the gene, or a region of the genome, as an independently acting cause in the development of the phenotype. The cardiovascular physiologist, Dennis Noble, traces this problem to the way the fundamental discoveries of molecular biology in mid twentieth century have been presented to the public and taught to students (Noble 2017). The problem is the oversimplification of "the central dogma of molecular biology" by distinguised scientists like Marshall Nirenberg and Donald D. Watson (in the first edition of his textbook, *Molecular Biology of the Gene*). Nirenberg and others had discovered how RNA is translated into protein, and Watson and Francis Crick had completed the work of many other scientists in developing the double helical model of the structure of DNA.

The simplified version says DNA makes RNA, which makes proteins, and proteins make everything else. That is not how the "central dogma" was formulated by Crick, however. He coined the term in fun and wrote that flow of information is from DNA to RNA and from RNA to protein but not the other way around. He modified the dogma after the discovery of reverse transcriptase, which transfers information from RNA to DNA. There is no suggestion of causation in Crick's version of the central dogma, and scientists agree that it remains correct as modified. Yet the idea of causation is inherent in the simplified version, which is still part of textbooks and part of what the public is led to believe.

What would be a better way to think about DNA? Noble argues that it would be better to think of DNA and genes as parts of a more complicated, multi-level, dynamic and perhaps never fully undestandable web of life. It was on a higher organisational level, in physiology, that his experiments ultimately led him to formulate a theory that he calls biological relativity (Noble 2017). Stated simply, the causal role of any agent in the etiology of a phenotype depends on its relationships with other, often

[5] A trial is unnecessary, of course, when effect of treatment is immediately apparent. Although they have nothing to do with the popular idea of personalized medicine, insulin treatment of diabetic coma and blood transfusion of patients with severe bleeds exemplify such immediate effects.

many, agents. Noble argues that there are no independently acting causal agents. This perspective contradicts the simplified version of the central dogma.

Organisational level is important to Noble's theory, as it is to everyone interested in the discipline called systems biology. You rise through levels of organisation as you move upward from atoms to molecules to cells to organs to whole bodies and on to social levels. Noble's own experimental observation was that there must be downward as well as upward causation in the determination of heart rhythm. Differences in concentrations of potassium and sodium ions (lower level of organisation) between the outside and the inside of the outer membrane of cells determine the voltage across the membrane (higher level of organisation) that allows the transmission of the impulses necessary for the rhythmic contraction and relaxation of heart muscle. In other words, the intracellular and extracellular concentrations of ions control voltage.

Noble could show, however, that the opposite also pertains: voltage affects ion concentrations, i.e. downward causation. The core statement in his argument is therefore that "there is no privileged level of causation." Neither organs, nor cells, nor proteins nor stretches of DNA ("genes") can be said to cause anything on their own. Causation in biology always involves agents, acting with greater or lesser effects, within and between levels of complex and dynamic molecular, biochemical and physiological networks.

Charles Sing and coworkers couch similar ideas in clinical and epidemiological terms when they write that finding that you are at low risk of poor health because of a favorable constellation of gene variants depends critically on the assumption that we know "which variations, in which genes and in which populations, are useful for understanding disease and predicting which individuals will develop disease in which strata of environmental histories" (Sing et al. 2003). That's a mouthful but also a useful condensation of the argument.

Without sacrificing scientific discipline, systems biology, however defined, is an approach to understand the bigger picture in biology. Another AHA statement about the "expressed genome in cardiovascular diseases and stroke" reflects these insights (Musunuru et al. 2017). The problem is to be holistic with discipline.

## 11.4 The Idea of Health

In the AHA statement about cardiovascular health (Lloyd-Jones 2010), discussed at the beginning of this chapter, the authors write that "although there appears to be substantial overlap between the components of cardiovascular health and general health, the committee acknowledges that there are other components to general health related to physical, mental and social functioning, among other things, that have not been addressed here." The caveat is intelligent, as would be expected of these authors, but health by organ system, cardiovascular health for example, nevertheless subverts the idea of health as defined by the World Health Organization (WHO).

The WHO defines health as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity". It is implicit in this

definition that health is more than the sum of states of normal function of various organs, i.e. that, in this case also, the whole is greater than, and certainly different from, the sum of its parts.

That concept of health is particularly clear in English, since health and healing are etymologically related to making whole and indeed to holism and holiness. That relationship holds partly in French, because santé derives from Latin sanitas, less well in German or Scandinavian, since gesundheit or sundhed is derived from svimja, swimming! But OK, it takes good health to swim well, and, at least in English, you're fine if you are doing "swimmingly". Danes are slightly better off than the Germans, since the Danish words, "helse", commonly used as a synonym for sundhed, and the first part of "helbred," have the same derivations as "health".

The concept of cardiovascular health is reductionist, i.e. it is not the health of the whole body or the body in a healthy society or physical environment. It is, instead, a reduction of a complex whole to manageable component parts such as LDL concentrations, blood pressure, answers to life style questions. The arguments against reductionist thinking are well rehearsed and will not be repeated here. In fact, it is a welcome relief from religion and superstition to reduce the well being and understanding of the whole to practical measurements of organs, cells, and molecules.

Health by organ system also matches the necessary specialisation of medicine. There is "cardiovascular health" because there are cardiologists, institutions that train cardiologists and institutions devoted to preventing or promoting heart disease (American or Danish heart associations, tobacco industry, respectively), etc. That also is reductionism.

Reductionism is necessary and fine as far as it goes, but, for the reasons given here, Noble (2017), Sing et al. (2003), Weiss (2017), and the systems biologists are right in fostering the "synthetic mindset" (Sing et al. 2003) that is at least as necessary for any disciplined attempt to understand more of biology.

Given these considerations, the WHO is right to stick to a holistic concept of health.

## 11.5 A Matter of Policy

Across the globe, myocardial infarction and stroke remain major causes of death, especially among older people and especially in the developing world, where these diseases are on the rise (Collaborators 2018). The AHA strategy and similar programs therefore continue to be necessary.

The large-scale occurrence of coronary artery disease and the various forms of stroke is not inevtiable. It increased in mid twentieth century in the Global North, as it is now increasng in the Global South because of many different genomic variants interacting with a host of environmental exposures evolving over time.

We can't do much about time or gene variants, even if we understand a few of them.[6] We can, on the other hand, do something about some of the environmental exposures that we do understand. They include tobacco smoke, certain foods and automobiles. The latter two are also far greater threats to human health than cardiovascular disease, because production of livestock and combustion of fossil fuels and biofuels contribute most of the greenhouse gases that will undo us. There are, in other words, shared causes of climate change and the lesser problem of cardiovascular disease (Faergeman 2007), both of which affect the poor more than the rich, especially in developing countries. It is axiomatic, therefore, that we could promote human health and help the biosphere at the same time by revising policies and subsidies for production of food and energy.

We can also turn to drugs to protect us from cardiovascular disease if not climate change. Precision medicine is at one end of thinking about this option. It is in tune with the individualisation that sociologists say hallmarks our time, but it is a strategy so sophisticated, and, despite the hope of funding agencies, likely to be so expensive, that it's hard to see how it will benefit most of the people at risk of these diseases.

At the other end is the polypill (Wald and Law 2003). It's a "one-size-fits-all" approach, i.e. the diametrical opposite of precision medicine. As an inexpensive combination tablet containing, typically, off-patent drugs to inhibit thrombosis and to lower blood cholesterol and blood pressure, it is a partial but straightforward and blunderbuss solution to the population scale problem of coronary disease and stroke. First suggested many years ago, it has been adopted in India and Iran, it is under consideration in Spain, and it has again been discussed recently in the USA (Joyner and Paneth 2019).

The polypill is by far not a perfect drug from a medical standpoint, but it is cheap and workable. The main problem, I suspect, is that it implicitly recognizes the reality of a dangerous environment which, like climate change, affects us all.

## 11.6 Conclusions

As developed by healthcare organizations, "cardiovascular health" is a good, practical but limited strategy to identify a set of risk factors for common diseases such as myocardial infarction and stroke that allows monitoring of risk in populations. It does not, however, have much to do with physiological function of the heart and blood vessels, and it subverts classical and etymologically faithful ideas of health. Because of the complexity of the genetics of very common diseases, moreover, it will be difficult for precision medicine to satisfy current expectations for population-scale cardiovascular health, however defined. Finally, we should acknowledge that myocardial infarction and stroke are just one aspect of culture, policy and economics that now are bringing us greater misfortune.

[6]Nor is there any reason to think that they have evolved in a way that can explain the waxing and waning of cardiovascular disease.

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# Chapter 12
# Characteristics of Healthy Blood


**Geetika Garg, Sandeep Singh, Abhishek Kumar Singh, and Syed Ibrahim Rizvi**

**Abstract** Blood is a specialized fluid consisting of plasma and cells that circulate through the entire body. Blood also contains essential nutrients, oxygen, and hormones in adequate quantity that makes the blood healthy. Some infections in the blood affect its overall health. These are bacteria and blood borne viruses that make the blood infected. Healthy blood is free from all kind of such infections. Blood plays an important role in regulating the body's systems and in maintaining the dynamic homeostasis. It carries oxygen, nutrients and hormones to living cells and takes away their waste products. Blood delivers immune cells to fight infections and contains platelets that can form a plug in a damaged blood vessel to prevent blood loss. Clinical markers associated with blood are used for the diagnosis of various health issues or pathological conditions. Biomarkers of oxidative stress in erythrocytes and plasma are extensively used to study physiological and metabolic processes. During the course of their natural aging erythrocytes can undergo an apoptosis-like cell death, termed eryptosis. This chapter provides an account of the composition and markers of healthy blood and its role in the maintenance of overall health.

**Keywords** Blood · Plasma · Erythrocytes · WBC · Health

## 12.1 Introduction

Blood is a specialized fluid connective tissue and a lifesaving liquid organ. Blood plays an important role in regulating the body's systems and maintaining homeostasis. It carries oxygen, nutrients and hormones to living cells and takes away their waste

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products. Blood delivers immune cells to fight infections and contains platelets that can form a plug in a damaged blood vessel to prevent blood loss. The blood that runs through the veins, arteries, and capillaries is known as whole blood. Whole blood is a mixture of cellular elements, colloids and crystalloids. Blood is circulated around the body through blood vessels by the pumping action of the heart. The arteries deliver oxygenated blood, glucose and other nutrients to the brain and the veins carry deoxygenated blood back to the heart, removing carbon dioxide, lactic acid, and other metabolic products.

The average human adult has more than 5 L of blood in their body, which is composed of plasma and several kinds of cells. Some of the most common blood tests determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

## 12.2 Characteristics of Healthy Blood

The first characteristic of blood is its colour. Blood that has taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a dusky red or dark red. This is because of binding capacity of hemoglobin to oxygen. Another characteristic of blood is its viscosity which is five times greater than water. It is a measure of fluid's thickness and is influenced by the presence of plasma proteins and formed elements. Viscosity affects the blood pressure and blood flow. The pH of blood also determines its quality, and it ranges from 7.35 to 7.45 in a healthy person. Buffers present in the blood help to regulate pH.

### *12.2.1 Components of the Blood*

Blood has four major components: plasma, red blood cells (RBCs), white blood cells (WBCs), and platelets. A brief description of the constituents of normal healthy blood is given below, and are listed in Table 12.1.

***Plasma***: Blood plasma is the yellowish liquid part of the blood that carries cells and proteins throughout the body. It makes up about 55% of the body's total blood volume. Plasma serves as a transport medium for delivering nutrients to the cells of the various organs of the body and for transporting waste products derived from cellular metabolism to the kidneys, liver, and lungs for excretion. Plasma contains proteins that help blood to clot, transport blood cells throughout the body along with nutrients, antibodies, hormones and proteins that help to maintain homoeostasis. Blood plasma also contains glucose and other dissolved nutrients that makes the blood healthy. Clinical diagnostic markers in plasma and serum are listed in Table 12.2.

***Red blood cells (RBC)***: The percentage of whole blood volume that is made up of red blood cells is called the hematocrit and is a common measure of red blood cell

**Table 12.1** Constituents of normal blood

| S. No. | Blood component | Reference range | |
|---|---|---|---|
| | | Male | Female |
| 1. | Red blood cells (RBC) | 4.3–5.9 million/$mm^3$ | 3.5–5.5 million/$mm^3$ |
| 2. | Hemoglobin (HGB) | 13.5–17.5 g/dL | 12.0–16.0 g/dL |
| 3. | Hematocrit (HT) | 41–53% | 36–46% |
| 4. | White blood cells (WBC) | 4500–11,000/mm3 | 4500–11,000/mm3 |
| 5. | Mean corpuscular volume (MCV) | 80–100 $\mu m^3$ | |
| 6. | Mean corpuscular haemoglobin (MCH) | 25.4–34.6 pg/cell | |
| 7. | Mean corpuscular hemoglobin concentration (MCHC) | 31–36% Hb/cell | |
| 8. | Platelets | 150,000–400,000/$mm^3$ | |

levels. Production of red blood cells takes place in the bone marrow under the control of the hormone erythropoietin and after approximately seven days of maturation they are released into the bloodstream. The morphology of RBC is essentially based on the size which varies in different animals. Generally, erythrocytes have a diameter of 4–10 μm. All non-mammalian (birds, reptiles, amphibians and fish) erythrocytes with a few isolated exceptions are nucleated and contain organelles in their cytoplasm. In humans, the mature form of healthy erythrocyte is normally a non-nucleated, yellowish and biconcave disk shaped (discocyte) when not subjected to external stress (Hillman and Finch 1996). The biconcave shape provides a large surface-to-volume ratio for oxygen delivery and better flexibility in narrow capillaries, and thereby RBCs can easily change their shape, which help them to fit through the various blood vessels in the body. However, while the lack of a nucleus makes a red blood cell more flexible, it also limits the life of the cell as it travels through the smallest blood vessels, damaging its cell membrane and depleting its energy supplies (Diez-Silva et al. 2010; Kuhn et al. 2017). Erythrocyte longevity varies across the major vertebrate groups, in humans the cellular half-life of erythrocytes is about 120 days, and is about 40, 600–800, 300–1400 and 80–500 days in birds, reptiles, amphibians and fish, respectively. These characteristics of RBC are essential for biological functions and can be affected by genetic or acquired pathological conditions. Healthy blood meets all these conditions to maintain fluidity and elasticity of membrane.

***White Blood Cells (WBCs or Leukocytes)***: The WBCs (also called leukocytes) are of two types (Greek "leukos" meaning "white" and "kytos," meaning "cell"). The granular leukocytes (eosinophils, neutrophils, and basophils) are named for the granules in their cytoplasm; the agranular leukocytes include monocytes and lymphocytes which lack cytoplasmic granules (Feher 2012). Pluripotent stem cells in the bone marrow produce myeloid and lymphoid progenitors. The myeloid progenitor differentiates further into a granulocyte/macrophage progenitor that further differentiates into the granulocytes and the monocytes while lymphoid progenitor produces

**Table 12.2** Clinical diagnostic markers in plasma and serum

| S. No. | Markers | Clinical significance | Reference range | Reference |
|---|---|---|---|---|
| 1. | Blood glucose | Supply energy to all cells in the body. Blood glucose higher than that of normal level indicate hyperglycemia and lower level indicates the hypoglycaemia | 70–90 mg/dL fasting, 140 mg/dL 2 h after eating | (Duckworth 2001; Kalra et al. 2013) |
| 2. | Total cholesterol | Used to build the structure of cell membrane and hormones. Help the metabolism to work efficiently | <200 mg/dL | (Lin et al. 2015) |
| 3. | Triglyceride | Stored in fat cells. Contribute to measure the heart health. Harden the artery wall, which increases risk for stroke, heart attack, and cardiovascular disease. High triglycerides are a sign of other conditions such as obesity, diabetes, hypothyroidism, and liver or kidney disease | <150 mg/dL or < 1.7 mmol/L | (Teixeira et al. 2019) |
| 4. | HDL | Helps to remove LDL from blood | 60 mg/dL | (Després et al. 2000) |
| 5. | LDL | Indicate the risk of heart attack, stroke, and atherosclerosis | <100 mg/dL | (Ivanova et al. 2017) |
| 6. | Troponin | Used to detect chest pain or heart attack | 0–0.4 ng/mL | (Al-Otaiby et al. 2011) |
| 7. | Total protein | Necessary for body's growth, evelopment, and health. Level indicated about disease status in different organs | 6–8 g/dL | (Krisko and Radman 2019) |
| 8. | Albumin | Help to diagnose liver and kidney dysfunction | 3.5–5.0 g/dL | (Chien et al. 2017) |

(continued)

**Table 12.2** (continued)

| S. No. | Markers | Clinical significance | Reference range | Reference |
|---|---|---|---|---|
| 9. | Bilirubin | Used to assess liver function. It helps to determine the cause of jaundice and diagnose conditions such as liver disease, hemolyticanemia, and blockage of the bile ducts | 0.2–1.2 mg/dL | (Vítek 2017) |
| 10. | SGPT (ALT) | Specific indicator of liver inflammation. Elevated level indicates the medical problems such as viral hepatitis, diabetes, congestive heart failure, liver damage, bile duct problems, infectious mononucleosis, or myopathy | 7–56 U/Liter of serum | (Ramaty et al. 2014) |
| 11. | SGOT (AST) | Commonly measured as a part of liver function test. Its level elevated also in diseases such as myocardial infarction, acute pancreatitis, acute hemolyticanemia, severe burns, renal disease, muscular dystrophyand trauma | 5–40 U/Liter of serum | (Mavis and Alonso 2015) |
| 12. | Urea | Serum urea concentration reflects the balance between urea production in the liver and urea elimination by the kidneys | 5–20 mg/dL or 1.8–7.1 mmol urea/liter | (Bowker et al. 1992; Vanholder et al. 2018), |
| 13. | Creatinine | Level elevated when there is a significant reduction in the glomerular filtration rate or when urine elimination is obstructed | 0.6–1.2 mg/dL in adult male and 0.5–1.1 mg/dL in adult female | (Winnett et al. 2011), |

(continued)

**Table 12.2** (continued)

| S. No. | Markers | Clinical significance | Reference range | Reference |
|---|---|---|---|---|
| 14. | Uric acid | High blood concentrations of uric acid can lead to gout and are associated with other medical conditions, including diabetes and the formation of ammonium acid urate kidney stones | 2.4–6.0 mg/dL (female) and 3.4–7.0 mg/dL (male) | (Jin et al. 2012; MacFarlane and Kim 2014) |
| 15. | Creatine kinase | Used to detect muscle dystrophy and myocardial infarction | 22–198 U/L | (Blanke et al. 1984) |
| 16. | Sodium | Sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia | 135–145 mEq/L | (Madan et al. 2011) |
| 17. | Chloride | Hyperchloremia, hypochloremia is more closely associated with increased mortality and should certainly be considered by intensive care physicians | 96–106 mEq/L | (Pfortmueller et al. 2018) |
| 18. | Phosphorus | Risk factor for cardiovascular disease | 2.5–4.5 mg/dL | (Gutiérrez 2013) |
| 19. | Lactate dehydrogenase | Lactate dehydrogenase and lactate dehydrogenase isoenzyme measurements in serum in the following main clinical fields: cardiology, hepatology, haematology and oncology | 140–280 U/L | (Huijgen et al. 1997) |

(continued)

**Table 12.2** (continued)

| S. No. | Markers | Clinical significance | Reference range | Reference |
|---|---|---|---|---|
| 20. | C-Reactive protein | Acute-phase marker in tissue injury, infection and inflammation and atherosclerosis. It now has a distinct status of a disease marker in cardiovascular diseases and is well known of its clinical and pathological significance | <3.0 mg/L | (Ansar and Ghosh 2013) |
| 21. | Thyroid hormone | Potent regulators of multiple physiological activities, including cellular metabolic rate, heart and digestive functions, muscle function, brain development, and bone maintenance | Adult: 2–10 μ U/mL Newborn: 3–18 μ U/mL | (Premachandra and Walfish 1982) |
| 22. | Steroid hormone | Help control metabolism, inflammation, immune functions, salt and water balance, development of sexual characteristics, and the ability to withstand illness and injury | NA | (Holst et al. 2004) |

lymphocytes. WBCs are an important part of the body's defense against infectious organisms and foreign substances. To defend the body adequately, a sufficient number of WBC receive a message that an infectious organism or foreign substance has invaded the body, and that they should get to where they are needed, and then kill and digest the harmful organism or substance. Adequate defense include different blood cells having different functions: some fight intruders such as bacteria, viruses, parasites or fungi themselves and render them harmless. Others produce antibodies, which specifically target foreign objects or viruses. Certain lymphocytes can also kill cancerous cells that have been produced elsewhere in the body. There are five types of WBC:

1. Neutrophils: each $mm^3$ of blood contains 4000 to 11000 WBCs of which neutrophils comprise of 50–70% of the white cell count. The neutrophils are the most numerous type of the leukocytes. During tissue injury, they leave the circulatory system early in the inflammatory response to bacterial invasions.
2. Basophils: These are the least in number comprising <1% of total WBCs. Structurally and functionally they resemble mast cells. However, basophils originate in the marrow whereas mast cells originate from precursor cells in the connective tissue. Both basophils and mast cells contain secretory granules that store histamine and heparin, among other chemicals.
3. Eosinophils: These cells make 4% of total WBCs but are readily identifiable in blood smears because their cytoplasmic granules take on an orange-red to bright yellow color when stained with eosin. They have roles in hypersensitivity and allergy and their number increases during allergic conditions such as hay fever and asthma.
4. Monocytes: These have several functions, including bacterial removal, are active in inflammation and in repair of damaged tissues, and are the largest of the leukocytes. They are released into the blood from the marrow in an immature form with little phagocytic ability. They circulate in the blood until they find a suitable home in the tissues, where they greatly enlarge to become tissue macrophages. Their life span varies from months to years, depending on their activity.
5. Lymphocytes: These are the second most common WBC (approximately 20–25% of the white cell count), and are divided into two major types: B lymphocytes, which make antibodies, and T lymphocytes, which destroy cells infected with viruses. All three cell types derive from a single lymphoid stem cell. The thymus modifies the cells that become T-lymphocytes and these cells promote cell-mediated immunity. The bone marrow influences the cells that become B cells, and these cells differentiate to form plasma cells which produce circulating antibodies that comprise humoral immunity. These cells work together to defend the body against foreign substances, such as bacteria, viruses, and cancer cells.

***Platelets***: These are small enucleate cell fragments that circulate in blood and play a crucial role in managing vascular integrity and regulating homeostasis. Primarily they are associated with hemostasis, which is to initiate blood coagulation. Although very dynamic, they usually remain in an inactive state and get activated only when a blood vessel is damaged. Hemostasis or blood coagulation is not the sole function of platelets; rather it is employed in several multifunctional attributes monitoring the homeostasis of the body.

## 12.3 Clinical Markers for Health Associated with Blood

Blood is continuously exposed to plenty of metabolites and free radicals. The overall health of organisms and a wide range of disorders associated with blood can be detected by complete blood count (CBC). A CBC test measures several components

and features of the blood, including RBCs, WBCs, hemoglobin, hematocrit and platelets. Abnormal increases or decreases in cell counts may indicate that a person has some kind of ailment that calls for further evaluation. The disorders of RBC can be divided into those of decreased RBC mass (anemias) and those of increased RBC mass (erythrocytoses). The excess RBC usually create no problems but may cause blood clots in some people.

A higher than normal count of WBC leads to a condition known as leukocytosis, which is usually caused by bacterial infection, tissue damage, and inflammatory diseases (Wahed and Dasgupta 2015). A lower count, a condition known as leukopenia, is often associated with bone marrow deficiency, certain viral infection, and severe bacterial infection. Platelets are also involved in the fundamental biological process of chronic inflammation associated with disease pathology. Primarily, platelet activity is associated with the initiation of coagulation cascades. The decrease in the number of platelets in the blood is known as thrombocytopenia. An increase in platelet count in which the platelets do not work properly is the condition known as thrombocythemia.

## 12.4 Blood Components as Markers of Health

Blood provides the necessary biological information for the diagnosis of various pathological conditions. In these conditions, biomarkers are used as indicators of a biological factor that represents the health status.

### *12.4.1 Role of RBC in the Maintenance of Health*

The most important and well-known function of erythrocytes is the transport of oxygen from lungs to tissues. Erythrocytes are also essential in maintaining blood pH and carbon dioxide transport. In addition, RBCs are well equipped with antioxidant systems, which essentially contribute to their function and integrity. Damage of red cell integrity, defined as hemolysis, has been shown to significantly contribute to severe pathologies, including endothelial dysfunction (Crawford et al. 2004). Erythrocytes are also involved in tissue protection and the regulation of cardiovascular homeostasis through NO metabolism and release of bioactive molecules (Cortese-Krott et al. 2012). RBCs contain numerous sources of oxygen along with high levels of iron, which in its free form acts as a catalyst of ROS production. RBCs also have limited capacity to restore damaged elements due to loss of protein expression during erythropoietic maturation (Zivot et al. 2018). The combined action of all endogenous antioxidant systems makes RBCs very resistant against oxidation as well as an efficient systemic redox buffering system. These properties help to keep RBC healthy and well functioned. The malfunction of antioxidant defense or conditions of increased oxidant production have severe consequences for RBCs at

subcellular level. This includes the degradation of Hb and other proteins, disturbance of ionic homeostasis, hindered RBC deformation, interference with erythropoiesis and enhanced exposure of phosphatidylserine (Mohanty et al. 2014). Furthermore, RBC membranes consist of high concentration of PUFA that make them susceptible to lipid peroxidation leading to loss of membrane integrity and decreased activity of enzymes associated with erythrocyte membrane (Kaestner and Minetti 2017).

### *12.4.2 Role of WBC in Maintenance of Health*

Normal WBC count is important for determining health status as it helps to understand what is going on inside the body during a variety of health situations. Besides acting as an indicator of current health status, white blood cell count has also been suggested as a predictive and prognostic marker for a number of chronic diseases (Madjid and Fatemi 2013; Wang et al. 2018). As the WBC count goes up, it could mean inflammation somewhere in the body. The role of white blood cell count in pathogenesis of various diseases such as diabetes, cardiovascular disease, and obesity-related disorders has been reported (Twig et al. 2012; Veronelli et al. 2004). Recent studies reveal that higher WBC contributes to atherosclerotic progression and impaired fasting glucose. Most white blood cell disorders are either a type of cancer or proliferative disorder.

### *12.4.3 Role of Platelets in the Maintenance of Health*

Platelet activity is associated with coagulation cascades. Blood vessel damage causes the sub-endothelial surface to be the primary target site for platelet action. Pro-aggregatory stimuli (platelet agonists) promote the action of platelet adhesion to the sub-endothelial surfaces. During this process, platelets change their shape, release their granule contents, and gradually form aggregates by adhering with each other (Vinik et al. 2001). Thus, platelets primarily function to minimize blood loss. Platelets are also involved in the fundamental biological process of chronic inflammation associated with disease pathology (Ghoshal and Bhattacharyya 2014). Platelets are actively involved in secretion of molecules like GPIIb, IIIa, fibrinogen, catecholamine, serotonin, calcium, ATP, ADP, which are involved in aggregation. Differential expressions of surface receptors like CD36, CD41, CD61 have also been measured in several diseases. Platelet activation and dysfunction have been implicated in diabetes, renal diseases, tumorigenesis, Alzheimer's, and CVD.

## 12.5 RBC and Aging

The aging process of RBC is considered an issue of special scientific and clinical interest. It represents a total of unidirectional, time-dependent but not-necessarily linear series of molecular events that finally lead to cell clearance (Aminoff et al. 1992). Under normal circumstances, human RBCs live approximately $120 \pm 4$ days in blood circulation, implying the existence of tightly regulated molecular mechanism(s), responsible for the programming of the lifespan and the nonrandom removal of senescent RBCs (Badior and Casey 2018; Franco 2009; Walsh et al. 2002). RBC is a favorite subject of investigation of cellular senescence (Clark 1988; Singh et al. 2016b). Although RBCs lose their subcellular organelles, they maintain a plethora of cellular functions like anaerobic glycolysis, the pentose phosphate shunt, cellular signaling and possibly even a variant of programmed cell death called eryptosis (Lang et al. 2005; Minetti and Low 1997). RBCs are maintained in a functional state until the very end of their life and go back to the bone marrow to die (Bernhardt and Ellory 2003). RBCs experience a range of continuous metabolic and physical damages as they age, such as membrane vesiculation, haemoglobin (Hb) modifications and progressive failure of both, cellular homeostasis and antioxidant defenses (Piomelli and Seaman 1993; Willekens et al. 2003). The increase in RBCs density, the nonenzymatic glycation of Hb and the deamidation of protein 4.1b to 4.1a have been widely used as sensitive RBC age markers (Bosch et al. 1992; Lutz et al. 1992; Mueller et al. 1987).

## 12.6 Markers of Oxidative Stress in Erythrocytes and Plasma

RBC and their membrane have always been important media for study due to the important role they play in various physiological and metabolic processes. Erythrocytes have been increasingly studied as they are the easiest available human cell type. Throughout its entire life, the organism is confronted with oxidative stress due to the production of ROS and reactive nitrogen species (RNS). ROS are normally generated as by-products of oxygen metabolism and generate free radical chain reaction. High levels of oxidative stress have been linked with the increased incidence of a variety of health issues. At moderate concentration ROS play several beneficial physiological roles in cell signaling and induce mitogenic response (Genestra 2007). They are needed to synthesize some cellular structures and to be used by the host defense system to fight pathogens.

Various markers of oxidative stress in erythrocytes and plasma are listed in Table 12.3. One of the most putative markers of oxidative stress is the measure of total antioxidant status. Total antioxidant status is measured in terms of 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH) assay, 2,2-azobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assay and ferric reducing ability of plasma (FRAP) assay.

**Table 12.3** Oxidative stress biomarkers in erythrocytes and plasma

| S.No. | Biomarkers | Clinical significance | Reference |
|---|---|---|---|
| 1. | Protein Carbonyls | Marker of plasma and membrane protein oxidation. Formed due to the protein-pro cross linking and oxidation of protein backbone | (Sangeetha et al. 2005; Singh et al. 2016a) |
| 2. | Advanced oxidation of protein products | Dityrosine-containing cross-linked protein products Plasma level of AOPP elevated during various diseases | (Garg et al. 2017) |
| 3. | Total thiols | Product of S-thiolation reaction, act as an antioxidant. Alteration in thiol-disulphide redox status has been observed in specific groups of diseases such as cardiovascular, cancer, and neurodegenerative | (Oliveira and Laurindo 2018; Singh et al. 2019) |
| 4. | Reduced Glutathione | Most abundant non protein thiol helps in maintaining intracellular redox environment. Erythrocyte GSH level get reduced during oxidative stress | (Singh et al. 2017, 2018) |
| 5. | Plasma Membrane Redox system | Oxidoreductase system, tranfers electron from intracellular donor to extracellular acceptor and provide antioxidant protection against induced oxidative stress | (Adlard and Bush 2011; Hyun et al. 2006; Rodríguez-Aguilera et al. n.d.; Singh et al. 2017) |
| 6. | Malondialdehyde | Byproduct of lipid peroxidation, play an important role in the pathogenesis and progression of several diseases. Affects the variety of membrane related functions, alteration in membrane fluidity, permeability and loss of function | (Garg et al. 2017; Singh et al. 2016a) |

(continued)

**Table 12.3** (continued)

| S.No. | Biomarkers | Clinical significance | Reference |
|---|---|---|---|
| 7. | Lipid hydroperoxides | Formed from lipid autooxidation and photooxidation. Plama and membrane level of LHP get elevated during diseases associated with oxidative stress | (Gönenç et al. 2006; Peña-Bautista et al. 2019; Singh et al. 2018) |
| 8. | Acetylcholine esterase | Maintains the erythrocyte membrane potential. Marker of erythrocyte aging and RBC membrane integrity | (Suhail and Rizvi 1989) |
| 9. | Sodium potassium ATPase ($Na^+/K^+$-ATPase) and Plasma membrane calcium ATPase (PMCA) | Maintains the intracellular ionic homeostasis and electrochemical gradients across the membrane. The activity of NKApump is considerably impaired during the alteration in homeostasis mediated by oxidative stress | (Marchesi 2008) |
| 10. | Sodium Hydrogen exchanger (NHE) | NHE activity contributes to overall cell damage. Play vital housekeeping roles in the maintenanceof intracellular ionic homeostasis | (Dubyak 2004; Singh et al. 2016b; Várady et al. 2015) |

There is a strong correlation between antioxidant capacity and oxidative damage during aging (Pandey and Rizvi 2010).

Under physiological aerobic conditions, erythrocytes are continuously exposed to oxidants derived from endogenous as well as exogenous sources. Exposure of erythrocytes to physiological oxidative stress leads to lipid peroxidation that could change the membrane composition, inducing conformational changes and protein cross-linking in membrane proteins and, these changes may lead to abnormal cell morphology and hemolysis (Garg et al. 2019; Berzosa et al. 2011; Ciccoli et al. 2013; Freikman et al. 2011; Pytel et al. 2013). Lipid peroxidation is usually measured in terms of malondialdehyde (MDA) and lipid hydroperoxides (LHP). RBCs have also been reported to be associated with a number of biomarkers for age and senescence, these include reduced glutathione (GSH), the plasma membrane redox system (PMRS), rate of cysteine influx and antioxidant enzymatic activity. Due to these robust and reproducible age biomarkers, erythrocytes have become a suitable model for aging research (Kumar and Rizvi 2014; Rizvi et al. 2006, 2009; Rizvi and Maurya 2008). PMRS is an oxidoreductase system that transfers electrons from intracellular donors to extracellular acceptors such as ascorbate free radical and convert it

into ascorbate. Erythrocyte PMRS provides antioxidant protection against oxidative stress. RBCs possess effective enzymatic antioxidant systems that neutralize the ROS into non/less reactive species. Superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and catalase (CAT) are some of the endogenous enzymatic defense systems in all aerobic cells which get affected by advancing age (Finkel and Holbrook 2000; Wojciech et al. 2010). They give protection by directly scavenging superoxide radicals and hydrogen peroxide (Pandey and Rizvi 2010; Scandalios 2005). These antioxidants counteract oxidative stress and mitigate its effects on individuals' health as they are free from important side effects. On the other hand, some prooxidants can be as well useful to human health particularly in cancer (Pizzino et al. 2017). Thus oxidative stress, although being one of the major harms to individual's wellness and health, can also be exploited as a treatment monitoring tool when finely tuned inside human organism.

## 12.7 Conclusion

In this chapter, we have reviewed the basic components of blood, including the different factors that can be used to determine the health status of the blood. Various clinical and oxidative stress biomarkers in the blood help to understand the dynamic homeostasis at the physiological level. Furthermore, blood analysis provides an array of the minimal-invasive procedures that can be used to assess important clinical biomarkers of health and deviations from it.

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# Chapter 13
# Immunity and Health


**T. Fülöp, A. A. Cohen, A. Larbi, and J. M. Witkowski**

**Abstract** Health is very difficult to define. In 1948 the WHO tried to conceptualise health, which was in its time revolutionary. This was slightly amended in 1986 by introducing a new approach and concepts. However, many authors from various scientific horizons criticized this definition and tried to give an alternative. One alternative is that of a dynamic process which contributes to a functional and complete life. This state of health should be maintained at each moment of life and we argue that immunity is meant to play this role by protecting an organism from external (pathogen, injury) or internal (cancerous transformation of the cells) challenges. It is in fact destined to do so during the entire lifespan and its dwindling capability to neutralize challenges results in a shortening of the lifespan. However, the constant challenges by environmental and endogenous pathogens/stressors to the immune system may dysregulate it and lead to chronic inflammation underlying most of the modern chronic diseases. This dysregulation may be avoided or reset largely thanks to a healthy lifestyle. Thus, health and immunity are intricately linked and it is important to understand the interactions to boost the immune system for sustaining health.

**Keywords** Health · Immunity · Innate immune response · Adaptive immune response · Microbiota · Vaccination

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## 13.1 Introduction

Health is a relative notion which has generated various definitions, concepts and ways to understand it (McCartney et al. 2019). In most cases, health is defined as a lack of disease, whether this is a physical, mental or cognitive disease. However, in many cases health should be something more complex including some other major attributes for being healthy (Leonardi 2018; Last 2007). There is of course a big difference between being healthy and feeling healthy. The former can be more objective and the latter more subjective. Another question is whether the concept of health is identical for everybody or is person dependent. Furthermore, heath is time, age, geography or space dependent (Card 2017). Finally, a legitimate question is how the various systems of the body are contributing to health on a local or more general level. Certainly, some systems, such as the immune or the neurological systems, are more integrative than others, like the muscle-skeletal system (Fulop et al. 2014). In this chapter, we will expose our view on what constitutes health and how it may be sustained by immunity.

## 13.2 What is Health?

### *13.2.1 Health is a Very Difficult Concept to Define*

Already in ancient societies there were priests who said prayers and addressed sacrifices to gods when somebody was ill or injured or for the well-being of the members of the community. Ever since medicine exists, there have been numerous attempts to conceptualise health against the religious belief that health was a gift from god and that when the person was no longer healthy this was a sort of punishment or the failing of the good will of the gods. Since Hippocrates, according to his time, health was more a public health-oriented concept embedding the individual's health into what we could call today a more appropriate health habit. This was in essence a more pragmatic approach as at this time no scientific definition of health could be conceptualised (Ustun and Jacob 2005). During the next centuries, health still remained a nebulous concept despite the growing scientific knowledge (Dubos 1959) and no real consensus appeared to emerge until 1948 when the World Health Organization came out with a definition which was meant to create unity on this important concept. This definition was, health is "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (Constitution of the World Health Organization 2006). At the time, this was a revolutionary definition as it stated that health is more than the absence of disease. However, the absolute statement of complete well-being is almost unattainable. It is also questionable whether and how science can contribute to this definition and to health per se considering that the determinants of well-being are very broad and from completely different fields. That is why some advocated to revise this definition in many aspects including the more

prominent role of technologies, psychology, culture, humanities and even philosophy (Starfield 2001).

Without completely putting aside the original WHO definition many have recently tried to challenge or at least better conceptualize the concept of health (The Ottawa charter for health promotion 1986). The WHO itself in 1986 better clarified what was meant in its definition by stating: "*A resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities.*" This is an important clarification as it means that from a steady state of health definition it moved to a dynamic definition conceptualizing that health is a resource to support an individual's function in wider society (Bircher 2005; McCartney et al. 2019). A healthful lifestyle provides the means to lead to a full life. This concept of health is much closer to a scientific conceptualization of health as it may include indirectly the notion of homeostasis/homeodynamics meaning that a resource may be used in several ways in a given environment and this can lead to better or poorer health (Rattan 2018). This notion also includes a personal responsibility towards health in a social setting. This "homeodynamic approach" has lead to further reflection from scientists who suggested defining health as the ability of a body to adapt to new threats and infirmities (Flick et al. 2003; Huber et al. 2011). They base this on the idea that modern science has dramatically increased human awareness of diseases and how they work in the last few decades (Chmielewski 2020).

### *13.2.2 Types of Health in View of the Larger Dynamic Concept of Health*

The most common components of health considered as a resource for functioning in a given setting of society are the physical and mental health. As mentioned, this is also determined by all the surroundings which could be spiritual, emotional or even financial. However, these are just environmental factors which impact on health but are not directly part of the homeodynamic definition of health.

Thus from a physical perspective health can be conceptualized as the balanced functions of the body from the molecular to the organismal level, i.e. being able to reset the homeostatic clock to the optimal functional level after any stress by reducing the effects of the consumption of the pre-defined reserves and as such diminishing the effect of homeostenosis (Fossion et al. 2018; Kahn et al. 2017). This also means that health is not a static property of 'lack of disease', but is rather a dynamic response of the whole organism to any challenge that could mobilize the body's resources at various levels and extents and not going back to the original state (Bircher 2005). Of course, challenges to the body differ in their nature, intensities, localisations, durations and extensions. This means that the more significant a challenge, the more resources are used and the more quickly the utilisation of the reserves will occur, either leading to acute or more permanent chronic diseases. This also implies that

with "smaller" challenges, our body can better maintain its health by readjusting or even increasing the threshold of dysfunction, leading to the capacity to tolerate greater offenses (Calabrese 2015). This phenomenon is called hormesis and is very important for the dynamic health concept (Mattson 2008).

These notions also imply that health as a dynamic process may be improved even in the absence of disease, not only by what we naturally called hormesis but also with a healthy lifestyle (Bodai et al. 2018). So, the peak performance of the body may increase the original reserve of the body by regular exercise, balanced nutrition, adequate stress management and rest (Ruegsegger and Booth 2018). Maintaining physical fitness, for example, can protect and develop/increase the endurance of a person's breathing and heart function, muscular strength, flexibility, and body composition (Lavie et al. 2019; Ozemek et al. 2018). Minimizing hazards in the workplace, practicing safe sex and good hygiene, or avoiding the use of tobacco, alcohol, or illegal drugs, may all help to reduce the risk of injury and maintain overall physical health and well-being (Katz et al. 2018). Nevertheless, the benefits of some of these interventions still depend on many factors considering that the person practising them should be in good health, or a least largely controlling some adverse risk factors, and that the social environment should also be favourable. While these interventions may just be wishful thinking in a hostile environment, the notion of health as a dynamic process may still apply to the person if we consider it as not being a perfect goal.

Going further, when the dysregulation of homeodynamics is important/strong enough a disease may appear, but this need not mean that health is no longer there. This may just be an "accident" and the consequences may be fixed which is the role of medicine by applying various treatments and either the organism returns to its original "healthy" functioning or adopts another homeostatic, functionally "healthy" state or in extreme cases may die. There may be many aggressions complying with this idea, like cardiovascular diseases and more specifically a myocardial infarction. In this case, the necrotic damage to the heart may be small enough for the patient to survive, but for the price of limited heart pumping function bearing on functions of all perfused organs, which apply their own homeostatic mechanisms to adapt to lower perfusion; thus, with time, the organism remains relatively healthy but the processes maintaining this state change. If the damage is large enough, perfusion (even if maintained) will be too reduced to support function of brain, kidneys etc. and the patient dies. Another homeostatic functioning "healthy" state may be in this way of thinking a chronic disease (Nordenfelt 2007). Indeed "health" is referred to here as a process rather than a state, spanning some range of adaptive reserves; in the presence of a chronic disease these reserves are not immediately and entirely depleted and so the patient may retain valuable means for a satisfactory daily life (Huber et al. 2011; Bradley et al. 2018).

Mental health refers to a person's emotional, social, and psychological well-being. Mental health is as important as physical health to a full, active lifestyle (Prince et al. 2007). However, this type of "health" is much harder to define than the physical one. Most of the time, mental health depends on the person's unique and very wide

experiences, which are largely determined by the surrounding social environment (Manwell et al. 2015).

Thus, it should be clear that physical and mental health are heavily interrelated and intricated. Neither of them exists without the other. That is why it is more adequate to speak about health as a whole, as the WHO defines it, rather than trying to split it into its components. Even if we approach "health" as a whole, rather than through its different types, we may still admit that perhaps one unifying holistic definition of health does not exist.

### *13.2.3 Determinants of Health as a Whole in the Perspective of a Dynamic Concept*

The WHO suggests that various factors may have an impact on health, such as where a person lives, the state of the surrounding environment, their genetics, income, educational level, and relationships with friends and family. These are of course very important factors for understanding health. However, as mentioned above, what is of basic importance for health besides genetics, which can be "favorable" or at different degree "unfavorable", is the whole homeostatic functioning of the body. In an evolutionary perspective, this homeostasis generally exhibits an optimal functioning to respond to adversity so that health may be maintained for reproduction purposes (Gluckman et al. 2011). This also suggests that health does not entirely depend on environmental factors (Leonardi 2018). They will of course modulate the basic bodily setting but this may nevertheless function very well even in adverse lethal conditions and the contrary may also be true. Thus, again health should be considered as a dynamic basic body function which may be strengthened and modulated by many environmental factors but is basically determined by its fundamental homeostatic biological functioning (Bradley et al. 2018; Wells et al. 2017).

It may be apparently true that a higher socioeconomic setting can lead to better health as individuals can have better lifestyles, better jobs and financial situations and consequently also better healthcare (McCartney et al. 2019). However, this is only a sort of plaster on the basic evolutionarily well-developed, dynamic homeostatic balance that underlies health.

In contrast, poorer individuals living in miserable conditions and experiencing heavy stress from their living, financial, mental conditions should experience a poorer health, and this is worsened if they do not have proper access to health care (Simandan 2018). While this is true on a social level, it may not be true on the biological level since the bodies of poor individuals are functioning in fundamentally the same way as those who are wealthy. Nevertheless, in practice, poor people generally have worse health than wealthy people. Very often as proof for this discrepancy, the longer life expectancies for those living in good socioeconomic conditions are compared to those living in lower socioeconomic conditions. However, the "blue zones" where people have the longest life spans are in the poorer zones of the world, such as

Sicily, Sardinia, Costa Rica (Buettner and Skemp 2016). These considerations do not entirely support the concept that health is strongly determined by the socio-economic, cultural environment but needs further research (Baum 2005). A "healthy" lifestyle does not depend exclusively on the wealth of the people or the country.

This suggests that the basic root of health is different for each person. Even if the basic biological networks of genes, molecules, proteins, sugars, lipids remain largely identical, the pathways linking these networks may differ in their connectivity from person to person. Of course, all this can be modulated by the environment, but only to a degree. This also means while it will never be possible to completely avoid disease, it is still largely attainable for individuals to do as much as they can, depending on their current condition, to develop and maintain homeostatic resilience to prepare the body and mind to deal with problems (Schorr et al. 2017).

Combining this concept of health with the increasing numbers of older individuals in society, could health still be defined as a state without any diseases, or can one be considered "healthy" even in the frame of chronic diseases? If the latter is true, this would certainly mean that there is not a binarity of 'healthy' or 'unhealthy' states, but rather a broader spectrum from "full health" to "full lack of health" (McCartney et al. 2019). In our lifetimes, we all experience periods of good and bad health. And we may even experience these two states at the same time.

In this context, Huber and colleagues (2011) suggested that the problem with the WHO definition is the absoluteness of 'complete' well-being. This, they suggest, inadvertently contributes to the 'over-medicalization' of the population. Furthermore, Huber et al. suggested that, owing to the aging population and the increasing focus on the management of communicable diseases, the WHO's definition is no longer fit for its purpose. They propose shifting the emphasis of health towards the ability to adapt and self-manage in the face of social, physical and emotional challenges. This echoes the concept of resilience, which has been defined as 'the capacity for populations to endure, adapt and generate new ways of thinking and functioning in the context of change, uncertainty or adversity' (Herrman et al. 2011). Ultimately, at an individual, not populational level, it is how we manage—and adapt to—these circumstances that defines our health status.

Considering the more advanced definition of health as described above, having a disease but still feeling healthy, are no longer mutually exclusive, especially for older adults (Lim et al. 2017). Managing multiple chronic diseases, which were previously considered as deadly diseases, is the norm for older people—approximately two-thirds of adults over age 65 and more than three-quarters over age 85 are managing two or more diseases, while many report being in good or very good health. High blood pressure, diabetes, high cholesterol, arthritis, kidney disease, thyroid conditions, and osteoporosis are among the most common chronic conditions, but with regular access to continuous medical care, these and many more can be managed, sometimes even without overt symptoms (Cordier et al. 2017). Indeed, in this way of thinking the elderly may feel "healthy" and because of this relatively efficient chronic disease management they can still function, which is presently either individually and socially overemphasized (Rigo et al. 2017). However, it should be clearly stated that this is not health but an adaptation of the concept of health to our current situation

with the graying of society (the "silver tsunami") (Huber et al. 2011). We should not consider chronic diseases as the normal attribute of aging and just claim that their management leads to some sort of health (Fulop et al. 2019a).

This was amplified in the 1986 Ottawa Charter for Health Promotion as already mentioned. The definition of health becomes "The extent to which an individual or group is able to realize aspirations and satisfy needs, and to change or cope with the environment". As already mentioned "health becomes a resource for everyday life, not the objective of living; it is a positive concept, emphasizing social and personal resources, as well as physical capacities" which largely exclude disease management as part of health, even if it seems to apply here. (Health promotion: a discussion document. Copenhagen, WHO 1984.)

After these considerations on health, and concluding that there is no "good" or "bad" definition of health as all of them carry some aspects of overall health, we can now ask whether there is a special function in the body that can extensively contribute to health. One can argue that there are several, but we would stress that one seems to be a super-agent for health and this is immunity. It is also true that this is better considered as the neuro-endocrine-immune system considering their intricate relationship.

## 13.3 Immunity Considered in the Perspective of Health

What is the role of immunity? The answer to this question will determine its relationship towards health. Immunity is meant to protect the organism from attacks coming from outside (pathogens) and inside (mainly neoplasms) at all moments of our life (Monti et al. 2017; Müller et al. 2019). While we might ask whether this is good or bad, in reality it is neither good nor bad as these notions are not scientific, but exclusively moral or religious.

The basic situation is that the body is under incessant attack and it should imperatively defend itself against these aggressions. The immune system does not know whether this is good or not but has exclusively one aim, which is to eliminate the aggressor as it could render the functioning of the whole body detrimental and even life-threatening. So, it will use every possible means inbuilt in its functioning to satisfy this need of the organism. Most of the time it is efficient, and we have a *restitutio ad integrum.* In other moments, it fails and various consequences may arise that threaten either directly or chronically one's health, such as in the case of inflammation-related pathologies (Fulop et al. 2019b).

So, the next question is: how is immunity built to defend the organism and as such maintain its health? There are two levels of immunity which are closely related but somehow sequential (Medzhitov and Janeway 1997; Kennedy 2010). The first is innate immunity, which exists in all living organisms (starting from invertebrates) and is a very complex system in humans (Robertson 1998). The next level is the adaptive immunity, which is an intelligent system as it may remember all specific

aggressions and can react specifically and quickly the next time (Bonilla and Oettgen 2010). The latter is called immunological memory.

Innate Immunity

Basically, innate immunity is meant to eliminate all aggressions without making any differences between the aggressors. This means that there are pattern recognition receptors to recognise patterns which are expressed by similar aggressors, such as viruses or bacteria. This system is more complex than was previously thought because of the cell–cell interactions, mediator-cell interactions and mediator-mediator interactions (Barik 2016; Kufer et al. 2016; Vidya et al. 2018). There are several cells comprising this system: some of them are very rapid to react, such as neutrophils (pas de majuscule) and NK cells, while others are somehow slower to react but last for a longer time, such as the monocytes/macrophages and dendritic cells (Fulop et al. 2019b). These cells secrete various substances called cytokines and chemokines. They also secrete powerful killing substances such as reactive oxygen and nitrogen intermediates, and anti-microbial peptides such as LL-37 and many more (de Paula and Valente 2018). In the meantime, intracellularly they generate phagosome acidification and autophagy induction to kill the invading pathogens (Münz 2014). This system is thus well equipped to eliminate the aggressors and keep the organism's health intact.

One very interesting newly conceptualised attribute of these cells is their trained innate memory (Kleinnijenhuis et al. 2012; Netea and van der Meer, 2017; Fulop et al. 2016; Topfer et al. 2015). What does it mean functionally and what does it mean for the maintenance of health? This concept states that each encounter with an aggressor being alive or being a substance makes epigenetic and metabolic changes inside of the long-lived cells such as macrophages and NK cells. These changes induce a permanent imprint in the cell machinery which during another encounter with a substance may react more rapidly and strongly to this new challenge. This is a complete paradigm change in immunity as this means that even the innate immune system is able to "remember," which strongly suggests that most of the time innate immunity is enough to eliminate an aggressor without calling adaptive immunity into action. This newly discovered function of the innate immune cells may have a far-reaching health maintenance effect.

What is the mechanism by which the aggressors elicit a response from the cells? These cells possess external/membrane receptors as well as internal receptors recognizing various aggressors (Gulati et al. 2018). These receptors, such as the TLR, the NOD-like or RIG-like receptors, are able to recognise the challenge and send powerful signals to the cell to secrete various mediators, either pro- or anti-inflammatory ones (Sellge and Kufer 2015). The numerous independent or interrelated intracellular signaling pathways lead to the activation of transcription factors, which when translocated to the nucleus induce the transcription of mediators (Cao 2016). These mediators are meant to participate in the clearance of the aggression. Once these mediators are secreted, they may reinforce the activities of the innate immune cells or go on to activate the adaptive immune system.

It should also be mentioned that soluble mediators, such as the complement system, are also part of the innate immune system (Hajishengallis et al. 2017). This system is extremely efficient to assist the innate immune cells to clear the aggressors.

The failure of any of the components of the innate system can lead to various dysregulations or even to overt diseases (Fulop et al. 2018). Thus, it is very important in a systems biology approach to consider each part not only alone (in silo) but in connection with the functioning of the others (Zak et al. 2014; Franceschi et al. 2017). Moreover, many other mediators secreted by the neuroendocrine system, such as insulin, acetylcholine, or adrenaline, influence the functioning of the innate immune system (Kvetnoy 2002; Bateman et al 2018). These mediators contribute to the homeostatic maintenance of the innate immune system for an efficient defence function.

Of course, one other very important determinant of this defence system is the metabolism, either inside or outside, of the cells. Inside of the cells, the possibility to switch from OXPHOS to the aerobic glycolysis is essential for a rapid and efficient clearing function (Hotamisligil 2017). This would ensure sufficient and effective ATP production via intact mitochondrial function. Concomitantly, the external metabolism assured by nutrition needs to supply enough macro- and micronutrients for optimal functioning (Scheja and Heeren 2018). Thus, for the innate immune system to fully play its health maintenance role a complex coordination of internal and external processes is necessary. Severe failures in this finely regulated system will lead to disastrous health consequences.

Adaptive Immune System

This part of the immune system has developed to continue to protect the organism when the innate immune system has failed or is not efficacious enough. This adaptive immunity is meant to help to develop a specific memory-controlled effector response to the specific Major Histocompatibility Complex (MHC-) restricted challenges, as well as to reinforce the activity of the macrophages. The $CD4^+$ T helper lymphocytes will orchestrate the immune response via various immune mediators (Schorer et al. 2019) and help the development of the cytotoxic $CD8^+$ T cells, which will ultimately kill or neutralise the aggressor (Zander 2019). The well-orchestrated function of the adaptive immune system is essential to the health of the organism.

$CD4^+$ T cells help the activity of other immune cells by releasing T cell cytokines (Sun and Zhang 2014). These cells may help, suppress or otherwise regulate immune responses (Chalmin et al. 2018). They are essential in B cell stimulation and antibody class switching, in the activation and expansion of cytotoxic T cells, and in maximizing bactericidal activity of phagocytes such as macrophages. IFNγ, also secreted by the innate cells, will induce the Th1-helper response. This will result in the immune inflammatory mediator secretion and the first step in the elimination of the immune challenge. This will lead to the formation of effector and memory cells. The latter will specifically remember the antigen which initiated the adaptive immune response.

$CD8^+$ T cells are effector/cytotoxic T cells (Tc) (Chen et al. 2018). They are activated by specific antigens presented via the immune synapse to the TCR which

will activate in the two-signal model the $CD8^+$ T cells responses. Thus, they will be able to eradicate the virus-infected cells and cancer cells. When exposed to these infected/dysfunctional somatic cells, Tc cells release the cytotoxins: perforin, granzymes, and granulysin (Baterman et al. 2018). Through the action of perforin, granzymes enter the cytoplasm of the target cell and their serine protease function triggers the caspase cascade, which is a series of cysteine proteases that eventually lead to apoptosis (programmed cell death). Perforin may also facilitate the entry of $Ca^{2+}$ into cytoplasm which in turn activates calpain proteases, themselves activating the caspases (Jones et al. 1990; Łopatniuk and Witkowski 2011). These Tc cells need the collaboration of dendritic cells (APC), $CD4^+$ T lymphocytes, other $CD8^+$ T cells, and the CD40 molecule. The orchestrated action of the adaptive immunity aiming to eliminate the aggression threatening the health of the organism is essential to remain healthy. This is also illustrated by the fact that if at any level of this response the cells become dysregulated then their health-keeping role can become a pathology-inducing role, such as with chronic viral infections, diabetes type 1, or autoimmune rheumatic diseases including rheumatoid arthritis (Laban et al. 2018; Carvalheiro et al. 2015).

Therefore, to avoid this dysregulation in-built mechanisms are there to control this activation, such as the T cell surface markers/receptors leading to the deactivation of the immune system (Curdy et al. 2019). This could be realised by the surface receptors such as PD1, CTLA-4 and LAG-3 leading to the exhaustion state of these T cells or by other surface markers such as the KLRG-1 leading to the senescence of these T cells. The more general system-wide immune inhibitory mechanisms are mediated by the regulatory T reg cells (Overacre and Vignali 2016). There is a complete balance between activation and inhibition to assure overall health without the preponderance of any arm of the immune regulation.

The vast majority of T cells express alpha–beta TCRs (αβ T cells), but some T cells in epithelial tissues (like the gut) express gamma-delta TCRs (gamma delta T cells), which recognize non-protein antigens. With the advances of science, there are also shifts in our traditional classification of the division of innate and adaptive immune cells.

Non Innate, Non Adaptive Immune Cells: Innate Lymphoid Cells (ILC) and Innate-Like T Lymphocytes

Innate lymphoid cells (ILC) are broadly classified into three main subsets: ILC1 (IFN-γ producing), ILC2 (IL4-, IL-5, and IL-13-producing) and ILC3 (IL-17- or IL-22 producing or both) (Nagasawa et al. 2018; Ebbo et al. 2017). ILCs are either present in the tissues or in the circulation. They can rapidly react to microbial and cytokine signals. They also rapidly induce the CXCL13 chemokine, which is the ligand of CXCR5 playing a role in the tissue accumulation of these ILCs. By their rapid response, these cells also contribute to the eradication of the microbes constantly invading the human organism and permanently threatening its overall health.

The innate-like T cells comprise cells displaying a γδTCR, mucosal associated invariant T (MAIT), INKT (Invariant Natural Killer T), GEMT (germline-encoded mycolyl lipid-reactive) and innate like B cells (Kotas and Locksley 2018). These

cells recognize foreign/self-lipid presented by non-classical MHC molecules, such as CD1d, MR1, and CD1a (Mangan et al. 2013). They are activated during the early stages of bacterial infection and act as a bridge between the innate and adaptive immune systems. Unlike their conventional counterparts, innate T cells rapidly recognize foreign pathogen signals and manifest immediate effector functions after activation (Uldrich et al. 2013). These innate T cells are implicated in immune responses to viral infections such as CMV, are able to recognize a broad range of cancer cells, as well as react to stress-induced molecules, such as MHC class I-related chains A and B (MICA and MICB) that are expressed on viral infected cells and also participate in the general antimicrobial defence (Vasudev et al. 2014; Chitadze et al. 2015; Bhat et al. 2019). The nature of the antigens recognized by innate T cells is also diverse and broadly non-overlapping involving metabolites, bacterial products, and lipids. INKT cells have been principally shown to respond to glycolipids, γδ T cells are potently activated by (E)-4-hydroxy-3-methyl-but-2-enylpyrophosphate (HMBPP) (Karunakaran and Herrmann 2014), and MAIT cells can be activated by riboflavin metabolites–reduced 6-hydroxy methyl-8-δ-ribitylumazine (rRL-6-$CH_2OH$), as well as folic acid metabolite, 6-formylpterin(6FP) (Kjer-Nielsen et al. 2018). So, they have some characteristics of innate immunity such as rapid effector functions, but also adaptive immunity because of the rearrangement of their TCR and thymic selection. This allows innate T cells to perform effector immune responses much earlier than conventional T cells, and act as an additional "bridge" between innate and adaptive immune responses. Studies demonstrate that unconventional T cells do indeed play an important role during bacterial infection and contribute to the ability of host organisms to clear and control certain bacterial infections. These cells are able to efficiently travel to the sites of inflammation and initiate rapid responses by means of cytokine production and cytotoxic activities.

### *13.3.1 The Special Case of Resisters to Infections Such as Tuberculosis as an Ultimate Example of the Power of Immunity to Maintain Health*

One very interesting phenomenon in the life-long *microbe*-host interactions is the development in some individuals of a natural resistance to one or several microbes, whereas all the other nearby individuals may be infected and either they heal, become a carrier or die (Kaipilyawar and Salgame 2019). It is very important to understand these resisters to threatening infections to better understand how the immune system should behave to naturally maintain health. A tuberculosis resister may present such an example that can instruct us on the real nature of immunity (Mave et al. 2019).

Tuberculosis is now the leading cause of death from a single infectious agent, *Mycobacterium tuberculosis*. It was as early in the 1930s that resisters were discovered in persons heavily exposed to this bacterium (Dickie 1950). They are exposed to this agent, but they never get the disease. They remain healthy, which means that

they have an immune system that efficiently protects them from this aggression. This can be a sort of natural experiment which underlies the power of immunity to protect and thus maintain health.

The host immune response relies essentially on the innate immune response including monocytes/macrophages and neutrophils (O'Garra et al. 2013). Macrophages are able to phagocytose the bacterium and secrete chemokines that will further recruit other phagocytic cells. These innate immune cells will initiate the bacterium killing machinery that a phagocytic cell may use (Bhatt et al. 2015). In some cases, the IFNγ will initiate a robust Th1 response (Behar et al. 2011). However, in the resister this part of the immune response remains elusive, though to some extent present. This implies that IFNγ may not be a reliable biomarker of the resister immune response (Tameris et al. 2013).

The most robust gene sets that were strongly associated with resistance are those associated with the histone deacetylase (HDAC) function (Seshadri et al. 2017). This signifies an epigenetic modulation resulting in a metabolic switch in these resisters' monocytes, which seems to indicate that the innate trained memory may play a role (Kaufmann et al. 2018). Another interesting finding was that the innate like T cells, mostly mucosal associated T cells (MAIT) and γδ T cells, which although they do not present changes in their number, were able to manifest a strong CD25 expression and granzyme B production (Vorkas et al. 2018). In this respect, the ILC3, known to produce a high amount of IL-17, seems the most linked to the resistance leading to robust antimicrobial peptide production as well as a strong ILC and Th-1 response (Mazzurana et al. 2018). Furthermore, the TLR polymorphism may also favor the resistance. In addition, the intracellular detection of microbes' DNA occurs via the cGMP synthase (cGAS) binding this microbial DNA to produce the 2′3′-cyclic GMP-AMP (cAMP) and activate the modulator of interferon genes (STING). This makes both STING and cGAS key targets of investigation not only for therapeutic manipulation for microbial resistance but also for maintaining a healthy immune system for combating invasion (Leiva Juarez et al. 2018). These persons also have an exceptional collection of very active antimicrobial peptides, such as LL-37, and β-defensins, such as HBD-2 and HBD-4 expressed under the stimulation of TLRs (Whitsett and Alenghat 2015). Some interesting cytokines, such as IL-17/IL-22, and IL-1 cluster cytokines, are able to increase their production (Ngo et al. 2018). The stimulation of TLRs and the inflammasome results in IL1β production, which in turn activates autophagy and increases the cell's potential via autolysophagosome to eliminate the bacterium (Pilli et al. 2012). This process occurs through the inhibition of mTOR and activation of the MyD88 pathways (Singh and Subbian 2018).

This exceptional resister status nicely illustrates the necessity of a coordinated sustained immune system to maintain health. When this coordination fails the person may become the victim of an aggression but he may either survive at a different level of health or die. Interestingly, the intestinal microbiome was also involved in the modulation of this microbe resistance mediated by the complex interaction of cells, mediators and molecules (Pandyan et al. 2019; Biagi et al. 2017).

### 13.3.2 Covid-19

The very recent (still ongoing at the time of writing this chapter) pandemic of COVID-19 disease caused by the coronavirus SARS-CoV-2 worldwide, may constitute another powerful example of a situation where the balanced immune health is essential to avoid the clinical symptoms of infection. Millions of examples exist now, showing that many infected people either recover or die, but at the same time many, even elderly, people who are in contact with them never get symptoms of the disease. This situation echoes that of tuberculosis resistance. The power of immunity is difficult to estimate at the individual or population level but nevertheless this is the most important survival factor in the face of infections. In the case of COVID-19, the resistance of children is remarkable, and this persists when the people are free of factors weakening the immune response. One has to remember that the deadly development of COVID-19 is the (proinflammatory) "cytokine storm" which kindles an excessively strong inflammatory reaction. This development, practically not seen in children, is a form of immune system imbalance—shifting to too high rather than too low reactivity. Thus, the COVID-19 pandemic incites the need for studies generating new data, which hopefully will ultimately clarify how to reinforce the immune system in a way to resist many microbial diseases.

### 13.3.3 Microbiota-Immune Interaction as Another Major Determinant of Health

The existence of a healthy microbiota is the gatekeeper of health (Chang and Kao 2019). Any dysregulation (dysbiosis) of the gut microbiota has very serious local and general consequences for our health (Weiss and Hennet 2017). Gut microbiota are comprised of a diverse set of species with individual-specific makeup and metabolic output and have emerged as a potent regulator of the host metabolism and immune system (Levy et al. 2017; Shi et al. 2017; Thaiss et al. 2016). During human evolution, these two entities became mutually intertwined, influencing each other. They can maintain a healthy environment or participate in pathological conditions. Health needs a relatively stable microbiota to adequately regulate immune responses. Various host factors have important impacts on the regulation of the gut bacterial composition and consequently on the immune response. Accumulating evidence has shown the role of innate immunity of the gut epithelium in shaping microbiota. Pattern recognition receptors (PRR) are able to sense the microbe-associated molecular patterns and as such promote the immune response by all means to control the normal microbiome. All classes of PRRs participate to some extent in the determination of the specific normal composition of gut microbiota. As already described, β-defensins are also involved in the normal gut microbiota maintenance. Other factors from the host shape the gut microbiota, such as miRNAs, oxygen products or secretory IgA (Wells et al. 2011).

In turn, the microbiota shape the host immune response. Microbes have a strong modulating effect on host immune cells (Wells 2011; Spencer et al. 2019). It was recently demonstrated that microbiota may shape the immunotherapy response in cancer patients (Gopalakrishnan et al. 2018; Li et al. 2019; Pandiyan et al. 2019). This underlines how the microbiota may be important in the determination of the immune system functioning for maintaining health. Certain bacterial metabolites are also able to shape the immune response. It is of note that microbiota are different between persons, populations, and continents. It is also clear that differences in diet in these settings shape the microbiota. Thus, an ideal microbiota is probably one which is relatively resilient enough to maintain an adequate immune system without increasing immune/inflammatory response, which is what we see in industrialized countries. The time dependant deregulation of the immune/inflammatory response leading to the increase of non communicable chronic diseases (NCCDs) may also be sustained by the diet-induced dysbiosis via disturbed barrier integrity (Noce et al. 2019). This means that a certain type of common taxa should exist for a minimum physiological immune functioning. Thus, an equilibrated microbiota should be attained to have a well-functioning immune system for maintaining health.

### *13.3.4 The Ultimate Role of Immunity to Avoid Lifelong Chronic Inflammation for the Maintenance of Health*

If we consider health as a dynamic modulable process we should not be surprised that immunity is also a highly malleable process of adaptation to aggressions, time, diets, stresses and dysregulations (Gururajan et al. 2019). This constant adaptation of immune parameters for the maintenance of health should ultimately aim to avoid death, but also the chronicisation of the immune response called inflammation. This inflammation underlies most of the modern chronic diseases starting at young age and manifesting during aging (Fulop et al. 2019b; Furman et al. 2019). Thus, the whole immune system at any moment of life should tend to adapt without any harm for a healthy immune response. However, with time there are so many attacks that can overwhelm the capacity of the immune system and prevent a return to a health-maintaining steady state (Christ et al. 2019). Thus, it is questionable until which limit the immunity is a friend or a foe.

Certainly, there are means to reinforce and reset the failing or dysregulated immune response as exemplified by the obligate anti-inflammatory response generated by an inflammatory response (Franceschi et al. 2007). In this context, healthy life habits such as exercise, healthy diet or stress management may be of great help. Thus, the whole organism should contribute at different levels to the system-based maintenance of the homeostatic immunity for sustained health. This health status may profit from a permanent adaptation to various stressors (Fulop et al. 2019a).

### *13.3.5 Vaccination: When Nature is Supplanted by Human Intelligence to Assure Health at All Ages*

Vaccines are the greatest public health achievement ever (Delany et al. 2014; Vetter et al. 2018). They assure a complete immune response, including the innate and the adaptive immunity, to the case of natural infections (Rappuoli et al. 2018). The aim is thus to procure a protection for health without having the clinical manifestations of the natural infection. However, this is not true for each vaccine and towards pathogens that would occur in nature. There are several types of vaccines, like live attenuated, inactivated or subunit vaccines. The variety of the vaccines and the elicited responses indicate that sometimes the natural infection has something more than just the targeted epitope included in the vaccine. Furthermore, in many cases adjuvants should be used to supplement the innate immune response activation for a complete and efficient immune response. The more our knowledge increases about the complexity of the immune responses induced by natural infections, the more our vaccines will be able to mimic them and assure the health of subjects at any age.

## 13.4 Conclusion

Health is at the center of controversies as its definition is very difficult. However, conceptually health seems to be a dynamic process that allows for a complete life for an individual in society. There are several determinants of health and even more risk factors to destroy it. Thus, evolution created several means to protect and sustain health, and one of them is immunity. This complex and integrative system tends to protect health by various ways which necessitate a tight coordination between the actors. Fundamentally, this is a very efficient system as it may ultimately protect humans for more than 100 years. However, it also depends on so many other parameters, such as microbiota, such that during the lifespan there are several possibilities to be dysregulated and result in the chronic inflammation underlying most of the NCCDs. Nevertheless, it can be reinvigorated by simple means that reset its functioning and maintain an adequate homeostasis for a long time. Thus, immunity is fundamental for health and health is fundamental for well-functioning immunity. Humans possess the whole machinery in their immune systems to live as a healthy centenarian.

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# Chapter 14
# What Is a Healthy Microbiome?


**Antonis Karamalegos, Mireya Vazquez-Prada, and Marina Ezcurra**

**Abstract** The development of new technologies has resulted in an explosion of studies of the gut microbiome. These studies have revealed a highly complex microbial community, forming an intricate ecosystem with the host and affecting many aspects of host health. In particular dysbiosis, an imbalance within the microbiome, is associated with a wide variety of diseases, and with ageing. Studies in laboratory animals show these links are not just associative, and that the microbiome can directly cause health and disease states in the host. These findings beg the question of what "healthy" microbiomes look like, and how we can use the microbiome to promote human health. Efforts to understand healthy microbiomes have revealed that microbiome composition varies widely between healthy individuals, and that there is no such thing as a single healthy microbiome. Current research shows that qualities of the microbiome ecosystem, such as diversity, robustness, resilience and ability to resist perturbations, are important for host health. Identification of the molecular basis of these qualities, as well as the genetic and biochemical functions of the microbiome ecosystems, will enable us to understand the core functions that define healthy microbiomes.

**Keyword** Microbiome · Microbiota · Microbe · Holobiont · Health · Ageing · Disease · Metagenomics · Immunity

## 14.1 The Holobiont—An Ecosystem Consisting of the Human Body and Its Microbes

The *microbiota* is the community of bacteria, fungi and viruses inhabiting different niches of the body, such as the skin, mouth, vagina and gut. The gut microbiota is by far the largest and most dense community of microbes that colonises our bodies, consisting of hundreds of microbial species which until relatively recently were largely unstudied and uncharacterised. The development of new technologies has

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resulted in an explosion of studies of the gut microbiome. These advances have revealed a highly complex microbial community. It has been estimated that the microbial cells that colonise the human body are at least as abundant as our own somatic cells, and that our bodies host between 500–1000 bacterial species (Sender et al. 2016). Each of these species has a genome containing thousands of genes, meaning that in addition to our biology being affected by our own genes, it is affected by millions/billions of microbial genes (Gilbert et al. 2018). Thus, our biology is not only governed by our genes and our environment, but in fact by our genes, our environment *and* the genes and functions of our microorganisms. The combined genome of our microorganisms is referred to as the *microbiome*, and this is the term we will mostly be using in this text.

Gut microorganisms perform a diverse set of functions important for the host, such as extracting energy from a wide array of host-indigestible carbohydrates, producing vitamins, promoting immunity and preventing colonisation of the gut by pathogens. The presence of intricate interactions between a host and its microbes has led to the concept of the "*holobiont*", meaning the biological entity of a host and its associated microorganisms. Accordingly, the human body is an ecosystem highly affected by dynamic host-microbiome interactions and is a 'superorganism' rather than an individual (Simon et al. 2019). The implication is that many aspects of our physiology and health are dependent on interactions within this ecosystem. Indeed, many studies have associated dysbiosis, that is disturbances of the composition of the microbiome, with a wide range of diseases, including intestinal disorders, metabolic syndrome, mood disorders and neurodegenerative diseases, suggesting that disturbances in the microbiome could be directly contributing to ill-health.

So, what do "healthy" microbiomes looks like, and how we can promote healthy microbiomes? These are important and unanswered questions, and there are huge efforts within the field to understand the relationship between the microbiome and health, and to move towards a better understanding of healthy microbiomes. One of the striking aspects of the microbiome is that there is huge variation in microbial composition between healthy individuals, even between genetically identical twins with similar lifestyles (Turnbaugh et al. 2007). This suggests that healthy microbiomes come in many different shapes and forms, and that what determines if a microbiome is healthy is far more complicated than simply its microbial composition.

## 14.2 The Renaissance of Microbiome Research

Research on the microbiome is booming—the number of studies mentioning "microbiome" or "microbiota" in their title or abstract was 11 in 1980, and has grown to over 13,000 in 2018 ('Hype or hope?' 2019). The reason for this explosion in microbiome studies is the development of affordable whole genome sequencing techniques enabling researchers to profile microbiomes and determine the identity of thousands of species. This is in stark contrast to early studies, in which microbes colonising the

human gut were identified by the cultivation and characterisation of their physiological properties. The cultivation-based approaches favoured microbes that grow well in laboratory environments and resulted in a skewed view of the gut microbiome. In the late 1800s and early 1900s the perception was that all healthy adults share a core microbiota, consisting mainly of *Escherichia coli*, which can be isolated from most people and is easily cultivated in aerobic conditions (Rajilić-Stojanović and de Vos 2014).

We now know that the vast majority of microorganisms in the human gastrointestinal tract are strict anaerobes, and that early cultivation studies only provided a partial view of the microbiome as it did not enable cultivation of anaerobes. In the 1970s, strictly anaerobic techniques were developed, allowing the recovery of more than 300 bacterial species from the gut. Studies during this period identified major gastrointestinal bacterial groups, including *Bacteroides, Clostridium, Eubacterium, Veillonella, Bifidobacterium, Fusobacterium, Lactobacillus* and anaerobic *coccus* (Rajilić-Stojanović and de Vos 2014; Lloyd-Price et al. 2016). More recently, culture-independent techniques based on DNA sequencing provided molecular tools to identify microbial taxonomy. Early sequencing studies in the late 1990s showed a large diversity in the microbiome composition in healthy people. These early studies also found that the majority of the microbial DNA sequences did not match any documented species at the time, revealing not only unexpected diversity but also a large number of previously unstudied bacterial species, sparking a revived scientific interest in the microbiome (Rajilić-Stojanović and de Vos 2014).

The microbiome research field evolved to another phase through the development of high-throughput sequencing techniques, including next-generation sequencing of entire genomic material of the microbiome. Next-generation sequencing showed that the human gut carries over 3 million microbial genes, mainly bacterial, of which the majority had not been previously characterised. The evolution of microbiome research has resulted in a view of the microbiota composition which is quite different from the view that existed prior to the molecular revolution. There are now huge amounts of studies demonstrating associations between the composition of our microbiome and diseases, and large amounts of information regarding the complexity of the microbiome and variation between individuals. As these advances implicate that the microbiome plays an important role in host health, they have resulted in a huge interest in the microbiome both by the scientific community, the media and the general public. The current explosion in microbiome research has also resulted in scepticism and raised questions regarding the state of the field and whether microbiome research is overhyped. Is the role of the microbiome as extensive as associative studies suggest, or are the current expectations overoptimistic? Only by dissecting the genes and biochemical functions of our microbiomes and pinning down the molecular mechanisms underlying the interactions between our bodies and our microbiomes will we be able to move from association to causation and to establish a real understanding of healthy microbiomes (Hanage 2014).

## 14.3 From Cradle to Grave—Changes in the Microbiome Throughout Life

The microbiome changes throughout our life course, playing an important role in human development but also for health outcomes later in life. In early life, the microbiome plays a central role in development of the immune system, and also in the nervous system and bone tissue (Sommer and Bäckhed 2013). In late life, immune dysfunction and dysbiosis contribute to inflammation and disease development.

### *14.3.1 Microbial Diversity Increases in Early Life*

Humans babies are first colonised by their mothers' microbiomes and this transfer occurs mainly through birth, during which they are exposed to the vaginal microbiome of the mother, and through breast feeding, exposing them to microorganisms in the breast milk. Babies born by C-section have microbiomes that differ from those with vaginal delivery and resemble skin microbiomes. Feeding babies with formula is also likely to give rise to microbiomes that differ from microbiomes from breast milk (Kundu et al. 2017). What the implications of different delivery and feeding methods for new-borns are on microbiome composition and overall health in later life are important and largely unanswered questions.

As infants start feeding on solid foods and rely less on breast milk, they are exposed to more microbes and the relatively simple microbiome acquired from the mother matures into a more complex microbiome (Fig. 14.1). During the first three years of life the microbiome undergoes a dramatic shift, from domination by *Bifidobacteria*, bacteria suited to process carbohydrates from milk, to a wider variety of species. During childhood and puberty the microbiome continues to develop and increase in complexity, until adulthood, when it reaches relative stability (Kundu et al. 2017). However, the human microbiome is highly dynamic and the composition can change in response to diet and other factors within hours and days (Gilbert et al. 2018), adding to the complexity of studying microbiome composition.

### *14.3.2 Microbial Diversity Decreases in Late Life*

After relative stability during adulthood, the microbiome changes again as we get old. Microbiotas in healthy individuals are characterised by high bacterial taxonomic diversity, but during ageing the composition of the microbiota changes, resulting in decreased diversity, expansion of pathogenic bacterial species, and alterations in microbial functionality. Also, variation between individuals increases, meaning that age-related changes are different in different individuals and might be linked to individual ageing trajectories (Vaiserman et al. 2017; Nagpal et al. 2018) (Figs. 14.1

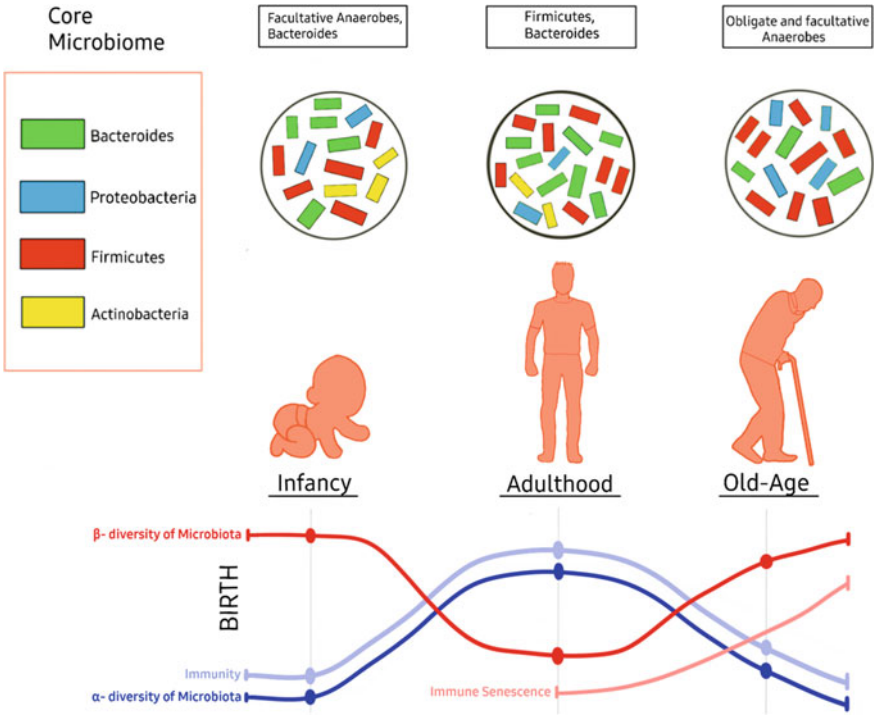


**Fig. 14.1 The microbiome throughout the life course**. Human foetuses are largely sterile, and babies are first colonised by their mothers' microbiomes during birth and through breast feeding. During early life, the microbiome undergoes a dramatic shift, increasing in diversity and including a wider variety of species (α-diversity). During childhood and puberty, the microbiome continues to develop and increase in complexity until adulthood, when it reaches relative stability. As we get old, the composition of the microbiota changes again, resulting in decreased diversity, expansion of pathogenic bacterial species and alterations in microbial functionality, while variation between individuals (ß-diversity) and immune senescence increase

and 14.2). Studies in which the microbiomes of centenarians, that is people who live to a 100 years of age or more, have shown that centenarians have microbiomes more similar to those of young adults than other elderly people, and other studies indicate that age-related frailty is associated with particular bacterial species/genera (Biagi et al. 2010; Nagpal et al. 2018). These studies link microbiome composition to ageing, and raise the question whether changes in the microbiome directly contribute to the ageing process or are merely a result of it. In addition to changing with age, microbiome composition is strongly affected by lifestyle, and by diet in particular. The implication is that we could use diet to acquire a healthy microbiome, but also that some of the detrimental effects that diet have on health might be acting through the microbiome.

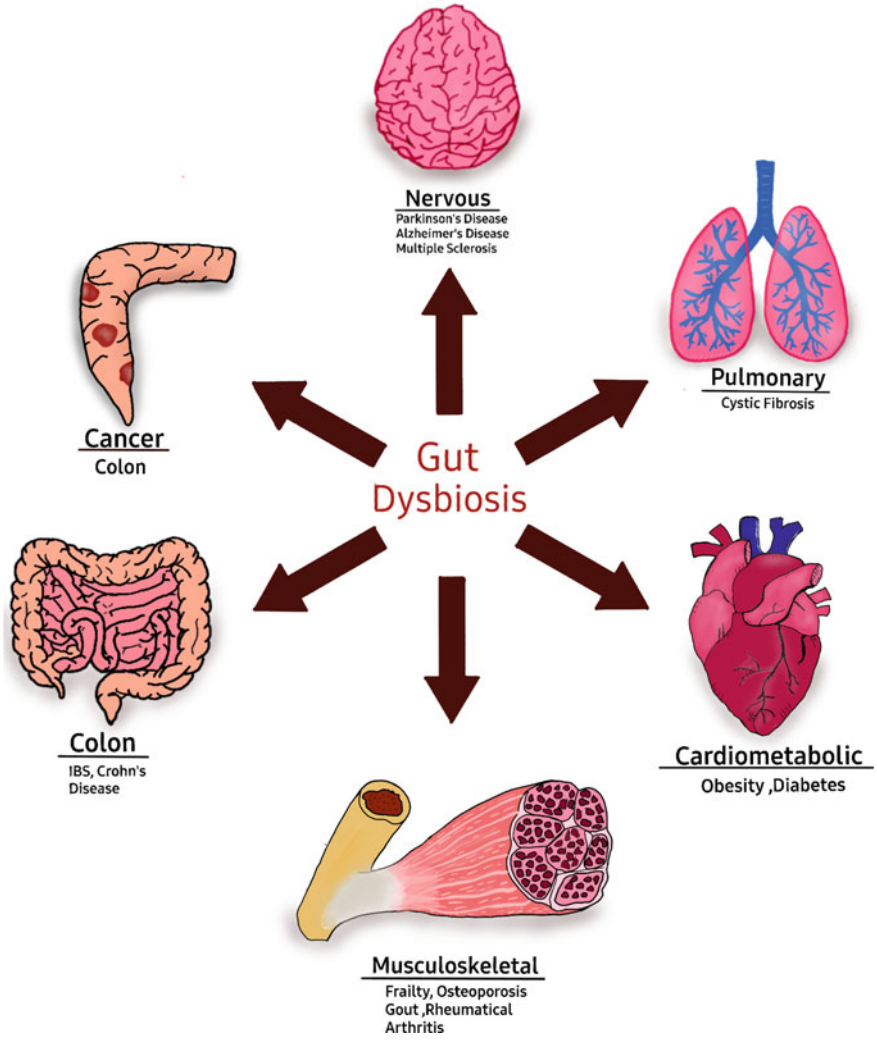


**Fig. 14.2 Dysbiosis contributes to ageing and disease**. The symbiotic relationship between the microbiome and the host is central to host health. Disruption of this relationship contributes to dysbiosis and imbalanced immune responses, resulting in autoimmune and inflammatory diseases. During ageing, a negative cycle of immune senescence and dysbiosis result in chronic inflammation, fuelling age-related diseases

## 14.4 Are We Losing Our Healthy Microbiome? The Disappearing Microbiota Hypothesis

A striking example of how the microbiome is connected to lifestyle is the difference in microbiome composition in different geographical populations. People living in Western industrialised countries have reduced gut microbiome diversity compared

with native populations living traditional lifestyles, such as hunter-gatherers. The Hadza in Tanzania are one of the last remaining hunter-gatherers in Africa, hunting animals and foraging berries, roots and plants, and living on a diet consisting of around 600 plant and animal species (Spector and Jeff Leach 2017). Compared to European urban dwellers they have distinct microbiomes with higher levels of microbiome diversity. The Hadza share microbiome features, such as bacterial families, with other traditional societies across the globe, meaning that these bacteria are not a feature of the local environment, but of adaptations to the host. Uncontacted Amerindians have substantially higher bacterial diversity than urban US populations, but also higher than semi-transculturated Amerindians (Yatsunenko et al. 2012; Dominguez-Bello et al. 2016). These microbiomes that are preserved across traditional populations are lost in industrialised nations, suggesting that a modern lifestyle has resulted in some bacteria going extinct in the human gut, an idea called the "disappearing microbiota hypothesis" (Schnorr et al. 2014; Smits et al. 2017; Fragiadakis et al. 2019).

What does the loss of our indigenous microbes mean for our health? As the large majority of studies of the human microbiome has been conducted in modern societies, we know very little about the bacteria that have been extinct by our modern lifestyle and we have no understanding of their biological functions. But there are good reasons to think that these microbes are beneficial for us and that their loss might have contributed to illnesses such as asthma, allergies, celiac disease and obesity (Dominguez-Bello et al. 2016). Most of the microbes in our microbiota appear to be host-specific microbes that need their host in order to survive. This means that the microbes benefit from the reproductive success of their host and that natural selection will favour microbes that have beneficial effects on the host, improving the success of both the host and the microbes. Indeed, the existence of indigenous microbiomes living in symbiosis with the host is ancient. Co-evolution of animals and bacteria can be traced back in our evolutionary tree and has existed for more than 800 million years, and there are many examples of how co-evolution provides the hosts with evolutionary advantages. Microbes produce essential vitamins, protect against pathogens and aid digestion. Overall, their beneficial activities affect many metabolic, physiological and immunological functions in our bodies (Blaser 2006).

The disappearing microbiota hypothesis parallels and competes with the well-known hygiene hypothesis, which suggests that improved hygiene and access to vaccines and antibiotics in modern society reduces exposure to parasites and pathogens early in life. This lack of pathogen exposure affects the development of the immune system, skewing towards autoimmune responses and resulting in an increase of allergic and autoimmune disorders in later years (Blaser 2006). The degree to which bacteria extinct in Western societies play a role in our health remains unknown, but that gut microbes play an important role in host health is becoming increasingly clear.

## 14.5 Emerging Links Between the Microbiome and Host Health

The recent development of sequencing techniques has enabled profiling of microbiomes in humans and resulted in an explosion of studies demonstrating associations between the composition of our microbiome and many different diseases. Some of these links are not surprising (intestinal infections and inflammatory bowel diseases), whereas others are less expected (obesity, cardiovascular disease) or completely unexpected (major depression, neurodegenerative diseases and autism spectrum disorder) (Gilbert et al. 2016, 2018; Sharon et al. 2016).

### *14.5.1 Protection Against Intestinal Infections*

For some diseases the links are well-established and direct, and microbiome-based approaches are already being used as treatments. The most striking example is intestinal infections with the bacteria *Clostridium difficile*. *C. difficile* infections are characterised by severe diarrhoea and can be deadly—an estimated 15,000 deaths a year in the United States alone are directly attributable to *C. difficile* infection. The first-line treatment for *C. difficile* infections is antibiotics, which wipes out *C. difficile* but also a large part of the healthy microbiome. Antibiotics leave the patients susceptible to new infections as *C. difficile* can easily establish itself in absence of a healthy microbiome, and about 20% of patients have reoccurring *C. difficile* infections. Faecal microbiota transplants are now becoming accepted as an effective treatment. Controlled trials of faecal transplants, in which stool from a healthy donor is transplanted to help re-establish a healthy microbiota, have reported over 90% efficacy in clearing reoccurring *C. difficile* infections. Due to the complexity and variability in donor stools, combined with a limited understanding of the ecological forces that shape the microbiota, faecal transplants are not free of risk for the receiver. For these reasons, next-generation microbiota-based medicines will likely become the preferred option. As we learn more about how the microbiome protects the host against pathogenic infections, defined interventions with rationally selected mixtures of microorganisms or their products that can be more reliably managed will be used (Giles et al. 2019; Hui et al. 2019).

### *14.5.2 Metabolic Syndrome*

Less expected is that the gut microbiome is associated with metabolic diseases such as obesity, type 2 diabetes and cardiovascular disease. The microbiomes of obese and lean people differ in striking ways; obesity, insulin resistance and fatty liver disease are associated with less microbial diversity and higher levels of particular bacterial

groups e.g. *Firmicutes*. Interventions that induce weight loss and improve metabolic functions in both animals and humans result in shifts in microbiota composition, indicating that the microbiome plays a role in metabolic disorder. More direct evidence suggesting that the microbiome directly influences metabolic function in the host includes faecal transfer of microbiotas into recipient human and animal hosts, which in some cases faecal transfer results in recapitulation of the metabolic phenotype of the donors (Everard et al. 2013).

So how does decreased microbial diversity contribute to metabolic disease and weight gain? A dominating current hypothesis is that an abnormal microbiome damages the gut barrier that keeps toxins and pathogens from crossing into the bloodstream. When this occurs, it can set off a cascade of inflammation, contributing to insulin resistance, cardiovascular disease and autoimmune conditions. A diverse microbiome protects and maintains the gut barrier and we are now learning about bacterial species and products that play a role in this protection.

### *14.5.3 Akkermanisa Muciniphia—A Bacteria with Beneficial Effects on Host Metabolism*

One such species is *Akkermanisa muciniphia* (*A. mucinphilia). Akkermansia* is a well-known health-associated genus protecting against inflammation and promoting a healthy metabolic homeostasis. In particular, the species *A. mucinphilia* has been demonstrated to have beneficial effects. Abundance of *A. mucinphila* is decreased in the microbiota of obese animals compared to lean animals and in middle-aged mice. In old animals it has almost completely disappeared (Anhê and Marette 2017). Oral administration of *A. muciniphila* reverses obesity and related complications in obese mice and strengthens the gut barrier, but surprisingly, pasteurised *A. muciniphila* is even more beneficial. Unlike live *A. muciniphila*, treatment with the pasteurised bacterium has additional beneficial effects, including decreasing adipocyte diameter and a decreased capacity of the host to harvest energy from the diet (Ottman et al. 2016).

Remarkably, *A. muciniphila* has beneficial effects on the host through a single bacterial protein, Amuc_1100, which is highly abundant and located on the pili (a hair-like appendage found on the surface of many bacteria) on the outer membrane of the cells. Amuc_1100 can be produced and purified in a laboratory, and when administered to animals it reproduces the beneficial effects of pasteurized *A. muciniphila* on obesity and many related parameters such as plasma-triglyceride levels, glucose tolerance and insulin resistance. It also improves the gut barrier function (Plovier et al. 2017). Further testing of Amuc_1100 and other bacterial molecules will reveal if bacterial proteins and compounds can be produced in laboratory settings and used as drugs for their beneficial properties on human health, independently of the gut bacteria that originally produced them. This will enable a more direct and controlled way to use microbiome-based therapies for human health.

### 14.5.4 Brain and Nervous System Disorders

For some diseases associated with the microbiome it can be challenging to envision possible causative links at first, such as autism spectrum disorder, major depression and neurodegenerative diseases. However, the gastrointestinal tract and the brain are physically and chemically connected to each other. The vagus nerve directly connects the gut with the brain, providing a means of neuronal transmission between these two organs. In addition, gut microbes produce chemical compounds, including neurotransmitters that directly affect neuronal activity, metabolites with neuroactive properties and other molecules that can be transported through the circulation and reach the brain and other organs (Sherwin et al. 2018). Considering that a direct bidirectional crosstalk between the brain and the gut has been demonstrated, with reciprocal influence on each other's physiology and function, it is not surprising that microbiome composition can affect brain health and brain function.

There is evidence, although preliminary and mostly from animal models, for a role for the microbiome in neuropsychiatric conditions, including major depression, autism spectrum disorder, schizophrenia and neurodegenerative diseases such Parkinson's and Alzheimer's diseases (Sharon et al. 2016). Animal models allow controlled experiments such as generating germ-free animals and performing faecal transplants. These kinds of experiments have demonstrated that gut microbes and the molecules they produce can promote or inhibit brain and nervous system disorders. They also show that the crosstalk between the gut microbiome and the brain is a complex network of interactions that we are only starting to understand.

### 14.5.5 The Immune System—The Mediator of Healthy Microbiomes

It is well established that interactions between the microbiome and the immune system play vital roles for host health. The lining of the gut is the largest surface area of human body that comes in direct contact with the foreign material. The immune cells of the mucosal immune system are positioned throughout the length of the gut and are in active cross-talk with the rest of the immune system through local lymph nodes. The gut-associated immune system needs both to tolerate the microbiota, preventing harmful systemic immune responses and at the same time control the microbiota, preventing growth of microorganisms and translocation outside the gut. The microbiome plays a fundamental role in the development and training of the host immune system in early life (Sommer and Bäckhed 2013).

Microbes and the molecules they produce are constantly sensed by the immune system, resulting in immune responses that have effects far beyond the gut, and that can promote or inhibit pathological conditions. Immune imbalances are likely mechanisms explaining the link between the microbiome and many diseases by causing inflammation. A healthy microbiome thus might be a microbiome that promotes

healthy and appropriate immune responses, in contrast to inappropriate immunity causing pathology. With age a negative spiral of dysbiosis of the microbiome and age-related dysfunction of the immune system contributes to sterile, chronic inflammation and age-related diseases (Fig. 14.2) (Nagpal et al. 2018).

## 14.6 What is a Healthy Microbiome?

Microbiome researchers have sought to answer this question, and several hypotheses have been formulated. An early suggestion was that a healthy microbiome consists of a core of microbial taxa which are universally present in healthy individuals, and that an absence of these core microbes would result in dysbiosis and disease. But studies of microbiome diversity, including The Human Microbiome Project, an initiative funded by the National Institute of Health to improve our understanding of microbiome effects on health, revealed an unexpected amount of variation in microbiome composition in healthy individuals (Turnbaugh et al. 2007). These studies suggested that there are many different types of healthy microbiomes of different compositions, and that characterising a "healthy" microbiome as an ideal set of specific microbes is therefore not a practical definition (Lloyd-Price et al. 2016).

### *14.6.1 A Core of Microbial Functions Required for Host Health*

An alternative hypothesis is that it is not the exact identity of microbes in the microbiome that matters, but rather their metabolic functions. Gut microorganisms carry their own genomes and perform a set of biochemical and metabolic functions, and there are many examples of microbial species that perform functions with positive effects on host physiology. Each of these functions does not necessarily always need to come from the same microbial species, and possibly a healthy microbiome consists of a core of functional reactions, rather than a core of microbial taxa or species (Shafquat et al. 2014). It is becoming clear that healthy microbiomes come in many different shapes and forms and that what determines if a microbiome is healthy is far more complicated than simply its microbial composition (Lloyd-Price et al. 2016).

### 14.6.2 Robustness and Resilience: Important Determinants of Healthy Microbiomes

Another important characteristic of a healthy microbiome may be its behaviour over time, in particular its resilience to internal and external changes and stresses. Perturbation of the composition of the microbiome, dysbiosis, is associated with a long list of diseases. Dysbiosis contributes to inflammation, providing an explanation of how the microbiota might affect diseases. It also explains links between the microbiome and ageing (López-Otín et al. 2013). Age-related inflammation is common among the elderly, and differs from the acute inflammation caused by pathogens, in that it is a chronic inflammatory response involving activation of the immune system in the absence of infection. One of the factors triggering age-related inflammation is dysbiosis. Our microbiome becomes less diverse with age and it has been proposed that a negative cycle of decreased gut function, suppressed immune function and imbalance of the microbiome results in gut dysfunction and increased gut permeability. This allows microbial metabolites to cross the intestinal barrier, resulting in additional inflammatory responses, including inflammation of the nervous system (Vaiserman et al. 2017; Nagpal et al. 2018) (Fig. 14.2), and other processes central to ageing, such as the accumulation of misfolded proteins and mitochondrial dysfunction (Biagi et al. 2010; Kim and Jazwinski 2018; Nagpal et al. 2018). Thus an essential aspect of healthy microbiotas is relative stability in terms of resistance to perturbations and the ability to recover from perturbations (Lloyd-Price et al. 2016).

### 14.6.3 Understanding How Microbial Species and Products Shape Host Health

The changes in microbiome composition that have been observed in different diseases range from changes in a single bacterial strain resulting in the production of a single bacterial metabolite to changes at the phylum and genus level, or in microbial communities in the gut (Gilbert et al. 2016). How these microbial changes translate to altered health in the host is the major research question within the microbiome field—in order to understand what a healthy microbiome is we need to pinpoint the mechanisms underlying the links between microbiome composition and health. For example, is it the overall diversity of microbes that are beneficial, or particular taxa, or specific communities? The biological functions of any organism are encoded by its genome, so it is likely that the genetic diversity or composition plays an important role, and that specific biochemical reactions and metabolic functions of the microbiome play a crucial part in shaping host health. Identifying the bacterial proteins and metabolites affecting human health and understanding how microbial species and communities act in terms of their biochemical functions will allow us to learn more about what a healthy microbiome looks like. So how can we drill down the mechanisms underlying

host-microbiome interactions and their effects on human health, including microbial genes and functions and community effects?

## 14.7 Transition to an Understanding of Healthy Microbiomes

The microbiome is enormously complex, consisting of thousands of species and millions of microbial genes. Typically, studies in humans yield correlations between microbiome composition and disease states, but determining causality and mechanisms requires performing experiments in laboratory conditions. Considering the technical and ethical limitations of human experimentation, laboratory animals are widely used. An important aspect of microbiome research is the ability to generate germ-free sterile animals which can be colonised with microbes of choice in order to generate comparisons between animals with and without microbiomes but also animals colonised with specific microbiomes, allowing direct testing of causative relationships (Fritz et al. 2013; Kim and Jazwinski 2018). Studies using these approaches in a variety of animal species show that that the microbiota is a direct cause of a number of different aspects of health, ranging from diseases and physiology to biological processes such as behaviour and ageing and longevity (Kim and Jazwinski 2018).

### *14.7.1 Gathering Evidence from Natural Host-Microbiota Interactions in a Variety of Animals*

Eukaryotic organisms, from the first unicellular eukaryotes to complex multicellular animals, have repeatedly entered into symbiotic relationships with microorganisms, enabling them to exploit otherwise unavailable habitats and unsuitable diets. This means there are a variety of animals of a wide range of complexities, ranging from nematodes to humans, that can be used to study host-microbiome interactions. These include invertebrate and lower vertebrates associated with microbiomes of lower taxonomic diversity than in mammals (Douglas 2018), and three traditional simple model organisms: the fruit fly *Drosophila melanogaster*, the zebrafish *Danio rerio* and the nematode worm *Caenorhabditis elegans*, which are very well-suited for laboratory studies. Compared to mammals, these simple systems enable straightforward protocols to manipulate the microbiota and assign function to individual microbial taxa, allow for cost-effective experiments over short timescales, and enable complex experimental designs to investigate how host-microbiome interactions affect fundamental animal processes such as development, immunity and neurobiology.

For these reasons, in particular *C. elegans* and *Drosophila* are attracting increasing attention in microbiome research. Non-traditional models are also yielding insights

into host-microbiome interactions. These include the honeybee *Apis mellifera*, the freshwater polyp *Hydra vulgaris*, the Hawaiian bobtailed squid *Euprymna scolopes*, the wax moth *Galleria mellonella*, crustacean species belonging to the genus *Daphnia*, the medicinal leech *Hirudo medicinalis*, the sea anemone *Nematostella vectensis* and the turquoise killifish *Nothobranchius furzeri* (Smith et al. 2017; Zhang et al. 2017; Ezcurra 2018; Douglas 2019). Microbiome studies in this wide range of animals are yielding novel insights into the multiple ways in which individual microorganisms and microbial communities influence host physiology, illuminating the cellular and molecular processes underlying these interactions.

By studying natural host-microbiota interactions in a variety of animal species we are learning about general principles governing host-microbiota interactions. These interactions are largely biochemical. Microbial effects are generally mediated by the release of bioactive molecules (metabolites, proteins, lipids and small RNAs) from microbial cells, and acting on host cellular and molecular pathways to modulate host physiology.

For example, animals without a gut microbiome have a hyperactive movement pattern, with increased movement speed and longer periods of movement. This has been shown in mice, zebrafish and *Drosophila.* A study in *Drosophila* demonstrated the mechanisms underlying how the microbiome affects host behaviour. In flies, the gut bacterium *Lactobacillus brevis* produces a sugar-converting enzyme, xylose isomerase, resulting in reduced levels of the sugar trehalose and increased levels of another sugar, ribose. These changes in sugar levels interact with neurons within the central nervous system, thereby influencing activity of the animal (Schretter et al. 2018; Douglas 2019). Although this research is not directly translatable to humans, it provides a mechanistic understanding of how the microbiome can affect host physiology. Discoveries made with simple systems are important because they can be used to construct precise hypotheses of function in less tractable models such as rodents. The identification of interactions that are evolutionarily conserved can then be used to formulate hypotheses about interactions likely to also affect humans.

### *14.7.2 Understanding Microbial Functions Affecting Human Health*

The major challenge in the microbiome field is pinning down host-microbiome interactions affecting human health. This will require gathering data from population-based microbiome studies and performing hypothesis-driven experiments in model organisms to investigate particular microbial species and functions to reveal causal relationships. These findings can then be used for intervention studies (Gilbert et al 2018). Transforming microbiome research from a descriptive to a causal and finally to a translational science will require researchers from different disciplines working together and combining data generated from population-based microbiome studies in humans, mechanistic studies in animal models and microbiological studies of

the genes, pathways and functions of individual microorganisms and microbial communities.

It will be particularly important to identify bacterial *functions* and map how they relate to metagenomic studies in order to identify bacterial pathways that contribute to host health. The human microbiome encodes at least 100-fold more genes than their human hosts and produces an extraordinary array of structural components, cell surface molecules, and metabolic enzymes and by-products. Half of these microbial genes are unknown or have poorly characterised functions. It is estimated that at least 10% of all circulating metabolites in the human body are microbially derived and play a role in a variety of human functions (Joice et al. 2014). An important challenge for microbiome research is therefore to determine the identity and function of these microbial products. Understanding the functions of the microbiome involves formulating hypotheses regarding their function and validating them by testing the bioactivity of microbial cells, microbial lysates and purified microbial compounds and proteins on model organisms, organoids or cell culture. Assessment of bioactivity can be e.g. enzymatic activity, immune cell activation, or physiology in animal models. Bioinformatic and statistical methods can be used to assess putative functions of microbial proteins (Joice et al. 2014). The large number of unknown genes in our microbiome dramatically inhibits our understanding of healthy microbiomes and how the microbiome contributes to health and disease. But it is also a fantastic opportunity to identify microbial products involved in microbe-microbe and host-microbiome interactions affecting health.

## 14.8 Utilising the Microbiome for Human Health—Hype or Hope?

Many human diseases have been suggested to be linked to the microbiome: inflammatory bowel disease, cancer, diabetes, obesity, atherosclerosis, fatty liver disease, malnutrition, autism, Alzheimer disease, depression, autoimmunity, asthma and more (Fig. 14.2). The implication is that the microbiome could be affecting many, if not all, aspects of human health. As a result, microbiome research has received a massive amount of attention in the media, with claims that there is a 'microbiota fix' for everything from gastrointestinal issues to mental health problems. Moreover, there are large numbers of microbiome-based services offering profiling of personal microbiomes, and a range of commercial microbiome-based therapeutics and products, including pro- and prebiotic products and DIY faecal transplants, with little to no scientific evidence backing up the claims of their health benefits. These developments have resulted in many microbiologists raising cautionary voices, warning both for hype within the microbiome field, and for the health risk associated with non-clinical use of e.g. faecal transplants (Hanage 2014; Ma et al. 2018).

### 14.8.1 Dietary Interventions as Means to Improve the Microbiome

The microbiome is becoming an increasingly attractive target for potential therapeutics and has a huge potential to improve health. It is possible to manipulate the microbiome through diet, prebiotics, probiotics and faecal transplants. Lifestyle, and *diet* in particular, has a significant and immediate effect on microbiome composition. Varied diets high in plants and fibre and low in processed foods promote diverse and resilient microbiomes (Sonnenburg and Sonnenburg 2019).

One central function of the microbiome is to digest carbohydrates that cannot be digested by the host, most commonly dietary fibre. The beneficial role of dietary fibre on human health has been known for decades, but recent studies are suggesting that the missing mechanistic explanation for the beneficial effects of dietary fibre may be largely attributed to digestion by the microbiome. There is a vast number of carbohydrates of different chemical composition and with different properties, and different gut microbes specialise in breaking down specific types of carbohydrates. This means that carbohydrates act as selective agents, altering the composition of the microbiome, but also dictating functional and metabolic output. Multiple studies have shown that diet acts as a potent force in shaping the microbiome; quantity and type of carbohydrates alter the gut microbiome, promoting certain species and taxa. Fibre-rich diets promote microbes that produce short-chain fatty acids, which are important mediators of microbiome effects on physiology, and have beneficial effects on host health by, for example, regulating metabolism and reducing inflammation. As this is a very active research field, we will certainly be learning more about how specific foods and carbohydrates can be used to boost microbial metabolic activities and acquire healthy microbiomes (Sonnenburg and Sonnenburg 2014).

### 14.8.2 Microbiome-Based Interventions as a Route to Health

In addition to diet, probiotics and prebiotics are increasingly popular. *Probiotics* aim at altering the microbial composition of the gut through exogenous administration of live microbes. *Probiotics* are widely used but there is little convincing evidence for their efficacy. *Prebiotics* are compounds that are consumed with the intention of affecting microbiome composition or function in a beneficial way. Prebiotics, like probiotics, are currently a relatively unspecific approach to microbiome-based interventions, and further studies are needed to fully characterise the effects of prebiotics on different bacterial species. As we learn more about the biology of the microbiome and host-microbiome interactions, the use of prebiotics will be evidence-based and more precise. *Faecal transplants* involve transplanting faeces containing microbes from healthy individuals to ill or old people to restore balance of the microbiome and is also gaining momentum. Grotesque as it might sound, there is increasing evidence in both animals and humans supporting this avenue to improve health. Currently

faecal transplants are mainly being used as a complement to antibiotics to treat *C. difficile* infections, but future research is likely to identify other instances where transplants from healthy donors can safely be used to achieve benefits for health.

### 14.8.3 Bypassing the Microbiome Through Secreted Microbial Metabolites

Alternatively, completely bypassing the microbiome and instead utilising microbial compounds and metabolites as pharmaceuticals offers a more controlled approach. Research over the past few years has revealed that the intestinal microbial community exerts much of its impact on host physiology through the secretion of small molecules that modulate cellular and organismal functions of the host, targeting host genes and proteins. These small molecules serve as an effective means of communication in host-microbe interactions. Rather than targeting the aberrant microbial composition, exogenous administration or inhibition of metabolites has the potential to counteract and correct the negative effects of imbalances of the microbiome.

Metabolite-based interventions are therapeutically attractive for several reasons. Metabolites are physiologically abundant at high concentrations, and thus the potential for toxicity is low. In contrast to the administration of live organisms, their dosage and routes of administration follow the principles of pharmacokinetics. Moreover, metabolites are present at most body sides and thus suitable for different routes of administration. Additionally, metabolites are generally stable in the systemic circulation and thus amenable for scalable modulation of their concentration. Metabolomics, that is the identification and characterisation of all metabolites present in a sample, is becoming a routine approach in the microbiome field. Combined with other techniques, it will enable researchers to define functional signatures for disease states that have so far been associated only with compositional and metagenomic changes. Although it is early days for metabolite-based therapeutics, this strategy is highly promising, and concerted efforts over the coming few years may well result in the development of treatments for microbiome-associated diseases (Wong and Levy 2019). In addition to the delivery of bacterial products, next generation microbiome-based interventions will involve using synthetic biology to engineer bacteria to produce certain compounds or proteins (Sonnenburg 2015).

### 14.8.4 The Potential of the Microbiome for Health

Among the general public there is increasing enthusiasm and interest in using products to modify one's individual microbiome to achieve a "healthy" microbiome, but we do not yet know what defines a healthy microbiome. Clinical translation of microbiota-based therapies has been slow, with one of the main obstacles being lack of

a mechanistic understanding of the metabolic and ecological interactions between microorganisms within the microbiota and interactions with the host. Nonetheless, the microbiota holds huge potential to understand human health and as a source of novel therapeutics. The microbiome research field has now reached a critical inflection point and is transitioning from descriptive and associative studies towards understanding the underlying mechanisms of action and developing new evidence-based microbiome interventions (Gilbert et al. 2018). This transition enables us to address critical questions regarding the microbiome and health and design interventions to establish and maintain healthy microbiomes.

## 14.9 Moving Towards an Understanding of Healthy Microbiomes

It is becoming clear that there is no such thing as a single healthy microbiome, and that there are huge variations in microbial composition between healthy individuals and between populations. Healthy microbiomes come in many different shapes and forms, and what defines a healthy microbiome is far more complicated than its microbial composition. Characterising a "healthy" microbiome as an ideal set of specific microbes is therefore not a practical definition. A better way may come from defining microbiome qualities. The qualities of healthy microbiomes include the *diversity* of microbial species, *robustness*, and *resilience* to internal and external stresses. These factors protect the host against imbalances in the microbiome which have been associated with a wide range of diseases.

It is likely that it is not the exact identity of microbes in the microbiome that matters, but rather their metabolic functions. Gut microorganisms carry their own genomes and perform a set of biochemical and metabolic functions, and there are many examples of microbial species that perform functions with positive effects on host physiology. Each of these functions does not necessarily always need to come from the same microbial species, and possibly a healthy microbiome consists of a core of biochemical and metabolic functions, rather than specific microbial taxa or species. Only by dissecting the genes and biochemical functions of our microbiomes and pinning down the molecular mechanisms underlying the interactions between our bodies and microbial functions, will we be able to move from association to causation and to establish a molecular understanding of host-microbiome interactions. Our current understanding of healthy microbiomes is quickly evolving, and during the coming years and decades we will develop a real understanding of healthy microbiomes.

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# Chapter 15
# Molecular Biomarkers of Health


**Jan O. Nehlin and Ove Andersen**

**Abstract** Every individual is endowed with a specific health trajectory during the course of life. Over time, health trajectories are gradually interspersed with the advent of biological faults that the body is not fully able to recover from, on its own, leading to the beginning of an aging trajectory and its sequel, an aging phenome. Molecular biomarkers of health are quantitative measurements of health status by means of analysis of nucleic acids, metabolites and cells in body fluids, scans of organs and assessments of organ function. Health is currently viewed as intrinsic to each age group e.g. the body function of elderlies will not perform equally well as the body of young adults, but older people can still be considered healthy. In contrast, viewing everyone's health as a collection of basal optimal values of true relevance for optimal body function, established during childhood to early adulthood, specific to each person, and used as a reference point, would allow to determine future health deviations from the individual norm. We here attempt to provide a glimpse to how a state of good health could be maintained by adhering to the individual reference values of personalized molecular biomarkers of health under periodical clinical supervision.

**Keywords** Health · Biomarker · Disease · Detection · Recovery · Vulnerability

## 15.1 Introduction

At birth, the maternal environmental exposure during pregnancy, parental epigenetic factors, inherited gene variants and gene dosage establish a health base from which a specific health trajectory will occur during the rest of the person's lifetime.

The original version of this chapter was revised: The term "Mmol" has been corrected to "micromolar" in Table 15.2. The correction to this chapter is available at https://doi.org/10.1007/978-3-030-52663-4_31

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Genetics and milieu will undoubtedly play an important role in the progression of each individual health trajectory (Veitia et al. 2017; Giuliani et al. 2018).

The analysis of human DNA variation has shown that each person is found to carry approximately 250–300 loss-of-function variants in annotated genes and 50–100 variants previously implicated in inherited disorders (Genomes Project et al. 2010). Moreover, many de novo mutations arise in the paternal and maternal lineages (Conrad et al. 2011; Jonsson et al. 2018) and increase with higher maternal (Wong et al. 2016) and paternal age (Taylor et al. 2019; Simard et al. 2019). The relationship between genotype and phenotype with regards to health maintenance is largely unknown because not all gene variants have been analyzed with respect to their role in optimal physiological function. Thus, at birth, each person will initiate their individual health trajectory based on their inherited genetic and epigenetic makeup.

The core of lifespan research consists in studying how individual health trajectories are shaped and how they unfold over time, from conception to death (Burton-Jeangros et al. 2015). Recent health registry data indicate that the health trajectories can be very different, and it is especially noticeable among multimorbid individuals (Juul-Larsen et al. 2020a, b; Held et al. 2016; Guisado-Clavero et al. 2018; Hsu and Jones 2012). The health phenome becomes gradually affected by an aging phenome,

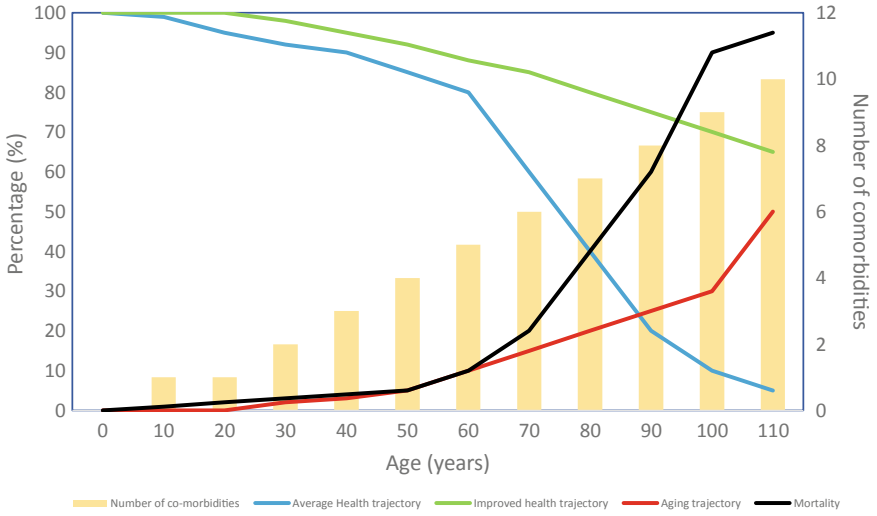


**Fig. 15.1** Tentative schematic representation of average health and aging trajectories at different ages. The number of chronic disorders (comorbidities) increase with age, which have an impact on the risk of mortality (Barnett et al. 2012; Divo et al. 2014). The type and number of health and aging trajectories among human subjects will require extensive characterization of several molecular markers, senescence burden and the sequence/order and type of comorbidity events in epidemiological and longitudinal clinical studies. The number of comorbidities depicted represent the number when at least 5% of the subjects have been diagnosed with a chronic disorder (Adapted from Barnett et al. 2012). The aging trajectory is thought to depict senescence burden, the percentage of senescent cells within the body. The improved health trajectory is a probable outcome of individually tailor-suited interventions that can maintain good health and delay aging

and compensatory mechanisms will attempt to reestablish normal function (Fig. 15.1) (Calimport et al. 2019; Gorgoulis et al. 2019; Hsu and Jones 2012) (see Sect. 15.4).

The appearance of health imbalances will depend on the intrinsic individual capacity to withstand and adapt to the impact of detrimental environmental factors and accidents. A recovery process takes place to bring back the impacted tissue or organ to its normal functional level, as it was before the imbalance. However, these recovery processes are not perfect endlessly; once the healing mechanisms are deficient or exhausted, a pathology or organ/tissue dysfunction develops, giving rise to symptoms that characterize a co-morbidity. The number of comorbidities increases proportionally with age and is larger in individuals 65 years and older, when multimorbidity (>1 disease) becomes very common (Barnett et al. 2012; Divo et al. 2014; Hvidberg et al. 2019; Capobianco and Lio 2013). The number of comorbidities will increase as a result of further health imbalances, giving rise to frailty, chronic inflammation and an increased risk of death.

Disease trajectories or health decay trajectories are associated to some extent with aging trajectories. Efficient body function maintenance, indicative of optimal health parameters, is reflected by a postponement of molecular markers of aging and disease. As long as the repair, resolution and recovery mechanisms are operating seamlessly, aging may be delayed.

Aging is associated with a loss of body function with time. Although aging occurs in parallel in all organs and tissues, the rate of aging may be different, according to the ability of the given tissue to adapt to the environmental factors to which they are exposed (Yang et al. 2015; Ori et al. 2015; Franceschi et al. 2018). Each organ and tissue are endowed with the basic mechanisms that allow them to function in a normal physiological manner. The term normal refers to the intrinsic capacity of the organ to operate, which is dependent of the age, and this capacity can be quantified with the help of molecular markers of health. Assessment of risk factors and biomarkers associated with risk of disease have been explored in multiple studies, both systemically and organ-specific. However, molecular markers that contribute to preserve body functions remain largely understudied.

## 15.2 General Considerations

### *15.2.1 Definition of Health*

Health was defined by WHO, already in 1948, as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (Halbreich et al. 2019; McClintock et al. 2016). This definition has encountered criticisms over the years, especially concerning the absoluteness of the word “complete” in relation to well-being, that it would increase medicalization of society benefiting only a few, that it is not operational or measurable, and that it addresses more the absence of illnesses than fitness capacity. Instead, it was proposed that the concept of health

should include the resilience or capacity to cope, maintain and restore one's integrity, equilibrium, and sense of well-being (Huber et al. 2011; Bircher and Kuruvilla 2014) and better measure and assess population health (McClintock et al. 2016). The persistent emphasis on complete physical well-being could result in higher levels of medical dependency and possible risks (Huber et al. 2011).

Classifying health as "normal" is a matter of definition. If we consider "normal" health as being ascribed a specific age-segment say 20–29, 30–39 and so forth, then older individuals may be considered healthy despite the fact that they do have some health issues that do not bother them significantly, but are still present, and if left untreated could lead to more serious health concerns with time. The issue is what and when is the appropriate threshold for intervention. The tools available today in a general practitioner's (GP) office, to define a person's health, involve a classical physical or medical examination and a traditional observation of the patients' medical signs or symptoms, behavior, reflexes, senses, cognitive abilities and a verbal interview that conveys messages about the person's physical and psychological well-being or not (Krogsboll et al. 2019).

Determination of health status through medical examination is age-biased as it might be expected, since the signs and values measured in childhood, adolescence, adulthood or elderly are not necessarily the same. Many elderlies are otherwise considered healthy, but they are probably not. General preventive care guidelines that have contributed to establish personalized estimates of benefit, to help to improve health, were attempted previously (Taksler et al. 2019; Taksler et al. 2013).

Novel methods have, in recent years, become available in specialized settings where early signs of disease can be detected many years before the outbreak of a disease or pathological condition. These technologies are not readily available at each GP's consultation room so many people may be deemed completely healthy without really being it (Pico et al. 2019; Hosen et al. 2020; Andersson et al. 2015).

Molecular signatures of basal personalized health will rely on the use of validated markers and other analytical technologies that can detect the presence of physiological abnormalities, beyond the standard measures of present-day clinical medicine. A personal health profile consists of a collection of basal optimal values of true relevance for optimal body function. Such values would not only reflect proper organ functioning but also the inherent capacity to recover and heal from possible wounds, traumas, illnesses, toxic environmental factors, and any other event that could adversely affect the human body.

## 15.3 Biomarkers

### *15.3.1 Molecular Markers of Health*

Ideally, deviations from the individual's norm, that cannot be explained by circadian fluctuations or other momentary life events, could be quantified by means of changes

from pre-established molecular markers of health values for tissues/organs, cells or fluids. Pre-established means measured in an individual at the time he/she reached early adulthood, that is, once major developmental changes have taken place that otherwise could affect the stability of several biomarkers. A molecular prodrome would serve as the earliest diagnostic tool to predict the onset of a disease before any visible symptoms or more diagnostically specific symptoms develop. Health trajectories will be different and unique for every individual, due to a myriad of factors affecting body function. Some general criteria that apply to all biomarker measurements is that they must be able to be tested repeatedly without harming the person and that the technical variability is below a minimal margin of error.

#### 15.3.1.1 Molecular Markers of Health: Tissue and Organ Level

Research on every single tissue or organ has provided insights into specific biomarkers associated with disease and disease progression. This knowledge requires thorough examination of molecular values and possibly imaging analyses linked with the diagnosis of a specific pathology.

A few examples can illustrate early disease detection which is synonymous with health decay.

##### Soluble Urokinase Plasminogen Activator Receptor

One marker that is a strong predictor of poorer health is the soluble urokinase plasminogen activator receptor (suPAR) (Desmedt et al. 2017), with a normal concentration of 2.1 ng/ml (Chew-Harris et al. 2019; Haastrup et al. 2014). Exposure to risk factors in childhood is associated with inflammatory burden in adulthood and higher suPAR levels, leading to health problems (Rasmussen et al. 2019). Health decay has been documented in adolescence and early adulthood, judging by recent data (Shah et al. 2019). Healthy lifestyles can reduce the levels of suPAR (Haupt et al. 2019).

##### Blood Pressure and Temperature

The human body's vital signs include blood, respiratory rate, heart rate, oxygen saturation and body temperature. The average blood pressure of the circulating blood, age standardized, measured as mean systolic over diastolic pressure has been 127/78.7 mmHg in men and 122.3/76.7 mmHg in women since 1975 (Collaboration 2017). Disorders of blood pressure can be either low (hypotension), high (hypertension) or fluctuating, and guidelines about its proper management are a matter of constant debate (Anker et al. 2020; Garrison et al. 2017). Persistent arterial hypertension is the major risk factor of stroke, heart attack, aneurysms and chronic kidney failure (Patel et al. 2016) and precipitates vascular aging (Nilsson 2020). Vasoconstriction is regulated by the Renin-angiotensin system (RAS), a complex peptidergic

system that regulates extracellular fluid volume. Preserving Angiotensin-converting enzyme 2 (ACE2) and Angiotensin 1–7 (Ang1–7) levels over time has emerged as protective against hypertension and heart failure (Patel et al. 2016).

A lower basal body temperature has been found to be associated with healthy aging in the absence of excessive adiposity, and is therefore considered a biomarker of health (Simonsick et al. 2016).

### Stress

Stress is the natural response of living organisms to environmental perturbations that is essential for survival. Stress can be acute or chronic, and it has become evident that excessive stress can result in pathologies and chronic diseases, and it can start as early as during pregnancy (Jawahar et al. 2015; Walsh et al. 2019). Efficient management of stress can help maintain good health and could result in extended lifespan. The hypothalamic-pituitary-adrenal (HPA) axis is the primary stress system in the body, is subject to diurnal variation, and its function changes over time. Altered stress-induced secretion of the hormone cortisol predisposes humans to negative health outcomes (Gaffey et al. 2016) (see Sect. 15.4). The HPA interactions with the hypothalamic-pituitary-gonadal (HPG) axis may explain the sex differences in the responses to stress, to preserve health (Oyola and Handa 2017).

Another type of stress caused by living in an environment with oxygen is oxidative stress. Biomarkers of oxidative stress include: (1) the oxidation products of lipids, proteins and nucleic acids, and molecules such as glutathione, that decrease following oxidation by reactive oxygen species (ROS); (2) activation of ROS-generating enzymes such as xanthine oxidase generating uric acid and allantoin, or myeloperoxidase in phagocytes that generates hypochlorous acid in the presence of $H_2O_2$ and chloride ion, needed in the host defense against pathogen invasion; (3) presence of antioxidants determining the susceptibility to oxidative damage such as superoxide dismutase, catalase, NADPH oxidase, nitrogen oxide synthase, xanthine oxidase, heme oxygenase, and small molecules such as vitamin C, E, bilirubin, etc. that can help to counteract damage; and (4) degree of mutations in the genes encoding enzymes implicated in ROS production or scavengers (Marrocco et al. 2017; Ghezzi 2020).

### Imaging

In the nanomedicine/nanotechnology fields, different types of nanoparticles such as nanoliposomes, solid lipid nanoparticles, nanospheres, dendrimers, quantum dots nano-biosensors, antibody-guided nanomedicines, as well as carbon nanotubes or fullerenes, have potential uses in the diagnosis and therapy of many diseases (Sarecka-Hujar et al. 2020; Ozaki et al. 2015; Oroojalian et al. 2020; Chen et al. 2018; Singh et al. 2018; Farahavar et al. 2019; Derakhshankhah et al. 2020). Multiple safety

studies are ongoing to validate their uses in vivo without adverse effects (Falahati et al. 2019).

Different types of imaging could be used to monitor health and disease, such as radioimmunoimaging (Martinez et al. 2019), near-infrared spectroscopy (NIRS) (Wilson et al. 2018), integrated positron emission tomography (PET)/magnetic resonance imaging (MRI) (Forte et al. 2019) and Raman spectroscopy (Eberhardt et al. 2017; Paolillo et al. 2019). Non-invasive detection of early signs of inflammation can be used as early targeted primary prevention. A novel imaging biomarker, the perivascular fat attenuation index, can be scanned in the heart by computer tomography angiography (Oikonomou et al. 2018). Photoacoustic (PA) imaging is a powerful imaging modality that relies on a PA effect generated when light is absorbed by exogenous contrast agents or endogenous molecules (Upputuri and Pramanik 2020). PA contrast agents have multiple applications as biosensors (in the sensing of metal ions, pH, enzymes, temperature, hypoxia, reactive oxygen species, and reactive nitrogen species) and in bioimaging (lymph nodes, vasculature, tumors, and brain tissue) (Fu et al. 2019).

Rapid developments in the area of wearable and implantable soft bioelectronics would allow real-time monitoring of specific physiological events and early detection of abnormal fluctuations or levels of specific molecular markers (Choi et al. 2019; Yang and Gao 2019).

#### 15.3.1.2 Molecular Markers of Health: Cellular Level

Safe diagnosis of cellular health could be performed either in vivo, by means of probes (Fu et al. 2019; Wallyn et al. 2019), or ex vivo, which requires isolation of cells from organs or tissues to assess their functional performance (Mandavilli et al. 2018). Optimal cellular health can be determined just as in general physical and metabolic exams and requires an individualized reference value as baseline. Some examples are provided below.

Proliferation Capacity

Different adult tissues vary in their growth rates, which is reflected by their proliferative capacity. The colony forming efficiency of skin fibroblasts (ECO-f), and the percentage of dense, mixed and diffuse colonies varied greatly among a group of middle age people. The senescence associated beta-Galactosidase (SA-βgal) (see Sect. 3.2) positive fraction was the largest in diffuse colonies, while expression of the proliferation marker Ki67 was reduced, indicating that quantification of diffuse colonies can help to reveal the extent of skin senescence (Zorin et al. 2017).

Lysosomal Function

The lysosomes are intracellular organelles that degrade extracellular materials during endocytosis and intracellular materials during autophagy. Three different signaling pathways integrate the metabolic inputs, organelle interactions and the control of longevity (Savini et al. 2019). Three main types of autophagy have been recognized, and the many autophagy receptors represent an intricate network responsible for processing damaged and redundant components to yield healthy cells (Abdrakhmanov et al. 2020; Cheng 2019). Enhanced autophagy improves health and delays aging (Fernandez et al. 2018).

Mitochondria Function

The mitochondria are intracellular organelles responsible for bioenergetic and oxidative output, and are therefore considered essential for cell and body health (Hahn and Zuryn 2019), coordinating circadian rhythms, metabolism, the microbiome and immunity (Aguilar-Lopez et al. 2020). Mitophagy is a mitochondrial quality control mechanism that enables the degradation of damaged and excessive mitochondria, preventing detrimental effects. It appears to be strongly associated with the emergence of age-related pathologies (Chen et al. 2020) and it involves defects in the crosstalk between mitochondria and lysosomes (Deus et al. 2020). The presence of a higher number of dysfunctional mitochondria in CD4+ T lymphocytes with age is indicative of defective mitochondria turnover by autophagy, or mitophagy (Bektas et al. 2019).

#### 15.3.1.3 Molecular Markers of Health: Systemic Level

Analysis of body fluids represents one of the least invasive, sensitive and innocuous ways to assess health. A healthy metabolism would be represented by a profile of circulating small molecules and metabolites that conforms with optimal functionality.

Table 15.1 summarizes the estimated values of the numbers of blood cells in subjects belonging to all age groups, according to the established guidelines (Zini et al. 2010; Nordin et al. 2004). The presence of an excessive number or aberrant cells may be a sign of blood cancer. Cytopenias where the number of specific blood subpopulations (erythrocytes, leukocytes, platelets) is reduced compared to normal may be due to nutrient deficiency, peripheral destruction, ongoing infection, autoimmune disease or the side effects of medication (D'Onofrio and Zini 2015).

Table 15.2 summarizes the estimated values of proteins and metabolites in subjects of different age groups. The quantification of such metabolites is, at present, used in clinical medicine to rapidly diagnose the most prevalent metabolic malfunctions. The levels of alanine transferase, albumin, basic phosphatase, bilirubin, carbamide (urea), coagulation factors II + VII + X, C-reactive protein (CRP), creatine, erythrocyte volume, hemoglobin, lactate dehydrogenase, potassium and sodium, are described for

**Table 15.1** Estimated values of the number of blood cell populations at different ages

| | | 0–14 days | 14 days–1 month | 1–2 months | 2 months–2 years | 2–12 years | 12–18 years | 18–125 years |
|---|---|---|---|---|---|---|---|---|
| Leucocytes | B | 5.5–19.3 × $10^9$/L | 6.9–19.9 × $10^9$/L | 6.0–16.3 × $10^9$/L | 6.2–16.2 × $10^9$/L | 4.5–12.5 × $10^9$/L | 4 4–10.5 × $10^9$/L | 3.5–8.8 × $10^9$/L |
| *Leucocyte type* | | | | | | | | |
| Basophyles | B | 0.0–0.5 × $10^9$/L | 0.0–0.3 × $10^9$/L | 0.0–0.3 × $10^9$/L | 0.0–0.3 × $10^9$/L | 0.0–0.3 × $10^9$/L | 0.0–0.2 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Blasts (unspec) | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.0 × $10^9$/L | 0.0–0.0 × $10^9$/L |
| Eosynophils | B | 0.0–0.9 × $10^9$/L | 0.0–0.9 × $10^9$/L | 0.0–0.9 × $10^9$/L | 0.0–0.5 × $10^9$/L | 0.0–0.5 × $10^9$/L | 0.0–0.5 × $10^9$/L | 0.0–0.5 × $10^9$/L |
| Leucocytes (unspec) | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.1 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Lymphocytes | B | 0.8–9.1 × $10^9$/L | 0.8–9.1 × $10^9$/L | 0.8–9.1 × $10^9$/L | 1.2–8.8 × $10^9$/L | 1.0–4.7 × $10^9$/L | 1.1–2.8 × $10^9$/L | 1.0–3.5 × $10^9$/L |
| Metamyelocytes | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.1 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Monocytes | B | 0.1–3.0 × $10^9$/L | 0.2–5.0 × $10^9$/L | 0.2–5.0 × $10^9$/L | 0.3–2.0 × $10^9$/L | 0.3–1.3 × $10^9$/L | 0.3–1.3 × $10^9$/L | 0.2–0.8 × $10^9$/L |
| Myelocytes | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.0 × $10^9$/L | 0.0–0.0 × $10^9$/L |
| Neutrophils | B | 1.7–11 × $10^9$/L | 1.3–11 × $10^9$/L | 1.1–6.0 × $10^9$/L | 1.2–9.6 × $10^9$/L | 1.2–8.9 × $10^9$/L | 2.0–7.1 × $10^9$/L | 1.6–5.9 × $10^9$/L |
| Plasmocytes | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.1 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Promyelocytes | B | N/A | N/A | N/A | N/A | N/A | 0.0–0.1 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Thrombocyte | B | 85–590 × $10^9$/L | 120–555 × $10^9$/L | 135–620 × $10^9$/L | 135–620 × $10^9$/L | 165–435 × $10^9$/L | 165–435 × $10^9$/L | 145–390 × $10^9$/L |

*B* Blood

**Table 15.2** Estimated values of proteins and metabolites at different ages

| | | 0–1 month | 1 month–4 year | 5–8 year | 9–13 year | 14–17 year | 18–125 year | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alanine transferase (all genders) | P | 1–40 U/L | 5–45 U/L | | | | | | | | |
| Alanine transferase (women) | P | | | 8–32 U/L | 8–32 U/L | 8–32 U/L | 10–45 U/L | | | | |
| Alanine transferase (men) | P | | | 8–27 U/L | 8–37 U/L | 8–47 U/L | 10–70 U/L | | | | |
| | | 0–11 month | 1–3 year | 4–5 year | 5–13 year | 14–17 year | 18–39 year | 40–69 year | 70–125 year | | |
| Albumin (all genders) | P | 26–34 g/L | 34–42 g/L | 36–48 g/L | | | 36–48 g/L | 36–45 g/L | 34–45 g/L | | |
| Albumin (girls) | P | | | | 39–47 g/L | 35–47 g/L | | | | | |
| Albumin (boys) | P | | | | 39–50 g/L | 39–50 g/L | | | | | |
| | | All ages | | | | | | | | | |
| Amylase | P | 10–65 U/L | | | | | | | | | |
| | | 0–15 days | 15 days–6 month | 6 month–2 year | 2–6 year | 6–10 year | 10–12 year | 12–14 year | 14–16 year | 16–18 year | 18–125 years |
| Basic phosphatase (all genders) | P | 90–273 U/L | 134–518 U/L | 120–470 U/L | 120–290 U/L | 120–370 U/L | 120–440 U/L | | | | 35–105 U/L |
| Basic phosphatase (girls) | P | | | | | | | 120–390 U/L | 50–270 U/L | 50–120 U/L | |
| Basic phosphatase (boys) | P | | | | | | | 120–530 U/L | 50–420 U/L | 50–280 U/L | |

(continued)

**Table 15.2** (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0–7 days | 7 days–4 year | 5–13 year | 14–17 year | 18–125 year | | | | | |
| Bilirrubin (all genders) | P | <250 micromolar/L | 5–25 micromolar/L | | | 5–25 micromolar/L | | | | | |
| Bilirrubin (girls) | P | | | 3–18 micromolar/L | 3–18 micromolar/L | | | | | | |
| Bilirrubin (boys) | P | | | 3–20 micromolar/L | 3–25 micromolar/L | | | | | | |
| | | 0–2 month | 2–23 month | 2–17 year | 18–49 year | 50–125 year | | | | | |
| Carbamide (all genders) | P | 1.4–5.4 mmol/L | 1,8–5.4 mmol/L | 2.5–7.5 mmol/L | | | | | | | |
| Carbamide (women) | P | | | | 2.6–6.4 mmol/L | 3.1–7.9 mmol/L | | | | | |
| Carbamide (men) | P | | | | 3.2–8.1 mmol/L | 3.5–8.1 mmol/L | | | | | |
| | | 1 day–1 month | 1–6 month | 6 month–125 year | | | | | | | |
| Coagulation factor II + VII + X (Therapeutic region 2.0–3.0 INR) | P | <1.6 INR | <1.3 INR | <1.2 INR | | | | | | | |
| | | All ages | | | | | | | | | |
| C–reactive protein | P | <10 mg/L | | | | | | | | | |
| | | 0–7 days | 7 days–1 month | 1–11 month | 1–5 year | 5–9 year | 9–11 year | 11–14 year | 14–18 year | 18–125 year | |
| Creatine (all genders) | P | 53–97 micromolar/L | 27–62 micromolar/L | 18–35 micromolar/L | 18–66 micromolar/L | | | | | | |

(continued)

**Table 15.2** (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Creatine (women) | P | | | | | 28–50 micromolar/L | 32–58 micromolar/L | 34–62 micromolar/L | 41–80 micromolar/L | 50–90 micromolar/L | |
| Creatine (men) | P | | | | | 26–49 micromolar/L | 31–59 micromolar/L | 39–68 micromolar/L | 52–93 micromolar/L | 60–105 micromolar/L | |
| | | 18–125 year | | | | | | | | | |
| Hemoglobin (women) | B | 7.3–9.5 mmol/L | | | | | | | | | |
| Hemoglobin (men) | B | 8.3–10.5 mmol/L | | | | | | | | | |
| | | 0–14 days | 14 days–1 month | 1–2 month | 2 v–2 year | 2–12 year | 12–18 year | 18–200 year | | | |
| Erythrocyte volume – MCV | Erc(B) | 91–106 fL. | 89–103 fL. | 83–96 fL. | 70–83 fL. | 74–88 fL. | 77–91 fL. | 82–98 fL. | | | |
| | | 0–18 year | 18–125 year | | | | | | | | |
| Hemoglobin–MCHC | Erc(B) | 20.0–22.0 mmol/L | 19.7–22.2 mmol/L | | | | | | | | |
| | | 18–125 year | | | | | | | | | |
| Hemoglobin (women) | B | 7.3–9.5 mmol/L | | | | | | | | | |
| Hemoglobin (men) | B | 8.3–10.5 mmol/L | | | | | | | | | |
| | | 0–1 month | 1 month–3 year | 4 year | 5–13 year | 14–17 year | 18–69 year | 70–125 year | | | |
| Lactate dehydrogenase | P | 125–765 U/L | 155–450 U/L | 100–345 U/L | 157–327 U/L | 121–271 U/L | 105–205 U/L | 115–255 U/L | | | |
| | | 0–7 days | 7 days–1 month | 1–5 month | 6 month–11 months | 1–4 year | 5–17 year | 18–125 year | | | |
| Potassium | P | 3.2–5.5 mmol/L | 3.4–6.0 mmol/L | 3.5–5.6 mmol/L | 3.5–6.1 mmol/L | 3.3–4.6 mmol/L | 3.3–4.3 mmol/L | 3.5–4.4 mmol/L | | | |
| | | 0–4 year | 5–17 year | 18–125 year | | | | | | | |
| Sodium | P | 137–144 mmol/L | 135–147 mmol/L | 137–144 mmol/L | | | | | | | |

Abbreviations *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *B* Blood, *P* Plasma

all age groups (Table 15.2) (Macy et al. 1997; Rustad et al. 2004; Munro 2019). This list is intended to reveal what general markers are used in current clinical practice, but there are numerous other markers that are useful in more disease-oriented settings.

Extracellular vesicles (EV) are membrane-enclosed nanoparticles, of varying size from 40 to >500 nm, that contain proteins, nucleotides, lipids and metabolites that are released by cells into body fluids. Their origin can be traced back to a given organ and they are therefore gaining a great deal of attention to describe their contents and their destiny, in connection with various disease pathologies. Many types of EV's have been discovered but much work remains to characterize their biological functions. For example, the precise biological roles of EV heterogeneity such as endosomal exosomes (Jeppesen et al. 2019) and exomeres with unique protein and lipid profiles (Zhang et al. 2019a) are currently being investigated.

Extracellular RNAs, such as microRNAs and circular RNA's, have been described as biomarkers of disease progression and could also be used as therapeutic targets (Das et al. 2019). Blood and body fluids contain cell-free DNA that can be analyzed for the early detection of genetic and epigenetic alterations from its cell of origin, and whose presence can help reveal cancer development long before an actual diagnosis can be established (van der Pol and Mouliere 2019). Also, the presence of cell-free DNA, to study age-associated changes to the epigenome, has been proposed as a biomarker of aging, and is increased in unhealthy individuals (Teo et al. 2019). Blood also contains circulating cell-free respiratory competent mitochondria whose function and fate with relation to health and disease progression is only beginning to be described (Al Amir Dache et al. 2020).

High-throughput NMR metabolomics was used to identify metabolic predictors of long-term mortality in the EDTA plasma and serum samples from 44,168 individuals (age at baseline 18–109). Out of 226 metabolic biomarkers, 14 proved to be better markers of all-cause mortality compared to conventional risk factors (see 1.1 Molecular markers of mortality) (Deelen et al. 2019b).

These efforts might help to estimate the disease vulnerability of elderly people that could be subsequently offered personalized interventions to try to fend-off further development of future disease states.

The human serum metabolome contains many more metabolites that might have even better predictive value than the most recent findings, but their identity remains to be explored in future studies (Psychogios et al. 2011). Biomarker profiling in 17,345 persons by nuclear magnetic resonance spectroscopy revealed 106 biomarkers that improved prediction of the short-term risk of death from all causes above established risk factors, but their role in health maintenance and how to prevent their emergence awaits further studies (Fischer et al. 2014).

Volatile organic compounds (VOC) detectable in breath, urine and feces, associated with the metabolome, have distinct profiles that can discriminate between young and old, and may represent future signatures of healthy aging (Conte et al. 2020).

In neurodegenerative function, plasma protein levels can predict conversion to dementia from prodromal disease, correlating well with disease severity and cognitive decline (Hye et al. 2014; Zetterberg and Burnham 2019).

Kidney function can be measured very reliably by estimating the glomerular filtration rate (eGFR), a value that decreases gradually with age. The rate of decline can be used as a predictor of disease (Levey and Inker 2017). However, several blood filtration biomarkers such as creatinine or plasma proteins such as cystatin C and serum stem cell factor showed strong associations with eGFR, indicating that they can reliably predict a decline in kidney function in healthy aging adults (Levey and Inker 2017; Zhang et al. 2019b).

### *15.3.2 Biomarkers of Aging and Their Association with Health*

Cellular senescence is a cell state implicated in various physiological processes and a wide spectrum of age-related diseases. Senescent cells have been identified during embryogenesis where they participate in tissue development but can also be detected at other life stages (Gorgoulis et al. 2019; Childs et al. 2017). Different types of senescence have been characterized that exhibit distinctive hallmarks (Hernandez-Segura et al. 2018).

An impaired immune surveillance accelerates the accumulation of senescent cells and aging (Ovadya et al. 2018). Clearance of senescent cells by the immune system is an important maintenance system governing their presence in the body (Prata et al. 2018).

Cellular senescence has since been identified as a response to numerous stressors, including exposure to genotoxic agents, nutrient deprivation, hypoxia, mitochondrial dysfunction, and oncogene activation and can be quantified with the help of aging biomarkers (Xia et al. 2017; Ferrucci et al. 2020). One of the world's longest running longitudinal studies, the Baltimore Longitudinal Study of Aging (BLSA) has rendered information to identify metrics of aging that may capture the hierarchical and temporal relationships between functional aging, phenotypic aging and biological aging based on four hypothesized domains: body composition, energy regulation, homeostatic mechanisms and neurodegeneration or neuroplasticity. This could help to classify the heterogeneity of aging trajectories that exist among individuals (Kuo et al. 2020), and will be helpful to reveal health trajectories based on successful recovery mechanisms (see Sect. 15.4).

Severe stress can induce the so-called stress-induced premature senescence (SIPS) characterized by accelerated appearance of aging features due to a number of causes, among them environmental exposure to stressors (Ott et al. 2018; Hernandez-Segura et al. 2018).

Hair greying is a phenotypic hallmark of aging, is associated with active hair growth, and several molecular markers are differentially expressed in white hair (Choi et al. 2011). Hair density, diameter, growth rate and anagen/telogen ratio are parameters affected by health status and aging (Schneider et al. 2009).

Determination of senescence burden in organs relies on identifying cells with senescent characteristics, based on a number of biomarkers. The most practical way to assess senescence burden is to identify the number of circulating blood immune cells such as T lymphocytes that are senescent. Also, the degree of DNA methylation in blood cells have been correlated with increasing chronological aging and can predict health span (Lu et al. 2019).

Cellular hallmarks of the senescent phenotype are cell cycle withdrawal, morphological changes, resistance to apoptosis, macromolecular damage, deregulated signaling pathways and metabolism, and a characteristic senescence-associated secretory phenotype (SASP) (Hernandez-Segura et al. 2018).

### *15.3.3 Molecular Markers of Frailty*

An increase in certain blood markers can be indicative of increased frailty, defined as a syndrome of physiological decline that increases the vulnerability to health outcomes, that is, defective or slow recovery from stressors such as trauma or acute illness. Frailty can be assessed by general approaches but quantification of the level of frailty using molecular markers has not yet been implemented. A preliminary study assigned 44 possible frailty biomarkers to six "hallmark of aging" pathways, e.g. inflammation (CXCL10, IL-6, CX3CL1), mitochondria and apoptosis (GDF-15, FNDC5, vimentin), calcium homeostasis (regucalcin, calreticulin), fibrosis (plasminogen activator, urokinase, angiotensinogen), neuromuscular junction and neurons (BDNF, progranulin), and cytoskeleton and hormones (α-klotho, FGF23, FGF21, leptin) (Cardoso et al. 2018), and awaits further validation in longitudinal studies.

Mitochondria stress elicits the production of stress response mitokines such as humanin, FGF21 and GDF15, which have been found to be associated with worsened parameters including handgrip strength, insulin sensitivity and triglycerides, and their levels are inversely correlated with survival in the oldest individuals (Conte et al. 2019). GDF15 is a predictor of mortality in patients with type 2 diabetes, cardiovascular disease or chronic kidney disease (Emmerson et al. 2018). Recently, GDF15 was reported as one member of the SASP (see molecules secreted by senescent cells (Basisty et al. 2020). Thus, early detection of the presence of SASP molecules in blood, could represent a warning signal of early health decay due to the presence and accumulation of senescent cells somewhere in the body.

Another biomarker of frailty is systemic beta2-Microglobulin (β2 M) accumulation in aging blood, which promotes age-related cognitive dysfunction and impairs neurogenesis (Smith et al. 2015; Annweiler et al. 2011).

The plasma levels of total and unmethylated cell-free DNA and the mitochondrial DNA copy number could serve as biomarkers of frailty (Jylhava et al. 2013). Circulating levels of serum monocyte chemoattractant protein-1 (MCP-1) also known as CCL-2 are elevated in frail older adults (Yousefzadeh et al. 2018).

### 15.3.4 Molecular Markers of Mortality

Given that optimal health implies the presence of optimal levels of health-promoting biomarkers, it is crucial to understand what brings about the presence of metabolic biomarkers associated with all-cause mortality and disease-specific mortality. The study by Deelen et al. (2019a, b) uncovered a short-list of 14 biomarkers that represent general health up to the highest ages and are not specific to specific disease-related death causes. Such molecular markers include several amino acids (histidine, isoleucine, leucine, valine, phenylalanine), glucose, lactate, acetoacetate, albumin, glycoprotein acetyls, total lipid levels in chylomicrons and very large VLDL (XXL-VLDL-L), total lipids in small HDL (S-HDL-L), mean diameter of VLDL particles (VLDL-D) and the ratio of polyunsaturated fatty acids to total fatty acids (%) (Deelen et al. 2019b). One reliable predictor of mortality is suPAR, as mentioned previously (Desmedt et al. 2017).

### 15.3.5 Markers of Rejuvenation

Parabiosis experiments led to the findings that exposure of an aged animal to young blood could counteract and reverse pre-existing effects of aging such as immune system impairment (Pishel et al. 2012), cardiac hypertrophy by means of Growth Differentiation Factor 11 (Loffredo et al. 2013), brain aging by rejuvenating synaptic plasticity and improving cognitive function (Villeda et al. 2014; Katsimpardi et al. 2014), hepatic function alterations through the restoration of autophagy (Liu et al. 2018), etc. GDF11 is considered a marker of successful aging (Elliott et al. 2017) but several contradicting reports state the opposite, that GDF11 is a frailty marker that increases with age and inhibits muscle regeneration (Egerman et al. 2015).

Another approach for rejuvenation is by means of inhibition of p38α and p38β mitogen-activated kinase pathway, associated with SASP, in old muscle stem cells, rendering a population that is regenerated that can be transplanted to strengthen damaged muscles of old mice (Cosgrove et al. 2014; Freund et al. 2011). The use of senolytics to eradicate senescent cells is another promising intervention avenue that could extend the health span (Kirkland and Tchkonia 2017).

The thymus regeneration, immunorestoration and insulin mitigation trial (TRIIM) used human growth hormone to successfully reverse epigenetic aging and immunosenescent trends by reducing the level of DNA methylation, a well-known marker of biological aging (Fahy et al. 2019).

## 15.4 Vulnerability and Recovery Strategies

Specific individual vulnerability to environmental cues might cause disease, affect health trajectories and accelerate biological aging. Some people are more susceptible to damage and are therefore prone to develop disease. This susceptibility can be specific to a given organ or generalized, though the former is well-studied in the pathogenesis of numerous diseases.

Strategies for recovery, coping, restoration or resolution are compensatory mechanisms of health preservation, physical or mental, to ensure that the body can continue its physiological function despite an alteration in natural function (Naviaux 2019). These mechanisms have evolved in all humans, but the efficiency of the processes is thought to vary from individual to individual. It is therefore important to identify the key processes in each individual health trajectory that can reveal whether the person is more or less vulnerable to a health-destabilizing effector.

The body is vulnerable to burden agents such as reactive oxygen species (ROS) that exert oxidative stress (Marrocco et al. 2017; Dubreuil et al. 2020), inherited mutations (Tenesa and Haley 2013; Jonsson et al. 2018), composition of gut microbiota (Flandroy et al. 2018; Kim and Jazwinski 2018; Marchesi et al. 2016), social inequalities (Cullati et al. 2018; Aburto et al. 2018; van Raalte et al. 2018), type of diet and meal timing (Fontana and Partridge 2015), environmental agents causing mutational signatures (Kucab et al. 2019), mechanical stress (Nava et al. 2020) and many more. Therefore, the genetic susceptibility to those cues, that can have adverse effects on the body, should be known very early on, under parental and professional guidance.

Numerous compensatory mechanisms have evolved to deal with functional imbalances, and involve interactions between all body systems such as the endocrine, immune, circulatory systems, and the interactivity levels depends on what organ or area of the body that is affected. For example, during acute trauma or in the event of disease, acute inflammation will take place. Systemic chronic inflammation is involved in the etiology of disease across the life span (Furman et al. 2019; Ferrucci and Fabbri 2018), indicating that health preservation strategies require avoidance of such events. Many attempts are being explored at understanding and strengthening the mechanisms behind the resolution of inflammation (Alessandri et al. 2013; Basil and Levy 2016; Serhan and Levy 2018; Sugimoto et al. 2019).

In other examples, compensatory mechanisms mediated by baroreceptor reflexes are at work when there is a sudden drop of blood pressure that elicits vasoconstriction and increased heart rate (Goswami et al. 2019) or when hypertension becomes chronic (Frame and Wainford 2018). Also, when exposed to $CO_2$, neural control of breathing is regulated via central respiratory chemoreception reflex (Guyenet and Bayliss 2015). Muscle weakness and fatigue was improved in geriatric patients with higher levels of Hsp27 (Beyer et al. 2012).

The presence of sugar in the blood elicits insulin production by the beta cells from the pancreas. Beta cell mass adaptation is a physiological process that occurs efficiently from birth to early childhood periods and during pregnancy, and it is a

highly regulated mechanism for establishing, maintaining, and adapting islet function to meet physiological demands (Salas et al. 2014). Understanding the compensatory mechanisms behind these adaptations, would help to prevent premature senescence involved in the etiology of type 2 diabetes by means of exogenous interventions (Palmer et al. 2015).

At the core of cellular turnover lies the stem cell compartments within the body. These reserves help to compensate for the loss of damaged cells but also participate in the programmed and periodical replenishment of the blood cell compartment. Sirtuins are NAD+-dependent enzymes that have crucial roles in stem cell maintenance and tissue regeneration, protecting against adult stem cell depletion in response to stress and aging (Fang et al. 2019). Optimal health has been associated with robust turnover capacity of the bone marrow stem cell reservoir. The in vivo dynamics of hematopoietic stem cells has been investigated (Scala and Aiuti 2019) and with age, clonal hematopoiesis with and without driver mutations arise, and for reasons that remain unexplained, some individual trajectories will lead to hematological malignancies while others can sustain a very long life with fewer chronic diseases (Zink et al. 2017).

Compartmentalization is a subconscious psychological defense mechanism that helps to put anger, sadness, fright, suffering, and disappointment feelings away until they can be dealt with efficiently. Psychological resilience may help reduce the harmful effects of cortisol secretion (Gaffey et al. 2016). Several neurobiological mechanisms of stress resilience have been uncovered that help preserve health, which has consequences for the aged population (Faye et al. 2018).

Improved health resulting in lengthening of the disease-free health span, and eventually leading to longevity, is a complex combination of genetic predisposition, epigenetic influence and dietary interventions (Costa et al. 2019). Exposure to mild stress can strengthen homeodynamics and can postpone senescence through the phenomenon of hormesis. Hormesis is any process in a cell or organism that exhibits a biphasic response to exposure to increasing amounts of a substance or condition. Within the hormetic zone, there is generally a favorable biological response to low exposures to toxins and other stressors (Rattan et al. 2018). For example, dietary restriction increases life span through endoplasmic reticulum hormesis (Matai et al. 2019). Numerous phytochemicals have hormetic effects on cellular responses resulting in the delay of aging and chronic diseases (Martel et al. 2019).

Successful aging trajectories are compensatory mechanisms that generate a seemingly healthy state that allows individuals to reach a relatively high age despite the presence of non-aggravating conditions. This is achieved by tissue-specific expression of multiple genes at chromosomes 5q13.3, 12q13.2, 17q21.31, and 19q13.32 and the strong influence of the APOE and GRP78 genotypes associated with longevity and health maintenance (Deelen et al. 2019a).

## 15.5 Conclusions

Heath profiles based on detectable markers of health could better contribute to estimate the potential risks of developing a pathology that eventually would lead to a chronic disease. Molecular signatures of personalized health will be based on each individual's optimal values, at the height of their function, e.g. in early adulthood, representing a baseline of reference; significant deviations from this baseline would require intervention.

Prophylaxis to avoid disease beyond vaccines, surgery, and consultations with medical doctors and dentists, has evolved among the general public to include lifestyle interventions such as exercise, nutrition, avoidance of toxic substances, etc.

Validation of several molecular markers of health in longitudinal studies will be needed to improve the knowledge regarding what causal factors and interventions can modulate those markers to preserve the physiological turnover. At present, much research focus is oriented at biomarkers of disease, frailty and mortality, but less on compensatory and recovery markers.

A state of good health could be maintained following preventive measurements and active intervention programs trying to avoid further worsening of the molecular health values or by attempts to bring them back to the person's known reference values. Postponement of the inevitable accumulation of damage leading to senescence, frailty and mortality will undoubtedly preserve health and render productive and functional human lives.

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# Chapter 16
# The Dynamic Pathosome: A Surrogate for Health and Disease


**Peter Lenart, Martin Scheringer, and Julie Bienertová-Vašků**

**Abstract** Regardless of chosen definitions, health, as well as disease, are in their essence only labels describing two enormous groups of phenotypes. Thus, to study either health or disease, we need to understand the factors affecting the development of specific phenotypes. The current paradigm used to explain the development of phenotypes oversimplifies the entire process by omitting the key factor of time. The novel concept of the dynamic pathosome aims to provide a much more detailed picture than the current paradigm. It provides a novel theoretical framework as well as practical applications, but most importantly can change how we perceive health and disease. This chapter reviews the concept of the dynamic pathosome and the benefits it could offer to biomedicine.

**Keywords** Disease · Health · Aging · Individualized medicine · Phenotype trajectories

## 16.1 Introduction

There are many ways to define health and disease. Moreover, these definitions develop over time and as a result, some conditions which were previously considered to be a disease, e.g., homosexuality (Ereshefsky 2009; Gonsiorek 1991; see also De Block's

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contribution to this volume), are not considered to be one anymore. On the other hand, some conditions which were not considered as diseases, e.g., obesity (De Lorenzo et al. 2019; Jung 1997), now are. It may thus seem that describing the general factors affecting the development of diseases is a futile attempt destined to be relevant only for a short period of time under the framework of one particular definition of disease. However, we think this is too pessimistic a viewpoint. Regardless of the chosen definition, a specific disease will always be characterized by a specific phenotype. There is no other way; disease always has to be described by a specific phenotype, otherwise there would be no way to diagnose it. Therefore, describing the general factors affecting the development of the disease is the same as describing factors affecting the development of phenotypes.

## 16.2 The Need for a New Paradigm

Most biomedical research currently operates under a simple paradigm stating that a specific phenotype is the result of interactions between a specific genotype and a specific environment. This framework is certainly useful and has been employed for so long that few even stop to think about it. Nevertheless, in its core it is a great simplification of a much more complicated story. To demonstrate this, imagine an experiment with three genetically identical inbred mice that are exposed to the same environmental stimuli. Will they develop the same phenotype? At first sight, many may be inclined to say yes. However, the correct answer is, it depends. For example, if the mice have a different age then they will most likely develop a different phenotype. As demonstrated by a 2017 study, this is true, at both behavioral and molecular levels, even for something as universal as a reaction to a painful stimulus (Sadler et al. 2017).

Stating that aging is an important factor contributing to the development of specific phenotypes may seem obvious to the point that some may even argue it is pointless to emphasize it. However, even though the importance of age in this context may be self-evident, a great portion of biomedical research continues to ignore it. Studies on mice often do not even report the age of used animals (Kilkenny et al. 2010) and different studies investigating the development of the same disease on the same animal models often use animals of different age (Jackson et al. 2017). And while disregarding the effect of age is certainly not the only factor causing the widespread problem of irreproducible results of preclinical studies (Ioannidis 2005; Voelkl et al. 2018), it likely plays at least some role. Another similar factor may be a widespread reluctance to consider effects of biological sex, which is best demonstrated by the fact that most rodents used in research are male (Beery 2018). It is easy to criticize such mistakes as an obvious flaw in study design. However, their prevalence clearly shows that the underlying paradigm guiding animal research insufficiently highlights the importance of these factors.

The situation with studies on human subjects seems to be better as it is rare to find a population-based study that does not at least report the age of its participants. However, studies working exclusively with human tissues are something else entirely.

It is not uncommon to find otherwise very well-conducted studies that compare healthy and, e.g., cancerous tissues without even reporting the age of patients from which the tissues were extracted. Thus, such studies fail to consider that the difference in e.g., miRNA expression profiles between tissues may be caused by the different age of subjects from which were they taken. This is made even more likely by the fact that the majority of chronic diseases including most types of cancer (Magalhães 2013) and cardiovascular diseases (North and Sinclair 2012) show a clear age-dependency. Surprisingly, such possible problems are rarely considered, even though it is well known that effects of single nucleotide polymorphisms (SNPs) (Doherty et al. 2017), expression of miRNAs (Huan et al. 2018), levels of metabolites in blood (Bunning et al. 2019) as well as gene expression change with age (Harris et al. 2017). Furthermore, a recent study even demonstrated that human plasma proteome changes with age in a non-linear fashion (Lehallier et al. 2019). To combat this prevalent problem, biology needs a new paradigm emphasizing the role of aging in the formation of phenotypes.

However, even the precise knowledge of biological age, current environmental factors, and genotype of an individual is not enough to determine a precise phenotype. There is one more aspect missing. Let us, once again, imagine an experiment with a group of genetically identical mice. They have precisely the same age and are subjected to the same environmental stimuli: inoculation with a deadly pathogen strain. Will they all develop the same phenotype and die? Possibly yes, but not necessarily. Some of them may have been vaccinated in the past and, in that case, unvaccinated mice will develop the disease and die while vaccinated mice will live on without serious problems. Once again, this example may seem trivial. But, it clearly shows that the history of environmental interactions often plays a crucial role in determining the final phenotypes including important health outcomes such as life and death. Nevertheless, the history of previous environmental interaction is probably even more underappreciated than aging in much of biomedical research, for a very simple reason: it is extremely hard to record.

As explained above, the optimal model trying to understand the development of any phenotype in a given individual should account for a genetic constitution (including biological sex) as well as for the current and former interactions with the environment and the process of aging. Unfortunately, while fully describing all these factors may one day be feasible in model organisms, it is unattainable in humans. Even though it is possible to determine the genetic constitution of studied individuals and it may one day become possible to determine their precise biological age [e.g., by some future variation of methylation age (Horvath 2013)] we cannot realistically hope to capture all their interactions with the environment. In other words, studies on humans are always limited only to a certain subset of environmental interactions for a given individual or population. Furthermore, even information about environmental interactions that we focus on, e.g., some chemical exposure, is limited to a specific time point or to a certain period. Therefore, even the best designed human epidemiological studies are unable to fully account for the effects of the environment, which likely limits their ability to explain their observations accurately and make useful predictions.

Nevertheless, we think there is a way how to overcome some of these obstacles in an evaluation of genotype-environment interactions. We have previously published a concept called the "dynamic pathosome" (Lenart et al. 2019), which aims to resolve some of the problems mentioned above. Before we describe our model in more detail, let us clarify two critical assumptions upon which the model is built. First, because the history of genotype-environment interactions strongly affects the phenotype, the phenotype itself reflects this history and can, therefore, be, in principle, utilized to estimate previous interactions with the environment. Second, for all practical purposes, all phenotypes are interlinked, and no phenotype exists in isolation. Every phenotype in any living organism has to have a preceding and a subsequent phenotype. Before a person develops a phenotype characteristic of a given pathology, he or she has to develop several preceding transient phenotypes. Furthermore, these transient phenotypes cannot, in principle, be random. They have to be ordered in a logical fashion as they all originate in the initial "healthy" phenotype and diverge from it only by a gradual accumulation of small changes.

## 16.3 The Dynamic Pathosome

The sum of the genetic constitution of a living system (including biological sex), the environmental factors affecting it in the present as well as in the past, and the process of aging may be visualized using a three-dimensional representation, e.g., a cube (Fig. 16.1). The specific place which an individual occupies inside this 3D-space at any particular moment then determines their phenotype or, in other words, their state of health or disease. This model comprising all dimensions affecting the development of diseases is termed the pathosome (Lenart et al. 2019).

Here it is important to emphasize that for the purpose of the pathosome model, the environment is understood in the widest meaning possible as everything which is not the organism itself, thus including even the effects of the microbiome or social stimuli. Furthermore, the epigenome is also contained in the pathosome because the epigenome itself forms as a result of genotype-environment interaction.

The concept of the pathosome implies that detailed knowledge about the genetic constitution and biological age should allow us to use phenotypic data to estimate the organism's previous interactions with the environment. This suggestion may seem far-fetched, however, in its essence, it is a principle long applied in many disciplines. For example, in certain cases it is possible to determine that individuals overcome a particular disease or injury due to the presence of a specific lesion, e.g., people who survived the smallpox were recognizable for the rest of their life by a distinctive indelible scarring (Regan and Norton 2004). Furthermore, forensic science, as well as anthropology, routinely utilizes phenotypic data to estimate some types of previous interactions with the environment. In addition to a well-known ability of these disciplines to determine causes of death by the shapes and types of wounds, these disciplines use many more subtle phenotypic clues to find out events from the life of studied persons. For example, the detection of a radiopaque transverse

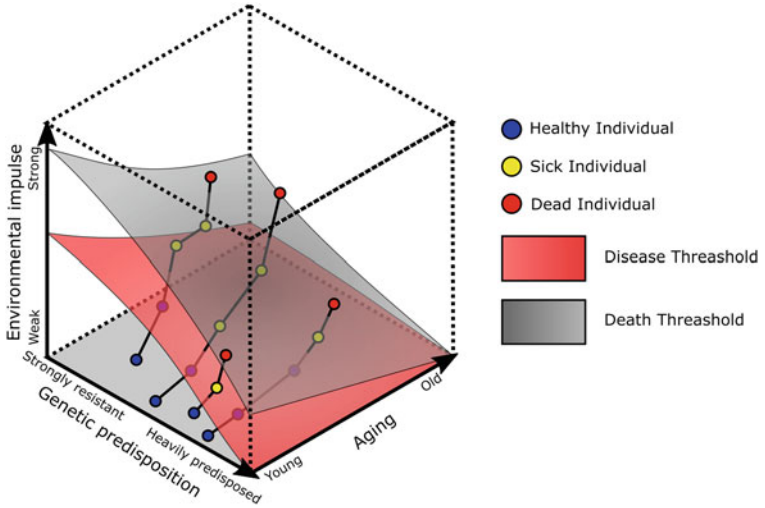


**Fig. 16.1** Graphical representation of the pathosome cube. With respect to a certain disease, some individuals are genetically more predisposed than others. Some will develop the disease even without any outside influence while others need stronger environmental stimuli for the disease manifestation to be initiated. Furthermore, the power of environmental impulses needed for disease development decreases with time and in some cases, progress in time may be all that is needed for the disease to appear. The phenotype of a given individual at a particular time is represented by a colored dot. With time, the phenotypes change, which is represented in this figure by a line connecting phenotypes of a particular individual, and the set of connected phenotypes of an individual represents an individual's phenotypic trajectory

line in the metaphysis of the long bones, known as the Harris line, is a well-established indicator of nutritional stresses, especially protein and vitamin deficiencies (Beom et al. 2014; Robb et al. 2001).

The pathosome framework also implies that large-scale environmental impulses cause profound phenotype changes while small-scale environmental impulses alter the phenotype to a lesser extent. Therefore, it allows us to compare the "impact" of the environmental impulse, which is in this view proportional to the extent of the phenotype change it inflicts on genetically identical individuals of the same age (Lenart et al. 2019). For example, it has been shown that if one monozygotic twin was sick more times than the other during their childhood he or she will also likely be smaller in adulthood than the sibling (Hwang et al. 2013). Nevertheless, the difference in the height of such monozygotic twins will be, on average, rather small and there are many stronger environmental factors which would lead to bigger changes in adult phenotypes e.g., childhood malnutrition.

As stated above, the pathosome framework assumes that any specific phenotype is shaped by the combination of three factors: genetic composition, environmental influences, and aging. It is important to further emphasize that by definition such a phenotype is not a static entity but continues to evolve over time as the age of the individual and environmental influences continue to change. The chain of evolving

phenotypes connected in time can be then visualized for an individual as a phenotypic trajectory (Fig. 16.1). A good example of a phenotype that clearly evolves over time is a body height that changes drastically during childhood but is also not static in adulthood as it can be affected by injuries, illnesses, and is in the end also affected by aging. No phenotype is static and even such phenotypes as the color of eyes, hair or even skin can, to some extent, change over time as a consequence of aging or various environmental stimuli (Burg 2019; Cho et al. 2019; Wistrand et al. 1997). Molecular phenotypes, by which we mean the expression levels of specific molecules (e.g., insulin, TNF-α, Thyroxine and countless others), are no different and also evolve over time. A recent study utilizing a longitudinal deep multi-omics profiling of 106 individuals aged 29–75 years conclusively showed that human molecular phenotypes change with age in patterns which may share certain similarities but are to a large extent specific to an individual (Ahadi et al. 2020). The authors of the study named these distinct aging patterns as "ageotypes", however they can also be considered as a clear example of phenotype trajectories.

The ever-changing nature of phenotypes means that there is no single universal "state of health" or "state of disease" but rather an incalculable number of states evolving from one to another continuously from a human's conception to death. From a more practical viewpoint, the ever-evolving nature of phenotypes is a factor that can complicate the diagnosis and therapy of many diseases as well as the promotion of health. The biggest problems arise from the highly cross-sectional nature of the current diagnostic methodologies, which are unable to take into account the longitudinal/temporal aspect. In its essence, any specific disease phenotype is only a static simplification of the real dynamic process similar to a comparison of a single photo to a video film. Therefore, even perfect diagnostic criteria designed according to such a "photo" may turn out to be unsatisfactory when applied to a real, dynamic "video", e.g., individuals from an age group different from those for which the criteria were originally tailored. This point, which we also raised previously (Lenart et al. 2019), was demonstrated with surprising clarity by a recent study published in *Nature Medicine* (Ahadi et al. 2020). Among many other results, this study showed that, while levels of creatinine were positively correlated with age at the cross-sectional population level in the studied cohort, in more than 70% of the studied individuals, levels of creatinine decreased with age (Ahadi et al. 2020). Thus, as we suggested before, biomarkers identified from cross-sectional population data may, in some circumstances, lead to entirely incorrect predictions when applied to individuals.

The most important novel implication of the concept of the dynamic pathosome is that the future phenotypes are shaped by previous phenotypes, both their sum and order. In many cases this is rather intuitive as e.g., obesity is well known to affect the risk of various other diseases but in other cases the role of previous phenotypes is more subtle. For example, it has been shown that epithelial tissue has an innate inflammatory memory which allows it to react faster to recurring damage and facilitate more effective tissue repair (Naik et al. 2017). It is probable that similar tissue memory works for other tissues as well. Thus, even after a phenotype seemingly recurs e.g., a small cut heals without leaving a scar, it still leads to lasting

changes at the molecular level that actively affect future phenotypes. Furthermore, an immunological memory or, in other words, the "ability of the immune system to recall previous exposure to pathogens and strongly respond upon re-encountering the same pathogens " (Martinez-Gonzalez et al. 2018) is a well-known mechanism by which a previous phenotype can affect the formation of phenotypes in the future. If an organism had a phenotype associated with a disease caused by a particular pathogen and is again exposed to the same or a related type of pathogen, the organisms will often develop very different phenotypes compared to those it would after the first encounter. Another, well-documented example of a phenotype being shaped by previous phenotypes is the pregnancy-specific condition characterized by hypertension and proteinuria known as preeclampsia. Even when women no longer show symptoms of preeclampsia they still have a higher risk of hypertension than women who never had preeclampsia (Garovic and August 2013). Furthermore, the recent study by Ahadi et al. (2020) demonstrated that levels of several biomarkers develop differently with age in individuals who are insulin-resistant compared to insulin-sensitive individuals (Ahadi et al. 2020). Such data thus strongly support the idea that our current phenotype also affects our future phenotypes at a molecular level.

In summary, the concept of the dynamic pathosome suggests that phenotypes develop over time and this development is not random but governed by certain regularities which can be studied and understood (Lenart et al. 2019). Phenotypic change over time may be then visualized in a form of a phenotypic trajectory, attributes of such trajectories (mainly size, shape and direction) can then be quantified and even statistically compared. Interestingly, there are existing fields outside of biomedicine already working with phenotype trajectories. Specifically, phenotype trajectories, even though placed on very different timescales, are already studied in evolutionary biology (Adams and Collyer 2009) and some approaches developed there could be easily modified for biomedical purposes.

## 16.4 The Central Presumption of the Dynamic Pathosome

There are five presumptions central to the concept of the dynamic pathosome.

First, for every individual in every environment, there is a continuum of health and disease phenotypes. The phenotypes change from one to another over time, placing an individual in various states of health and disease. In other words, phenotypes are not static. Every phenotype can change with time. Most of them change spontaneously, first rapidly during growth and then at a slower pace during aging. However, even those rare phenotypes which are not affected that much by growth and aging, such as eye color or skin pigmentation, can change as a consequence of disease or injury.

Second, every organism at its conception has the potential to achieve a vast number of future phenotypes, limited only by its genetic constitution and maternal/paternal influences. However, as time progresses more and more options are inevitably lost, and the number of possible future phenotypes gradually decreases. Therefore, as time progresses it is easier to place specific phenotypes on specific phenotype trajectories

and estimate their future development. For example, at birth, one may with a certain accuracy predict an adult height of a newborn based on its genetics (i.e., heights of the parents). However, at his or her 15th birthday, we can certainly make the same prediction with much greater accuracy based on their current height and growth patterns.

In a sense, the second assumption of the dynamic pathosome is somewhat similar to the concept of cell fate determination long used in developmental biology. In the beginning, there are totipotent cells that have the potential to differentiate into all cell types. However, with successive differentiations, the number of cell types to which the cell can differentiate decreases until the cell is committed to a certain cell fate. At this point, if the cell is not affected by some disturbing stimuli it will, in most cases, continue its differentiation along one pre-determined path. Further along the cell's journey, the cell fate becomes determined, at which point, under physiological conditions, no matter what happens, the cells differentiate into one final, specific cell type.

In the framework of the dynamic pathosome, we can think about the phenotypic potential of any organism along similar lines. At the time of conception, the number of possible future phenotypes is maximal. As time progresses some of these options are no longer available. They may have been lost because they were accessible only up to a precise time point in development, or because an organism acquired some injury or chronic disease and can no longer develop phenotypes characterized by their absence. This point can be nicely illustrated by a hypothetical scenario. Let us imagine a young and healthy Chef in a high-pressure environment of a highly ranked restaurant. One day, he cuts his left hand. In the best-case scenario, he will have a small, barely visible scar. In the worst-case scenario, he will deeply cut his finger and develop an antibiotic-resistant infection which will force doctors to amputate his left hand. One way or another, his set of possible future phenotypes (SPP) decreases. If he gains a scar, he will no longer be able to achieve any phenotype without the scar and his SPP will thus shrink a little. If he loses his hand, he will no longer be able to achieve any phenotype with his hand, making his SPP much smaller. Later in life, this unlucky person may develop hypertension, which will further reduce his SPP, because now he will no longer be able to attain any phenotype that excludes hypertension. Accordingly, all injuries and illnesses reduce our SPP, which in turn shrinks more and more as time progresses.

The third presumption is that the temporal aspect is inseparable from the phenotype. Greying of hair at ten is not the same as greying of hair at sixty, meaning that the same phenotype at different ages may be part of much different phenotype trajectories. To give a more specific example, a sarcoma diagnosed in a person above sixty is most likely caused by a history of genotype-environment interaction that we would often simply call "bad luck", whereas a sarcoma diagnosed in a person under forty-five is a strong indicator of the Li-Fraumeni syndrome caused by a mutation in TP53 (Varley 2003). A less extreme example can be the timing of the first menstrual cycle in women, i.e., menarche. Earlier menarche is associated with a higher BMI in adulthood (Gill et al. 2018), metabolic syndrome (Stöckl et al. 2011) increased risk of breast cancer (Morris et al. 2010), increased all-cause mortality (Charalampopoulos

et al. 2014) and others (Dvornyk and Waqar-ul-Haq 2012). Thus, even the timing of a regular physiological process can tell us a lot about future phenotype trajectories of an individual. The only plausible exception from the rule that the temporal aspect is inseparable from the phenotype are organisms with negligible senescence such as hydra, naked mole-rat, and others (Jones et al. 2014; Martínez 1998; Ruby et al. 2018; Schaible et al. 2015).

Fourth, after reaching a certain threshold, organisms may reset some parameters (e.g., blood pressure) to remain adaptive under the current conditions. However, such resets often constitute a certain trade-off between short- and long-term goals, and may, in the end negatively affect the long term survival of the organism. In general, the thresholds mentioned above may be characterized by the level of stress, and because of that, the power of environmental stimuli in the pathosome framework may also be estimated as the level of stress caused in an organism by an action of a stressor.

Unfortunately, while the concept of stress is utilized across many disciplines ranging from psychology to cell biology, there is currently no established method able to objectively assess stress or quantify and compare its levels within and between individuals. Nevertheless, this does not mean such an assessment of stress is inherently impossible. For example, the concept of stress entropic load (SEL) intends to estimate the levels of stress by calculating the entropy production of an organism (Bienertová-Vašků et al. 2016). The logic behind this approach is rather simple. Entropy production is directly related to energy flow and since every adaptation has to have some energy costs, measuring the entropy production of living organisms should reflect the adaptation costs in any given moment and hence measure stress (Bienertová-Vašků et al. 2016). However, while a small pilot study has shown that SEL can indeed be measured in humans and seems to predict a prolonged mental effort (Zlámal et al. 2018), it is still a long way from becoming an accepted marker of stress. Nevertheless, should SEL ever become a recognized marker of stress it will also become a useful tool for interpreting the dynamic pathosome.

Fifth, the process of adaptation to the surrounding environment is a never-ending struggle of an organism to balance the costs and possible gains of adaptation. The temporal aspect is also important here because the costs, as well as possible gains of adaptation, can profoundly change with the organism's age. From this, it follows that the dynamic pathosome, which represents a unique pattern of phenotypic variability in time and space, also represents a personal adaptation trajectory.

In the fourth and the fifth presumption, the concept of pathosome has a strong similarity with the much better-known concept of adaptation through change formulated by Sterling and Eyer over thirty years earlier (Sterling and Eyer 1988). Their model presumes that an efficient regulation is anticipatory, i.e., learns from previous events, and that optimal regulation is orchestrated by a command center in the brain. Furthermore, Sterling and Eyer envisioned their allostatic regulation as a system trying to achieve optimal and efficient operation with minimal energetic expenditure (Sterling and Eyer 1988). Latter, McEwen and Stellar introduced term "allostatic load" defined as "the cost of chronic exposure to fluctuating or heightened neural

or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful" (McEwen and Stellar 1993).

The main difference of the dynamic pathosome from these older concepts is that the dynamic pathosome operates with a notion of a flexible adaptation cost over time. The cost of adaptation to the same stimuli is different for a ten-year-old child, a 30-year-old adult in his prime health and a 90-year-old. Such a viewpoint is close to the theory of homeodynamic space, which aims to determine an individual's chance to survive as well as the ability to maintain a healthy state (Demirovic and Rattan 2013; Rattan 2006; see also Rattan in this volume).

Another model that also suggests that previous phenotypes can affect future phenotypes is the Developmental Origins of Health and Disease approach (DOHaD) (Grandjean 2008; Wadhwa et al. 2009). However, while the DOHaD focuses only on how the embryonal development and infant phenotypes (e.g., birth weight) affect future adult phenotypes, the concept of the dynamic pathosome presumes that all phenotypes, including those of adults, are interlinked and might be theoretically used to predict future phenotypes trajectories.

## 16.5 The Pathosome and Bioinformatic Approaches

The preceding parts of this chapter introduced the concept of the dynamic pathosome as well as its implication and potential uses. However, some may wonder if such a framework has any use since we may simply use machine learning independently of any underlying theory. To show that frameworks such as the dynamic pathosome are still necessary, we will first highlight problems associated with machine learning and then list some benefits of the dynamic pathosome and how can it be used to guide machine learning algorithms.

Machine learning algorithms are often only as good as the data used to train them. The famous example is a Tay twitter bot developed to engage with people from 18 to 24. This bot was programmed to learn from the behavior of other users and as a result, in a mere 12 h, it went from its first innocuous tweet "hellooooooo world!!!" to stating that feminists "should all die and burn in hell" (Garcia 2016). Moreover, machine learning is extremely prone to arrive at trivial conclusions and recapitulate common prejudices and even racism. This is a great problem as machine learning algorithms often only report their results and people using them are often unaware that these results are based on wrong associations. A very troubling example is a finding that that the proprietary algorithms widely used by judges in the USA to help determine the risk of reoffending are almost twice as likely to mistakenly flag black defendants than white defendants (Crawford and Calo 2016; Julia Angwin 2016). What is worse, these algorithms are not particularly precise and predicted recidivism wrongly in 39% of the cases. It is quite easy to imagine that similar problems could be encountered in biomedical research but the type of data and "black box" nature of machine learning would make the detection of such problems even harder.

Another problem, this time concerning mostly deep-learning algorithms, is that they are surprisingly easy to fool. For example, an artificial intelligence (AI) trained to recognize traffic signs can be tricked to misread stop signs as e.g., speed limits by few rectangles pinned to the sign (Eykholt et al. 2018) or an AI trained to see images of animals can be fooled to recognize a lion in a white noise (with 99.99% certainty) (Nguyen et al. 2015). These results have profound implications for biomedicine because the great variability inherent to almost every aspect of biology makes the likelihood of similar mistakes quite high. Furthermore, a recent study shows that pixels added to a picture of a medical scan can fool a deep learning neural network to wrongly diagnose cancer (Finlayson et al. 2019). The exploitation of this finding poses a serious security threat to hospitals. Pictures altered by few pixels are almost indistinguishable from the originals by human eyes and thus there is almost no chance that hospital staff would recognize any wrongdoing while the consequences of such alteration could be fatal for patients. Therefore, while deep learning may be beneficial in the biological context, it should always be implemented, and its results interpreted, with great caution.

The concept of the dynamic pathosome has some benefits in comparison to machine learning algorithms. First, unlike the result of most machine learning algorithms, the dynamic pathosome can provide a meaningful explanation of observed phenomena and serve as a useful framework for result interpretation. Most machine learning algorithms used to date are constructed as black-boxes and are thus inherently hard to interpret. Furthermore, while people often try to interpret their results afterward, this is a flawed approach and should be abandoned in favor of constructing inherently interpretable models instead (Rudin 2019).

Second, the concept of the dynamic pathosome suggests substantial changes in the way the data are collected and recorded. Machine learning algorithms could only hardly achieve something similar as they only analyze the data you "feed" them with and do not provide guidance for future data generation.

Most importantly, however, the use of the dynamic pathosome framework does not exclude utilization of machine learning algorithms. On the contrary, it requires them, and it could be used to guide and focus them. Training of pure machine learning algorithms requires an enormous amount of data. Interestingly, young animals (including humans) require much fewer data to learn the same thing (Zador 2019). This is caused by the fact that unlike pure machine learning algorithms animal brains are built with certain built-in "expectations". A nice example illustrating this is a simple riddle "what is the next number in the sequence "2,4,6,8?". Although for most people 10 is an obvious answer, a machine learning algorithm without any inbuilt preferences would not be able to reach the same conclusion as easily. The reason for this is that the same numbers may also be fitted to a polynomial function which may predict that the next number can be literally any number e.g., 42 (Zador 2019). The only way to make the machine learning algorithm identify the answer to be "10" from only these 4 numbers is by programming it to have some preferences. For example, preferring simpler solutions given by fitting the numbers on a line. Similarly, there may not be enough data for a pure machine-learning algorithm to describe useful phenotypic trajectories. However, machine learning algorithms programmed to look for them

(for example, by preferring longitudinal associations for groups of individuals over cross-sectional associations at the level of an entire population) may find hundreds of them. Thus, the concept of dynamic pathosome could be used to guide future machine learning algorithms.

## 16.6 Practical Applications of the Dynamic Pathosome

Beyond serving as a theoretical framework, the concept of the dynamic pathosome has far-reaching practical implications for various fields. The most obvious of them is that the more detailed analysis of connections between phenotypes (phenotype trajectories) could produce new diagnostic tools able to detect diseases before their clinical manifestation and allow for more individualized treatment. In other words, if we consider most chronic diseases, it is almost certain that some people who do not yet show any symptoms of a given disease are already on a phenotype trajectory leading to this disease in the future.

Furthermore, more appreciation of the phenotype trajectories could improve results of studies investigating the molecular mechanisms of disease onset and progression. There are many molecular studies comparing e.g. tissues from healthy donors and donors with a disease. Some of them study gene expression (Shamir et al. 2017; Yokota et al. 2006), others differences in proteome (Yang et al. 2016), miRNA production (Iorio et al. 2005; Sempere et al. 2007; Taslim et al. 2016) and other changes. However, almost every such study suffers from the same potential problem, namely contamination of "healthy" controls with samples from people who are on a brink of a given disease. As a consequence, no matter how sophisticated and reliable the final measurement is and how many subjects are analyzed in the study, such "contamination" of the controls generates noise or even bias in the data which can obscure important changes leading to the development of a given disease.

Implementation of the pathosome concept could, over time, also help partially reconstruct the history of previous environmental interactions. This application of the pathosome concept would, however, need to be preceded by a systematic study of phenotype trajectories of a given phenotype. How would this work? First, separate longitudinal studies designed to study phenotype trajectories would identify a certain phenotype trajectory connected to certain environmental stimuli. Then, any future longitudinal study with enough data points to identify a given trajectory (fewer data points are needed to identify a trajectory than to describe it) would be able to, with a certain probability, assume that subjects with a given trajectory were also subjected to a given environmental stimulus. Such an approach could possibly generate a lot of new data not only for future but also for already existing datasets and could, in principle, lead to a discovery of many new associations and useful connections.

However, utilizing the concept of the dynamic pathosome in its full potential would require a massive gathering of data for the construction of the phenotypic trajectories in big longitudinal studies. Furthermore, such studies would need to

have a special design that would allow for the description of phenotype trajectories. First, all data would need to be gathered as frequently as possible; the common practice of many longitudinal studies to gather phenotypic data only once every few years would not be enough for this task. For some parameters, this goal could be elegantly achieved by already available self-tracking technology. Second, the phenotypes would need to be described as precisely as possible. This would be in contrast to the common practice of using an arbitrary threshold to assess phenotypes in a simplified yes/no fashion. Such simplified categorization may be useful in terms of diagnosis or therapeutic decision making, but it always introduces bias and noise into the data. The use of categorization generally results in decreased power and inaccurate estimates, it usually leads to multiple hypothesis testing with pairwise comparisons, and it makes it difficult to compare multiple studies (Bennette and Vickers 2012). Furthermore, from the point of view of the pathosome concept, categorization also hides different phenotypes that may lie on different phenotype trajectories. E.g. two subjects with BMI values of 30.1 and 45 may both be categorized as obese, however, quite obviously, their phenotypes, as well as phenotype trajectories they occupy, are very different. Accordingly, even classical qualitative traits can be often reported in a quantitative fashion and for the needs of the pathosome concept, this should be the preferable approach. However, such quantizing may also be arbitrary in some cases (Sandelowski et al. 2009) and, therefore, should be applied with caution.

## 16.7 The Pathosome and a New Perception of Health and Disease

The dynamic pathosome distilled to its essence is a simple hypothesis. It suggests that phenotypes are interlinked into phenotypic trajectories and that they are affected by an interaction of genotype, environment, and aging (both their sum and order). If accepted, the dynamic pathosome could, in addition to providing several important applications in biomedicine, profoundly change our perception of health and disease.

Currently, a disease is perceived by the majority of people as a discrete set of symptoms, distinct from the states of health. However, the dynamic pathosome framework paints a quite different picture. Most diseases are parts of phenotypic trajectories which also include phenotypes we would classically define as healthy. As you move along such a trajectory from the “healthy” state towards “disease” or even from “disease” to “health” you inevitably encounter a string of phenotypes that cannot be easily put under a healthy or sick label. Therefore, in contrast to the current paradigm, the framework of the dynamic pathosome emphasizes that disease is not just an isolated event but a gradual process, often without a clear end and beginning.

Such a view is especially potent when applied to chronic diseases. Many seemingly healthy people are already on a phenotypic trajectory leading them to the full clinical manifestation of some chronic disease. Furthermore, in many cases, even

after successful treatment of a chronic disease and the disappearance of its symptoms, the patients still have long-term, sometimes lifelong problems originating from the chronic illness itself or its treatment. Are such people sick or healthy? With a classic black-and-white view on health and disease, this is hard to decide. However, from the viewpoint of the dynamic pathosome, such a question is unnecessary. These people simply occupy a specific place in the pathosome cube and on their personal phenotypic trajectory defined by their unique history of genotype-environment interactions. Therefore, from this point of view, labels such as healthy or sick are mostly subjective and maybe in such cases, left to be decided by the particular person.

Furthermore, broad terms such as health or disease have little to no practical meaning in biomedicine. We can label three people as "sick" and yet, they may have next to nothing in common. You are sick if you have a common cold just as well as if you have an osteosarcoma or Alzheimer's disease and yet, the reality of these diseases is incomparable. The same can be said about "health". Healthy people may occupy a very different phenotype trajectory which may imply very different things for their future. A healthy person may be a marathon runner at the peak of their physical and mental performance just as well as a person who spends entire days indoors playing videogames. From the biomedical perspective, it does not help us at all to give them the same label. Thus, at least from the view of the dynamic pathosome, the words "health" and "disease" are superficial in biomedicine and should be abandoned in favor of more specific and accurate descriptions.

In the optimal scenario, physicians would and could entirely omit the words such as healthy or sick and talk strictly about specific symptoms (i.e., phenotypes) and their progression or lack of thereof. It may seem like a radical idea to abandon the use of words health and disease in biomedicine, but it is not. And one can arrive at the same conclusion even without the concept of the dynamic pathosome (Hesslow 1993).

However, while the concepts "health" and "disease" may be unhelpful in biomedicine and we should discourage their use in scientific texts as much as possible, they are essential for other fields such as public health. Designing preventive measures and public policies protecting the health of entire populations requires some definition explaining what "health" and "disease" mean. The dynamic pathosome could also be useful for this purpose since it could help policymakers to identify "health-promoting" or "disease-promoting" phenotype trajectories and environmental stimuli affecting them.

This may seem like a contradiction; why should the concepts of "health" and "disease" be abandoned at one level but retained at another? The reason for this is that public health and health policies operate with populations while biomedicine inevitably has to work with individual patients. When you are trying to design some preventive measures aimed at the entire population, such as a campaign against smoking, the concepts of health and disease are important. However, when you are a patient or a clinician, when you want to treat a disease or study its etiology, words such as "health" or "disease" are devoid of all meaning. In such a situation, all that matters is specific symptoms and disease.

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# Chapter 17
# The Sleep Prism of Health


**Jean-Arthur Micoulaud-Franchi, Julien Coelho, Kevin Ouazzani Touhami, and Pierre Philip**

**Abstract** To assess the importance of sleep for health, this chapter proposes that sleep should be analyzed through the prism of the physiology, behaviors and representations that impact sleep health, sleep complaints and sleep disorders. This chapter proposes the following roadmap: (i) to develop and evaluate an integrative model of the center of the prism in order to predict and simulate successfully the relationship between sleep and health, functioning and longevity; (ii) to develop an iterative approach between the sleep behavior change model, sleep health/complaints/disorder/representation psychometric models, and a physiological model; and (iii) to provide the evidence that specific interventions or programs that improve sleep health truly impact health, functioning and longevity outcomes. It is essential for clinicians to be able to help patients get their sleep back on track by using a multifaceted tool. Improving the sleep health of the public at large can only have a positive knock-on effect for us all.

**Keywords** Sleep health · Sleep disorder · Behavior · Representation · Public health · Functioning · Longevity

## 17.1 Introduction

**Sleep is an essential part of physical and mental health**. It is a core function to maintain the homeostasis of the entire organism, ensuring a dynamic state of equilibrium, optimal organ function and promoting longevity (Kryger et al. 2010). Sleep

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has many restorative and transformational effects that optimize neurobehavioral and physiological functions during wakefulness, and it is related to two kinds of public health constructs: sleep disorders and sleep health.

**Sleep disorders** are medical conditions that are related to perturbations or dysfunctions of sleep interfering with normal physical and mental **health, functioning and longevity**. They have been classified in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association 2013), which is promoted by the *American Psychiatric Association* (APA), and in the *International Classification of Sleep Disorders* (ICSD) (American Academy of Sleep Medicine 2014) under the aegis of the *American Academy of Sleep Medicine* (AASM). Historically, sleep disorders have been the seminal constructs studied and treated in order to optimize public health related to sleep (Fischer et al. 2012; Pevernagie et al. 2009; Pevernagie and Steering Committee of European Sleep Research 2006; Strollo et al. 2011; Stradling 2007).

Recently a new construct emerged (Buysse 2014; Grandner 2019): **sleep health**, which is a broader but no less functional concept than sleep disorders. Sleep health is related to sleep quality, which can impact physical and mental health, functioning and longevity. The concept of sleep health paves the way for new studies and strategies to ensure public health by targeting **sleep as a behavior** (Knutson et al. 2017; Ohayon et al. 2017; Hirshkowitz et al. 2015; Consensus Conference et al. 2015; Watson et al. 2015).

The first part of this chapter defines sleep. Indeed, to understand what sleep health is, we need first to understand how sleep has been conceptualized as a behavior and as a disorder. We then discuss sleep health in detail with regard to definitions, measures and outcomes. The third part focuses on the link between sleep health and sleep representations in order to promote interventions improving health.

## 17.2 Sleep

### *17.2.1 Definitions*

The principal textbook on sleep medicine defines sleep as follows: "According to a simple behavioral definition, *sleep is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment*. It is also true that sleep is a complex amalgam of physiologic and behavioral processes. Sleep is typically (but not necessarily) accompanied by postural recumbence, behavioral quiescence, closed eyes, and all the other indicators commonly associated with sleeping" (Kryger et al. 2010).

The Research Domain Criteria (RDoC) project, an initiative being developed by the *US National Institute of Mental Health*, has defined many dimensions (including sleep and wakefulness) that are important for health, functioning and longevity. Unlike the DSM, the RDoC project is creating a biologically valid framework for

studying mental health problems. However, despite focusing on the physiological aspects of mental health, it also includes behavioral factors. It states the following: "Sleep and wakefulness are endogenous, recurring, behavioral states that reflect coordinated changes in the dynamic functional organization of the brain and that optimize physiology, behavior, and health. Homeostatic and circadian processes regulate the propensity for wakefulness and sleep" (Cuthbert 2014).

Thus, sleep is considered as a **behavior** that is crucial for health and involving a dynamic interaction between the behavior of the individual and the physiological activities of the organism. A (bio)behavior can be defined as all activities organized to act outside the organism and which can be related to and/or can impact the inner homeostasis dynamic. Behavior can be measured in the form of observation units that are liable to change. Behavior translates into action the representation of the situation and the construction of an individual's perpetually changing environment.

As a (bio)behavioral state, sleep should be conceptualized as a concept at the interface between behavior and physiology, which is affected by experiences and representations during wakefulness but also by physiological regulation involving the cellular, neural circuit and biological systems. In this line, sleep can be considered as a health behavior that can be measured by **self-reporting, behavioral analysis and physiological data**.

### *17.2.2 The Two Models of Sleep*

**A health behavior** is any organized activity undertaken voluntarily or involuntarily by a subject for the purpose of preventing or detecting a disorder or for improving health, functioning and longevity. If we are to conceptualize sleep as a health behavior, we need an **interactive model that combines physiological and behavioral factors** in order to set up interventions that modify an individual's health through sleep.

- Two physiological components ensure that sleep occurs at night, in line with the so-called **"Two-process model of sleep"** of Borbely (Borbely 1982; Borbely et al. 2016), which has served as a major conceptual framework in sleep research. The first component causes pressure to fall asleep (homeostatic sleep process or **Process S**), whilst the second dictates the circadian rhythms of sleep (circadian process or **Process C**). These two processes involve cellular, neural circuit and biological system levels. The factors involved in process S are the following: adenosine; the ventrolateral preoptic nucleus (VLPO), which is a small cluster of neurons situated in the anterior hypothalamus; and the cortico-basal ganglia-thalamo-cortical loop (CBGTC loop), which is a biological system of neural circuits in the brain. The factors involved in process C are as follows: melatonin; the suprachiasmatic nucleus (SCN), which is a tiny region of the brain in the hypothalamus; and the retinohypothalamic tract (RHT), which is a biological system of neural circuits that originate from the photosensitive retinal ganglion

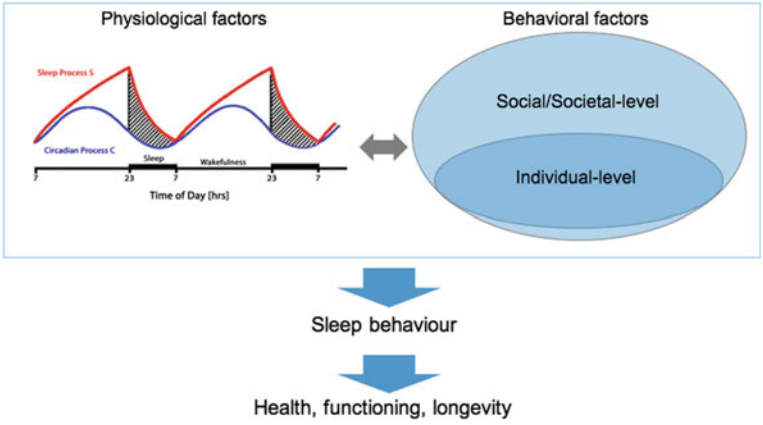


**Fig. 17.1** Physiological ("Two-process model of sleep") (Borbely 1982; Borbely et al. 2016) and behavioral (simplified "Social-ecological model of sleep") (Grandner 2014, 2019) factors related to sleep as a behavior and to health, functioning and longevity

cells (ipRGC). These two processes work together to create a balanced sleep–wake cycle (see Fig. 17.1). The model successfully simulates the timing, intensity and duration of sleep in diverse experimental protocols.

- Behavioral components ensure that sleep can be conceptualized as a behavior, in line with a model called the **"Socio-ecological framework"** of Grandner (Grandner 2014, 2019) inspired by (Bronfenbrenner 1977), which served as a new conceptual framework to conceive sleep behavior in the context of individual, social and societal demands:
  - The individual level concerns representations that can impact sleep behavior (i.e. "sleep is important for health"),
  - The social and societal levels are factors that are related to individuals but which exist even without the latter (i.e. school schedule constraints).

Representations of sleep are all the individual's cognitive processes during wakefulness that can influence sleep. In the health behavior perspective, these factors are very important when studying the links between sleep behavior, health, functioning and longevity, and they constitute useful targets for promoting sleep health behavior in real-world settings (see Fig. 17.2).

### *17.2.3 Sleep Disorders*

The first Diagnostic Classification of Sleep and Arousal Disorders (DCSAD) was proposed by the "*Association of Sleep Disorders Centers*" and the "*Association for*

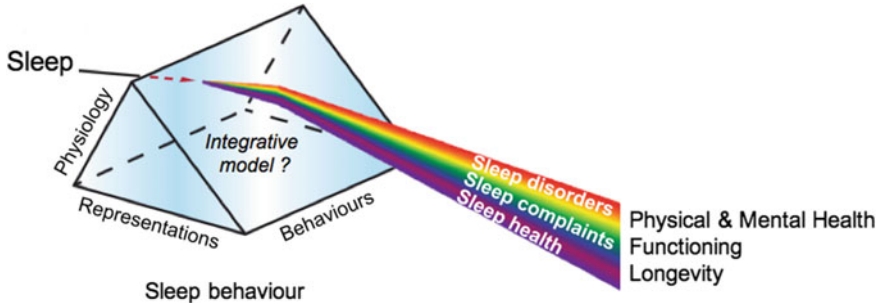


**Fig. 17.2** The proposed sleep prism of health

*the Psychophysiological Study of Sleep*" in 1979 and was published in *Sleep* (Association of Sleep Disorders Centers and Association for the Psychophysiological Study of Sleep 1979). The DSM-III, which was published in 1980 (American Psychiatric Association 1980), was the first international classification to fully incorporate the diagnostic classification of sleep disorders, including them in the vast field of mental disorders. Since 1980, sleep disorders have remained a separate section of each version of the DSM.

Interestingly, the DCSAD relied on a clear sleep behavioral approach to classify the phenomenology of the disorders. Sleep disorders were divided into three major sleep complaints (symptoms):

- insomnia complaints, in the "*Section A <tha > classifies the disorders of initiating and maintaining wakefulness (DIMS), comprising types of disturbed and inadequate sleep"*;
- daytime somnolence complaints, in the "*Section B <that> covers the disorders of excessive somnolence (DOES), discussing types of excessive sleep and inappropriate sleepiness"*;
- abnormal behavior occurring during sleep, in the "*Section D <that> describes the dysfunctions associated with sleep, sleep stages, or partial arousal, comprising abnormal behaviors and medical symptoms appearing in sleep*" (Association of Sleep Disorders Centers and Association for the Psychophysiological Study of Sleep 1979).

The delineation between the normal and the pathological was based on the severity and the consequences of sleep complaints. For example, even if obstructive sleep apnea syndrome is caused by repetitive episodes of nocturnal breathing cessation due primarily to upper airway collapse, the number of nocturnal breathing cessations was considered to be insufficient to characterize the condition as pathological (Rodenstein and Duran Cantolla 2013). Obstructive sleep apnea syndrome was defined as "Sleep Apnea DIMS syndrome", or as "Sleep apnea DOES syndrome". Thus, insomnia and somnolence complaints were considered as very important to delineate sleep apnea as a sleep disorder (Micoulaud Franchi et al. 2018a, b). What is important to note is

that insomnia and somnolence complaints are related to upper airway collapse but also to a complex combination of factors related to sleep behavior.

Interestingly, unlike the DSM, neither the DCSAD nor the ICSD proposed a general definition of sleep disorders. For this reason, we propose that **sleep disorders** should in fact be conceptualized as "**sleep behavior disorders**". We think that this proposition is in line with: (i) what was implicitly meant in the DIMS and DOES definitions of the DCSAD, (ii) the fact that sleep disorders have been integrated in the classification of mental disorders, (iii) the understanding that sleep is a behavior, and iv) the link between physiological and behavioral factors of sleep considered as a (bio)behavior. Thus, as mental disorders are "syndrome(s) characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning", we suggest that **sleep disorders are syndromes (insomnia complaints, daytime somnolence complaints, abnormal behavior occurring during sleep) characterized by a clinically significant disturbance in an individual's sleep-wakefulness behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying sleep-arousal regulation, neurobehavioral and physiological functions**. In line with the DSM definition, sleep disorders are also usually associated with significant distress or disability in social, occupational or other important activities (Micoulaud Franchi et al. 2018a). Note that, if sleep disorders can be considered as physiological disturbances that impact sleep behaviors, sleep behaviors can in turn negatively impact the physiological process of sleep regulation, so sleep behavior disorders should be conceptualized as a recursive causality between physiological and behavioral factors rather than in terms of a simple unidirectional relationship between physiological abnormalities and behavioral consequences. Moreover, a distinction should be made between the proposed terminology of "sleep behavior disorder", i.e. disorders of sleep considered as a behavior, and the following sleep disorders of the ICSD-3: parasomnia, and in particular "rapid eye movement sleep behavior disorder (RBD)", which are disorders related to abnormal behavior occurring during sleep.

This proposition for definitions makes it possible to include the new thinking on Patient-Related Outcomes Measures (PROM) for sleep disturbance and sleep-related impairments in the evolution of the ICSD to define sleep disorders. The PROM Information System (PROMIS) is a National Institutes for Health-funded consortium that aims to build item pools and develop core questionnaires that measure key health-outcome domains manifested in chronic disorders, including sleep disorders (Buysse et al. 2010). In fact, PROMIS aim to redefine sleep complaints especially from the point of view of the patient in order to establish the major symptoms affecting health status and quality of life. For sleep, a first questionnaire of 27 items for sleep disturbances and 16 items for sleep-related impairment has been developed. Two short 8-item versions have also been developed (Yu et al. 2011). The value of the PROM for sleep is to propose a concept similar to the initial distinction of the DIMS and DOES. The challenge is now to incorporate the PROM concept into the way we define sleep disorders in the ICSD. To do so, we need a consensual and pragmatic definition of sleep disorders, as outlined above (Micoulaud Franchi et al. 2018a).

**Table 17.1** Items of global sleep assessment questionnaire (GSAQ) by (Roth et al. 2002)

| | |
|---|---|
| 1 | Did you have difficulty falling asleep, staying asleep, or did you feel poorly rested in the morning? |
| 2 | Did you fall asleep unintentionally or did you have to fight to stay awake during the day? |
| 3 | Did sleep difficulties or daytime sleepiness interfere with your daily activities? |
| 4 | Did work or other activities prevent you from getting enough sleep? |
| 5 | Did you snore loudly? |
| 6 | Did you hold your breath, have breathing pauses, or stop breathing in your sleep? |
| 7 | Did you have restless or "crawling" feelings in your legs at night that went away if you moved your legs? |
| 8 | Did you have repeated rhythmic leg jerks or leg twitches during your sleep? |
| 9 | Did you have nightmares, or did you scream, walk, punch, or kick in your sleep? |
| 10 | Did the following things disturb you in your sleep: pain, other physical symptoms, worries, medications, or other (specify)? |
| 11 | Did you feel sad or anxious? |

Until now, the PROM questionnaires for sleep disturbances and sleep-related impairments have not been used to screen for sleep disorders in the general population. A recent systematic review analyzed the psychometric properties of the available questionnaires (Klingman et al. 2017b). Surprisingly, only two self-reported questionnaires proved particularly useful regarding their brevity, comprehensibility, reliability and validity:

– the global sleep assessment questionnaire (GSAQ) (Roth et al. 2002), Table 17.1,
– the sleep disorders symptom checklist (SDS-CL) (Klingman et al. 2017a), Table 17.2.

And only the SDS-CL covered the six categories of the sleep disorders of the ICSD-3 (American Academy of Sleep Medicine 2014).

In order to optimize public health related to sleep, the first step is thus to screen for sleep disorders in the population. Indeed, many studies have linked sleep disorders with **health** (morbidity), **functioning** (performance) and **longevity** (mortality) outcomes. A recent review has listed them (Garbarino et al. 2016; Kendzerska et al. 2014; Engleman and Douglas 2004). As sleep disorders seem to be endemic in our contemporary society (about 18% in Europe and 23% in the U.S.) (Uehli et al. 2014), the overall impact might be significant. The most studied category is certainly sleep-related breathing disorders (SRBD), which include obstructive sleep apnea (OSA) and its association with cardiovascular comorbidity and sleep-related functioning. Concerning functioning, driving performance has received particular attention in subjects with somnolence due to the impact of impaired driving performance on road accidents. Interestingly, driving performance is a very good example of the need to consider sleep as a behavior, and to take into account the interaction between the severity of sleep disorders (e.g. number of nocturnal breathing cessations), sleep behavior (e.g. sleep during the night before driving, recognition of

**Table 17.2** Items of sleep disorders symptom checklist (SDS-CL) by Klingman et al. (2017b)

| Over the past year: (place an X in the box) | Never | Seldom (1 × year) | Sometimes (1–3 × month) | Often (1–3 × week) | Frequently (>3 × week) |
|---|---|---|---|---|---|
| 1. It takes me 30 min or more to fall asleep | | | | | |
| 2. I am awake 30 min or more during the night | | | | | |
| 3. I am awake 30 min or more prior to my scheduled wake time or alarm | | | | | |
| 4. I am tired, fatigued or sleepy during the day | | | | | |
| 5. I sleep better if I go to bed before 9:00 pm and wake up before 5:30 am | | | | | |
| 6. I sleep better if I go to bed late (after 1:00 am) and wake up late (after 9:00 am) | | | | | |
| 7. I fall asleep at inappropriate times or places | | | | | |
| 8. I have been told that I snore | | | | | |
| 9. I wake up during the night choking or gasping | | | | | |

(continued)

**Table 17.2** (continued)

| Over the past year: (place an X in the box) | Never | Seldom (1 × year) | Sometimes (1–3 × month) | Often (1–3 × week) | Frequently (>3 × week) |
|---|---|---|---|---|---|
| 10. I have been told I stop breathing when I sleep | | | | | |
| 11. I feel uncomfortable sensations in my legs, especially when sitting or lying down, that are relieved by moving them | | | | | |
| 12. I have an urge to move my legs that is worse in the evenings and nights | | | | | |
| 13. I wake up frequently during the night for no reason | | | | | |
| 14. I have experienced sudden muscle weakness when laughing, joking, angry or during other intense emotions | | | | | |
| 15. I have been told that I walk, talk, eat or act strange or violent while sleeping | | | | | |
| 16. I have nightmares | | | | | |

(continued)

**Table 17.2** (continued)

| Over the past year: (place an X in the box) | Never | Seldom (1 × year) | Sometimes (1–3 × month) | Often (1–3 × week) | Frequently (>3 × week) |
|---|---|---|---|---|---|
| 17. For no reason, I awaken suddenly, startled, and feeling afraid | | | | | |

somnolence, adjusted driving behavior countermeasure, etc.), and driving conditions (e.g. nocturnal driving) to better predict outcomes (road accident) (Philip et al. 2019; Bioulac et al. 2018).

To summarize, sleep disorders are crucial factors for health, functioning and longevity, even though the absence of sleep disorders is not necessarily related to good health, functioning and longevity. Indeed, sleep can have an impact on these outcomes beyond the presence or absence of sleep disorders. For this reason, the concept of sleep health has been recently developed.

## 17.3 Sleep Health: A New Concept

Poor sleep health is not only related to sleep disorders but also to other important dimensions. The first dimension largely studied was sleep quantity, i.e. sleep duration, as **insufficient sleep** (also called sleep deprivation, sleep loss or short sleep). Insufficient sleep is not a sleep disorder per se. It affects many people (around 30% of the population) and is associated with an increased morbidity and mortality rate (Cappuccio et al. 2010). Recently, the *National Sleep Foundation* tried to go a step further by defining not only insufficient sleep but also **sleep quality** (Knutson et al. 2017; Ohayon et al. 2017; Hirshkowitz et al. 2015; Consensus Conference et al. 2015; Watson et al. 2015). An important dimension of sleep quality is sleep quantity. Also important, however, are sleep latency (amount of time to fall asleep), wake time after sleep onset (amount of time awake at night), and sleep efficiency (proportion of time in bed spent sleeping), which can be summarized by sleep continuity. There is also the daytime dimension, especially daytime somnolence. All these dimensions may be used to define adequate/inadequate sleep and how it leads to good/bad health, independently of the presence or not of sleep disorders. This is an important public health challenge.

### 17.3.1 Definition

The concept of health is clearly a dimension of sleep. Good sleep goes a long way to ensuring good **sleep health**, so good sleep is **healthy sleep**. The WHO charter of 1986 defined health as a state of complete physical, mental, and social well-being, with an individual or group needing to be able to identify and realize their aspirations, satisfy their needs, and to change or cope with the environment (Potvin and Jones 2011). It adopts a **positive and dynamic** view, describing health as a state and a process of well-being that places health in the context not only of the individual but of **society** as well. This definition and its implications have been applied to sleep to create the notion of "**sleep health**" as defined below. Sleep health is related to sleep quality, which can lead to a healthy status as described above, including physical and mental **health**, **functioning** and **longevity**.

Buysse define sleep health as "a multidimensional pattern of sleep-wakefulness, adapted to individual, social, and environmental demands, that promotes physical and mental well-being. Good sleep health is characterized by subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours" (Buysse 2014). This definition does not include any particular **sleep disorder**. Rather, it focuses on attributes of sleep-wakefulness per se that can be measured in any individual with or without sleep disorders. The definition is most appropriate for adults, but could be adapted to infants, children and adolescents. It expresses sleep health as a **positive and dynamical attribute**. It can be **measured** at self-report, behavioral, and physiological levels. The definition recognizes that sleep health is best understood in the context of individual and social/environmental demands, i.e., that good sleep health may not be the same in every situation or every individual. Finally, the definition solidly underpins the dimensions of sleep health.

### 17.3.2 The Six Dimensions of Sleep Health

Just as health is a multidimensional concept, so too are sleep and sleep health. Definitions of sleep health focus on measurable dimensions of sleep that are most clearly associated with physical, mental and neurobehavioral well-being.

- **Regularity**: This dimension refers to going to sleep and waking up about the same time every day. High regularity is positively associated with health, while low regularity (irregularity) can increase cardiometabolic or psychiatric disorders (Lunsford-Avery et al. 2018).
- **Satisfaction**: This dimension refers to the subjective assessment of "good" or "poor" sleep. Individuals who report having good sleep quality are less likely to suffer from cardiometabolic or psychiatric disorders (Hoevenaar-Blom et al. 2011).
- **Alertness**: The ability to maintain attentive wakefulness during the day and not to experience unwanted daytime somnolence. Sustained vigilance during the day

reduces the risk of cardiovascular and psychiatric morbidity, and at least mortality (Newman et al. 2000).

- **Timing**: The placement of sleep within the 24-h day. Being awake in the middle of the night is associated with more cardiometabolic and cancer disorders, an increased risk of accidents, and higher mortality (Knutsson 2003). This dimension has received particular attention in the case of night-workers and shift-workers, since these working conditions can disturb sleep–wake rhythms by circadian misalignment, i.e. sleep time not synchronized with the body's natural circadian rhythms. This can lead to short-term sleep disturbances but also to specific long-term medical conditions.
- **Efficiency**: The ability to sleep a large percentage of the time in bed, as indicated by the ease of falling asleep at the beginning of the night and the ease of returning to sleep after waking up during the night. Poor efficiency enhances the risk of cardiometabolic or psychiatric disorders, and at least mortality (Cappuccio et al. 2010; Medic et al. 2017).
- **Duration**: The total amount of sleep obtained per 24 h. Short sleep is the most studied dimension of sleep health and has shown several associations with cardiometabolic disorders and mortality. Interestingly, however, long sleep has also been found to be a risk factor of cardiometabolic disorders and mortality (Yin et al. 2017). Sleep may be considered healthy when it is of adequate duration (Buxton and Marcelli 2010).

These six dimensions are appropriate indicators of sleep health for several reasons. First, each is associated with **health, functioning and longevity outcomes**, albeit with somewhat different outcomes for each dimension. Second, they can each be **expressed in positive terms**, i.e., we can characterize their "better" directions. This is not to say that they are all unidirectional. For instance, sleep duration and sleep timing are "good" if they fall within certain ranges, but "poor" if they deviate too far in either direction from these ranges. It is also important to acknowledge that, while these dimensions can be expressed in positive terms, studies have focused largely on their negative directions and consequences. Hence, few studies have specifically examined the potential *benefits* of *good (appropriate)* sleep. Third, most of the dimensions can be **measured at self-report, behavioral, and physiological levels**.

Tools and criteria are thus needed to quantify sleep health. The existing literature provides guidance in devising such tools by identifying health risk thresholds associated with different dimensions of sleep. One potential tool for measuring sleep health is a self-report scale referred to by the acronym RUSATED (Buysse 2014) (Table 17.3):

- RegUlarity
- Satisfaction
- Alertness
- Timing
- Efficiency
- Duration.

**Table 17.3** Items of RUSATED (regularity, satisfaction, alertness, timing, efficiency, duration) questionnaire by Buysse (2014)

| | | Rarely/never (0) | Sometimes (1) | Usually/always (2) |
|---|---|---|---|---|
| Regularity | Do you go to bed and get out of bed at about the same times (within one hour) every day? | | | |
| Satisfaction | Are you satisfied with your sleep? | | | |
| Alertness | Do you stay awake all day without dozing? | | | |
| Timing | Are you asleep (or in bed) between 2:00 a.m. and 4:00 a.m.? | | | |
| Efficiency | Do you spend less than 30 min awake at night? This includes the time it takes to fall asleep plus awakenings during sleep | | | |
| Duration | Do you sleep between 6 and 8 h per day? | | | |

Total for all items ranges from 0 to 12
0 = Poor Sleep Health
12 = Good Sleep Health

The RUSATED scale assesses six key dimensions of sleep that have been consistently associated with health outcomes, and it incorporates specific quantitative criteria for four of the six. It is brief and takes no more than a minute or two to complete. Consistent with the proposed definition of sleep health, it addresses positive dimensions of sleep-wakefulness that are present to some degree in every person. Its validity, reliability and psychometric properties have been studied and its performance is good (Ravyts et al. 2019; Benitez et al. 2020). However, the RUSATED scale is not the only way to measure sleep health. The National Sleep Foundation proposed the Sleep Health Index in 2017 (Knutson et al. 2017): a self-administered 14-item scale that assesses the same six dimensions as the RUSATED (Table 17.4). In 2019, the NSF proposed a sleep health measure on a 10-item somnolence scale for the alertness dimension, the Pittsburgh Sleep Quality Index (PSQI) for the satisfaction dimension, and a sleep diary (Dong et al. 2019) for the other dimensions of sleep health. Also in 2019, mixed self-reported data for sleep satisfaction and behavioral data were measured by actigraphy for the other dimensions and collated into a scale to quantify sleep health (DeSantis et al. 2019; Lee et al. 2019).

Finally, the Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire created in 1989 (Buysse et al. 1989) and widely used to assess sleep quality based on 19 individual items summarized in seven components (sleep quality, sleep duration,

**Table 17.4** Items of sleep health Index (SHI) by Knutson et al. (2017)

| |
|---|
| 1. In general, how would you rate your sleep quality? Would you say it's excellent, very good, good, only fair, or poor? |
| 2. Thinking about just the past 7 days, what time did you most often go to bed on workdays? Please answer about weekdays if you did not work last week.[response: clock time] |
| 3. What about on non-workdays or weekends—what time did you most often go to bed on those days? [response: clock time] |
| 4. What time did you most often wake up for the day on workdays or weekdays? [response: clock time] |
| 5. What about on non-workdays or weekends—what time did you most often wake up for the day on those days? [response: clock time] |
| 6. During the past 7 days, how many days did you wake up feeling well-rested, if any? [response 0–7 days or don't know/refused] |
| 7. How many nights did you have trouble falling asleep? [response 0–7 days or don't know/refused] |
| 8. And how many nights did you have trouble staying asleep? [response 0–7 days or don't know/refused] |
| 9. Still thinking about the past 7 days, how many days did poor or insufficient sleep significantly impact your daily activities, like your work performance, socializing, exercising, or other typical activities? [response 0–7 days or don't know/refused] |
| 10. How many days did you fall asleep without intending to, such as dozing off in front of the TV or in any other situation? [response 0–7 days or don't know/refused] |
| 11. How many nights did you take over-the-counter or prescription medication to help you sleep? [response 0–7 days or don't know/refused] |
| 12. Have you ever been told by a doctor that you have a sleep disorder, such as insomnia or sleep apnea, or not? [response yes, no or don't know] |
| 13. Have you ever discussed any sleep problems you were having with a doctor or medical professional, or has this not come up? [response yes, no or don't know/refused] |
| 14. How many hours of sleep do you need per day to be well-rested and feel your best? [response 0–24 h or don't know/refused] |

sleep latency, sleep efficiency, sleep disturbance, use of sleep medication, daytime dysfunction). As four of these components refer to four sleep health dimensions, the scale may be considered to measure sleep health, at least partially. Its role should be redefined in this new context.

Some limitations, however, should be addressed concerning the operationalization of this sleep health measure. First, sleep health is a construct that includes both causes and consequences. Indeed, while individuals can modify their sleep timing and sleep regularity, their sleep efficiency and sleep satisfaction result from their sleep behavior. As a result, sleep health may not be a functional tool for behavioral change but more a measure of a health status. Moreover, sleep health combines six dimensions into one, considering that they are all independent and have the same weight. However, findings suggest that some dimensions are more important than others (Wallace et al. 2018). Moreover, the link between sleep health and objective sleep measures needs additional research, as suggested by (Allen et al. 2018). Furthermore, measuring sleep

health in different ways might in fact be tantamount to measuring different forms of sleep health. For example, the alertness dimension can be measured by counting sleeping time during the day, as did (Lee et al. 2019), or by asking individuals whether they doze off during the day (as does the RUSATED). Clearly, these two methods might give two different answers for the same subject, due to the possibility or not to sleep at work, for example. Lastly, a more phenomenological approach to investigate sleep health through a qualitative study of subjective experience was proposed (Goelema et al. 2018). They analyzed 206 statements obtained from a sentence-completion questionnaire. One interesting result was that the two most frequent statements emerging when participants were asked to define "good sleep" concerned the next-day state ("*State of well-being directly after waking up*") and the before-bed state ("*Mental and physical well-being before going to bed*"). Therefore, this suggest that some aspects of sleep are perhaps not addressed sufficiently in the widely used sleep health questionnaires, and that a non-negligible part of their experience refers to states related to sleep instead of sleep itself.

### *17.3.3 Sleep Health and Longevity*

As we have already seen, each dimension of sleep health is associated with health, functioning and longevity. While this subject has been studied less than the relationship to sleep disorders, it is now arousing much interest.

Concerning **health**, poor sleep health may increase the risk of morbidity related to several disorders. Using the RUSATED scale, researchers found an association between sleep health and major depressive disorder in a large cohort of women in 2017 (Furihata et al. 2017). In 2019, good sleep health was found to be associated with a lower risk of cardio-metabolic and psychiatric disorders in a young population (Dong et al. 2019), and older men with poor sleep health were more likely to suffer from systemic inflammation (Lee et al. 2019). These results suggest that sleep health is a central dimension connected to all components of health. The link between sleep health and mental/physical health might involve several pathways that have been thought to be related to the immune system, which plays a central role in biobehavioral functioning (Irwin and Opp 2017).

In addition, poor sleep health can impair human **functioning**. In 2019, it was found that young students with poor sleep health were more likely to have worse physical health (Benham 2019). This finding is consistent with an association found with physical and mental functioning the same year (Desantis et al. 2019). Furthermore, an association was found between sleep health and self-perceived health status in a large cohort. The association was stronger than the association with diet or physical activity, suggesting that sleep health is a key health determinant (Dalmases et al. 2019). Finally, a study investigated the link between sleep health and **longevity**. Not only did this study find an association, they also found that sleep health was more predictive of longevity than several usual health determinants such as smoking status, alcohol consumption, chronic arterial hypertension, chronic obstructive pulmonary

disease, self-reported health status, diabetes, BMI, education, stroke and mental depression (Wallace et al. 2018).

To summarize, sleep health seems to be strongly associated with health, functioning and longevity, maybe even more than objective sleep measures (Buxton et al. 2018), suggesting that it is a very useful and relevant measure of health as defined by the WHO. Moreover, it is a very promising target for public health interventions. In this line, the representations of sleep need to be defined.

## 17.4 Sleep Representations

### *17.4.1 Definitions*

Sleep representations are very important when investigating sleep behavior and sleep health (Brown et al. 2002). For the sake of clarity, we choose here to define sleep representations as a general concept that can be analyzed through the notions of "**Belief**" (that encompass knowledge) and "**Attitude**".

**Beliefs can be defined as facts or ideas about sleep that are considered to be true by a subject**, but which are not necessarily based on scientific evidence. For example, "one needs 8 h of sleep to be healthy" is considered to be a belief, as much as "sleep is an expandable requirement for health" (Knowlden et al. 2012). On the other hand, when a belief is based on scientific evidence, we call it "knowledge". Knowledge about sleep is exact information regarding the state-of-the-art science of sleep, understanding of the factors influencing sleep, sleep requirements, sleep disorders, and the health consequences of sleep (Peach et al. 2018). For example, the statement "alcohol consumption causes short- and long-term sleep disturbances" can be viewed as a belief, but it is also knowledge because it is supported by strong scientific evidence (Ebrahim et al. 2013; Sharma et al. 2018; Thakkar et al. 2015; Clasadonte et al. 2014; Peeke et al. 1980). On the contrary, "alcohol has no side-effects when used for sedative purposes" is not knowledge. The distinction between belief and knowledge is not solely a semantic issue. In fact, many preventive interventions aiming at improving sleep behavior focus on improving knowledge, e.g. via education programs (Blunden et al. 2012). The reason why beliefs are not addressed globally is because there is a lack of tools to measure them (Grandner 2014, Grandner et al. 2014).

**Attitude, according to the *Theory of Planned Behavior*** (detailed below) (Ajzen 2002), is intertwined with the concept of behavior: **attitude towards a behavior is defined as "an individual's overall feeling of like or dislike toward a given behavior"** (Knowlden et al. 2012). In this line, behavior can be defined as an individual's observable reactions in a given situation, in relation with his/her environment. For example, going to bed earlier when the subject feels tired is a behavior. An attitude toward this behavior would be "The subject feels favorable to his/her behavior of going to bed earlier when he/she is tired".

Beliefs and knowledge, and their relationship with attitudes and behavior toward sleep (and thus sleep health), have received particular attention in the vast realm of insomnia disorder (Palagini et al. 2014; Peach et al. 2018; Lacks and Rotert 1986), and recently in the realm of adherence to treatments for obstructive sleep apnea syndrome (Micoulaud-Franchi et al. 2019; Philip et al. 2018; Weaver 2019). In fact, perceived sleep quality reported with self-questionnaire is not directly associated with an objective sleep measure such as polysomnography (Moul et al. 2002). Therefore, the missing link here might simply be beliefs. Indeed it was found that subjective insomnia sufferers with a positive diagnosis of insomnia disorder and a normal polysomnography had more dysfunctional beliefs about sleep than self-described "normal sleepers", who may have confirmed disturbed sleep on polysomnography (Edinger et al. 2000). These data found in the field of insomnia disorder suggest **that objective sleep measures are not sufficient to evaluate sleep (**Westerlund et al. 2016**), and that both sleep behavior and sleep representations should be taken into account.** Validated questionnaires have been developed for this purpose.

### *17.4.2 Evaluation of Sleep Beliefs and Knowledge*

As mentioned earlier, perceived sleep quality is related to beliefs and knowledges about sleep itself. The first challenge in designing interventions to change sleep behavior for improving health is to have tools that correctly evaluate pertinent outcomes.

**Concerning belief**, a few tools are available. Although they were developed with insomnia disorder in mind, they may also serve to assess beliefs about sleep. Morin and al. proposed a tool to evaluate sleep (dis-)beliefs. The **Dysfunctional Beliefs and Attitudes about Sleep** (DBAS-16) is a 16-item self-report measure designed to evaluate a subset of sleep-related cognitions (see Table 17.5). The 16 items are derived from a 30-item questionnaire, clustered around 5 themes: (1) misconceptions about the causes of insomnia, (2) misattribution or amplification of its consequences, (3) unrealistic sleep expectations, (4) diminished perception of control and predictability of sleep, and (5) faulty beliefs about sleep-promoting practices (Morin et al. 1993, 2007). Similarly, the **Sleep Beliefs Scale** (Adan et al. 2006) is a 20-item questionnaire that was developed to assess beliefs about the influence on sleep of (1) drug consumption (alcohol, caffeine, nicotine, sleep medication …), (2) diurnal behaviors (physical exercise and naps) and (3) activities and thoughts previous to sleep (eating, studying, relaxing, worries) (see Table 17.6). Both scales were designed to assess sleep in the context of specific sleep disorders, and neither was developed with any behavioral change theory in mind (Grandner et al. 2014).

**Concerning knowledge** about sleep, many studies examining educational programs (Katz and Malow 2014; Kloss et al. 2016; Knowlden et al. 2012; Lin et al. 2018; Blake and Gomez 1998; Mastin et al. 2006) to improve sleep behavior have led to tools to evaluate knowledge about it. These tools lack psychometric validation, but in fact were usually developed as a form of objective assessment in which

**Table 17.5** Items of dysfunctional beliefs and attitudes about sleep (DBAS-16) by Morin et al. (1993)

| | Items |
|---|---|
| 1 | I need 8 h of sleep to feel refreshed and function well during the day |
| 2 | When I don't get a proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer |
| 3 | I am concerned that chronic insomnia may have serious consequences on my physical health |
| 4 | I am worried that I may lose control over my abilities to sleep |
| 5 | After a poor night's sleep, I know that it will interfere with my daily activities on the next day |
| 6 | In order to be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep |
| 7 | When I feel irritable, depressed, or anxious during the day, it is mostly because I did not sleep well the night before |
| 8 | When I sleep poorly on one night, I know it will disturb my sleep schedule for the whole week |
| 9 | Without an adequate night's sleep, I can hardly function the next day |
| 10 | I can't ever predict whether I'll have a good or poor night's sleep |
| 11 | I have little ability to manage the negative consequences of disturbed sleep |
| 12 | When I feel tired, have no energy, or just seem not to function well during the day, it is generally because I did not sleep well the night before |
| 13 | I believe insomnia is essentially the result of a chemical imbalance |
| 14 | I feel insomnia is ruining my ability to enjoy life and prevents me from doing what I want |
| 15 | Medication is probably the only solution to sleeplessness |
| 16 | I avoid or cancel obligations (social, family) after a poor night's sleep |

respondents are asked to select only correct answers from choices offered as a list in a similar format that is most frequently used in educational testing. Educational programs were found to be effective in improving knowledge, but did not always change sleep behavior, as they did not always rely on a validated behavior change theory that encompasses all dimensions of change (motivation, context, beliefs as a whole) (Blunden et al. 2012).

Recently, Grandner et al. developed the Sleep Practices and Attitudes Questionnaire (SPAQ) (Grandner et al. 2014), which explores sleep behavior but also sleep knowledge and beliefs. It has 151 items with 16 subscales. Despite its length, it was designed on the basis of two well-validated behavior change models: the ***Health Belief Model***(HBM) and the ***Theory of Planned Behavior*** (TPB). It is thus of great interest since improving knowledge and addressing dysfunctional beliefs is still the easiest target to aim for in sleep health, especially in younger people (Katz and Malow 2014; Robbins and Niederdeppe 2015), even though it needs to be integrated into a whole theory of behavior change to be effective.

**Table 17.6** Items of sleep beliefs scale by Adan et al. (2006)

| | Positive effect | Neither effect | Negative effect |
|---|---|---|---|
| 1. Drinking alcohol in the evening | | | |
| 2. Drinking coffee or other substances with caffeine after dinner | | | |
| 3. Doing intense physical exercise before going to bed | | | |
| 4. Taking a long nap during the day | | | |
| 5. Going to bed and waking up always at the same hour | | | |
| 6. Thinking about one's engagements for the next day before falling asleep | | | |
| 7. Using sleep medication regularly | | | |
| 8. Smoking before falling asleep | | | |
| 9. Diverting one's attention and relaxing before bedtime | | | |
| 10. Going to bed 2 h later than the habitual hour | | | |
| 11. Going to bed with an empty stomach | | | |
| 13. Trying to fall asleep without having a sleep sensation | | | |
| 14. Studying or working intensely until late at night | | | |
| 15. Getting up when it is difficult to fall asleep | | | |
| 16. Going to bed 2 h earlier than the habitual hour | | | |
| 17. Going to bed immediately after eating | | | |
| 18. Being worried about the impossibility of getting enough sleep | | | |
| 19. Sleeping in a quiet and dark room | | | |
| 20. Recovering lost sleep by sleeping for a long time | | | |

### *17.4.3 The Different Models of Sleep Behavior Change*

Describing representations is not just about providing more precise tools for researchers to improve evidence-based facts about sleep knowledge, beliefs and attitudes and the relationship with sleep behaviors. The ultimate goal of any public health intervention is to improve the health of the beneficiaries, so state-of-the-art, validated, theory-based, behavior change techniques are essential for targeting sleep representations effectively.

There is no consensual, unique, "perfect" model theory that fits all the requirements for accurately describing health behavior changes. The ***Health Belief Model***

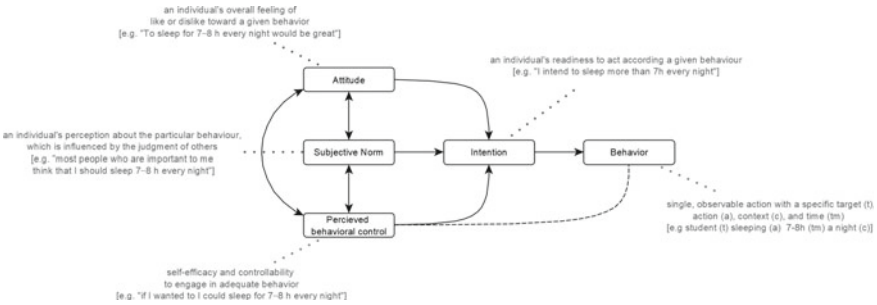


**Fig. 17.3** Theory of planned behavior applied to sleep behavior (Ajzen 2002)

**(HBM)** was the first model, and it is the one to which most of the others refer in education programs targeting sleep behavior (Katz and Malow 2014; Kloss et al. 2016; Knowlden et al. 2012; Lin et al. 2018; Murawski et al. 2018). The HBM posits that individuals undertake health-related behavior under the pressure of avoidable negative health outcomes, while believing that they are able to take this action and that it will avoid the negatively perceived outcome.

There are more recent models such as the ***Theory of Planned Behavior*** (TBP) (Ajzen 2002) which takes a broader set of parameters into account, such as belief, attitude, and behavior, in a model predicting change and resulting behavior according to this representation. The TBP describes human behavior as rational, guided by logical cognitive operations on representations, even if it is based on beliefs or attitudes that are not necessarily based on scientific evidence. The TBP was applied to sleep behavior change in undergraduate college students (Knowlden et al. 2012) (see Fig. 17.3). In this model, changing beliefs and attitudes can help in improving behaviors for better health, and it is relevant for a vast array of interventions and domains.

While the TBP describes very well how an intention, and then a behavior, may emerge from one's beliefs or attitudes, it has limitations regarding its application to health. Firstly, it does not take **the "direct effect" of dys-beliefs on sleep** into account**,** independently of the behavior. Yet, beliefs and attitudes probably have a direct link with sleep quality perception, at least in insomnia disorder, as they are both the cause and consequence of poor sleep quality, as discussed above (Edinger et al. 2000). One may also hypothesize that better sleep perception is possible without any sleep behavior change. Secondly, it implies that sleep can be narrowed down to a well-defined behavioral target, whereas it should be seen in a multifaceted manner through a prism that encompasses the specific physiological states of individuals (see Fig. 17.1). Studies have suggested that pre-sleep cognitive and physiological arousal contribute to sleep quality perception. Among the beliefs and knowledge about sleep, pre-sleep arousal may be seen as **the mental/brain-state resulting from one's experience of the day that has just passed**. This state before sleep could be a very important characteristic of sleep health, as discussed above (Goelema et al. 2018). It can be investigated by scales such as the Pre-Sleep Arousal Scale (PSAS), which

evaluates cognitive and somatic arousal (Jansson-Frojmark and Norell-Clarke 2012; Nicassio et al. 1985; Shoji et al. 2015; Ruivo Marques et al. 2018), the Ford Insomnia Response to Stress Test (FIRST), which evaluates the susceptibility of sleep disturbance in response to commonly experienced stressful situations, also called "sleep reactivity" (Drake et al. 2004; Kalmbach et al. 2016; Ford 1930), and the Arousal Predisposition Scale (APS), which evaluates arousability, i.e. the responsiveness of individuals to variations in environmental conditions (Coren 1988; Coren and Mah 1993). While these scales were designed for insomnia disorder, their incorporation into a broader sleep health model and sleep behavior change model might be pertinent in future research. Thirdly, the TBP does not take into account potential sleep disorders, such as obstructive sleep apnea syndrome, which can impact health independently of the representation of the subject, especially through the physiological arousal effect during sleep, e.g. sleep arousal induced by apnea.

Thus, it is important to develop a sleep behavior model that includes the components of arousal (pre-sleep and during sleep). We propose the COM-B model (**Capability-Opportunity-Motivation- Behavior**) (Michie et al. 2011), which is a synthesis based on previous models such as the TBP. The COM-B can be narrowed down to three basic components, hence its name: **capability, opportunity, and motivation**. **Capability** is defined as the individual's psychological and physiological capacity to engage in an action. For sleep, we suggest adding the concept of arousability (pre-sleep arousal) and sleep arousal (during sleep, in particular related to sleep disorders). Interventions to reduce arousability would be of interest here, such as coping interventions to target pre-sleep arousal (Morin et al. 2003) or the treatment of sleep disorders to target arousal during sleep. Attention should also be drawn to the fact that sleep health involves specific behaviors during wakefulness. **Motivation** is defined as all the processes that influence behavior, in particular representations such as beliefs, knowledge and attitudes. Interventions illustrating model behavior would be of interest here, as an example for people to aspire to or to imitate. **Opportunity** is defined as all the factors that lie outside the individual and which make the behavior possible or prompt it. We suggest adding all the environmental and societal factors that provide an opportunity for sleep or not. Interventions that promote environmental restructuring are appealing in this context, such as changing the physical or social context via tools for clinicians and patients.

To summarize, the concept of sleep representations is useful to link together sleep disorders, sleep as a behavior, and sleep health. Sleep representations have mostly been investigated in insomnia disorder, but deserve to be studied in the broad range of sleep parameters such as sleep health, sleep complaints and sleep disorders. Moreover, sleep representations are a promising target for public health interventions aiming to improve health, functioning and longevity through sleep.

## 17.5 Conclusion

Sleep health (beyond the presence or the absence of sleep disorder) is associated with many important health, functioning and longevity outcomes, and is thus central to promote overall health. Sleep health is characterized by subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours. To investigate and optimize these dimensions we still need: (i) to develop and evaluate an integrative model of the center of the prism in order to predict and simulate successfully the relationship between sleep and health, functioning and longevity; (ii) to develop an iterative approach between the sleep behavior change model, sleep health/complaints/disorder/representation psychometric models, and a physiological model; and (iii) to provide the evidence that specific interventions or programs that improve sleep health truly impact health, functioning and longevity outcomes (Irish et al. 2015; Blunden et al. 2012). To take the importance of sleep into account, we are convinced that sleep should be analyzed through the prism of the physiology, representations and behaviors that impact sleep health, sleep complaints and sleep disorders (see Fig. 17.2). An integrative model and new interventions could allow public health prevention measures to be improved.

This chapter has focused on interventions targeting individuals through the concepts of sleep representation and behavior. Furthermore, public health programs focusing on individuals should not neglect the importance of working with organizations and driving policy change in society at large (Grandner 2017). This calls for a broader range of approaches, in particular sleep health lobbying, in order to influence the actions, policies, decisions of officials, legislators and members of regulatory agencies, which go beyond the scope of this chapter (Wimbledon 1974). A sizeable advantage of the COM-B model is that it can be applied to describe not only individuals but also the global context of an intervention such as policies and infrastructures, and it is designed specifically to help create pertinent public health interventions. In a society that is undergoing probably the fastest changes that the world has ever witnessed, it is essential for clinicians to be able to help patients get their sleep back on track by using a multifaceted tool. Improving the sleep health of the public at large can only have a positive knock-on effect for us all.

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# Chapter 18
# 1974 and All That: A Tale of Two Approaches to Healthy Sexuality


**Andreas De Block**

**Abstract** Disease and health are important concepts, not because they do a lot of scientific work, but because they matter morally, as is illustrated by the debate on the medical status of homosexuality. In this contribution, I argue that the moral aspects of disease and health attributions should have an effect on the method of conceptual analysis. What we want disease and health to mean, should be taken into account by philosophers who engage in the analysis of these concepts. This is not a plea for a normativist account of health and disease, but it is a plea for a pragmatic approach to the conceptual analysis of health and disease.

**Keywords** Disease · Health · Homosexuality · DSM · Conceptual analysis · Ameliorative approach

In June 2012, a retired biology professor from Ghent University, Alexander-Karel Evrard, found himself in the middle of a social media firestorm after he published a letter in a local publication from a Belgian nature conservation organization. In that letter, Evrard argued that homosexuality was a disease, comparable to Down-syndrome and clubfeet. Immediately, his own university distanced itself from Evrard's view, and the nature conservation organization apologized publicly and stated clearly it should have never published the letter (De Block & Adriaens 2015).

This incident suggests that for many people it is a sign (or even a symptom) of homophobia to call homosexuality a disease. But although it is probably correct that in our societies homonegative individuals tend to agree more with statements like 'homosexuality is a disease' (Haslam & Levy 2006), it is not very easy to get a full grip on the philosophical issue. What exactly is wrong (both morally and theoretically) with the claim that homosexuality is a disorder? This is the issue I want to explore in this contribution, in which I want to defend the view that moral concerns with regard to the disease judgment should guide our conceptual analyses of health and disease.

In the first section, I give a very brief overview of the medicalization and demedicalization of homosexuality. The second section discusses the friction between the

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grounds for the decision to remove homosexuality from psychiatric nomenclature and so-called naturalistic accounts of disease. In 1974, it was decided by the American Psychiatric Association that homosexuality was not a disorder, and those who advocated for this removal argued that their stance was dictated by science. Yet, philosophers who think that the distinction between disease and health is a matter of scientific facts, seem to be less sure that science really tells us that homosexuality is not a disease. If they are nevertheless reluctant to call homosexuality a disorder, their reluctance seems to be based on moral concerns. The third section tries to explain what these moral concerns are. In the fourth section, I will argue for a pragmatic approach to the conceptual analysis of disease that takes the ethically motivated reluctance not just seriously, but even as the basis of a criterion for any successful conceptual analysis of health and disease. The last section compares this pragmatic approach with other approaches.

## 18.1 A Short History of the Medicalization and Demedicalisation of Homosexuality

In 1886, Richard von Krafft-Ebing published *Psychopathia Sexualis*. The book was a kind of catalog of sexual 'perversions', peppered with lots of case studies. *Psychopathia Sexualis* is generally seen as a historical milestone in the pathologization of homosexuality. Of course, the book did not come out of the blue. From the middle of the 19th Century onwards, sexual behavior became more and more a psychiatric/medical issue, all over Europe, and especially in France and Germany. Historians have tried to explain why this pathologizing tendency started then, and not earlier.

A first answer refers to Foucauldian biopolitics. At that time, there was indeed a growing political concern among both utilitarians and nationalists about the vitality and health of nations and peoples. Politicians called in the help of doctors to reduce the risk of depopulation and so-called degeneration (Oosterhuis 2000). Secondly, historians and philosophers have pointed out that as long as madness was primarily seen as a disease of the human intellect, sexual deviation could not be easily understood as a mental disorder, because sexual deviations usually do not affect intellectual judgment. In the 1860s, however, psychiatrists expanded the traditional rationalistic conception of insanity. They proposed new definitions of insanity that emphasized how the will and the emotions can also be disordered. This made a psychiatric description of some sexual desires and preferences possible (Shorter 2008). Thirdly, in much of the eighteenth Century, scientists thought of sexuality as mainly a matter of anatomy and behavior. In the 19th Century, sexuality became more and more thought of as an instinct, and hence as a psychological issue (Shortland 1987). People began to reason that if you really want to understand sexuality, you have to focus on people's emotions, desires, preferences, and attitudes.

That being said, the influence of Krafft-Ebing's book on psychiatric thinking about homosexuality is hard to overestimate. During the first half of the twentieth Century, the large majority of psychiatrists agreed with Krafft-Ebing in labeling homosexuality a disorder. And even though Freud himself seemed to reject the medicalization of homosexuality, most other psychoanalysts agreed with other psychiatrists on the pathological status of homosexuality. Hence, when the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) appeared in 1952, it came as no surprise that one of the conditions it dealt with was homosexuality.

Of course, what the first edition of DSM (APA 1952) wrote about homosexuality was more than just a rehash of what Krafft-Ebing had written. For one, DSM-I was mostly psychoanalytically oriented. Moreover, the first edition of the DSM should be understood against the background of WWII (Grob 1991). Lots of American soldiers came home after the war with psychological complaints. In the psychiatric handbooks of that time there was almost no discussion of these less severe symptoms and disorders. So the authors of the first DSM wanted to give more medical/psychiatric weight to the less severe complaints and psychological problems. One of the categories in the first DSM was the category of personality disorders in which many of the non-psychotic problems were placed. A subcategory of these personality disorders was called 'Sexual deviations', of which homosexuality was one. Yet, the medicalization of homosexuality by (or in) the first DSM should not be judged too harshly. Individuals to be placed in the subcategory of sexual deviations were said to be "ill primarily in terms of society and of conformity with the prevailing cultural milieu, and not only in terms of personal discomfort and relations with other individuals" (APA 1952, p. 38).

In 1968, the second edition of the DSM was published. This publication was an attempt to rework the first DSM in the light of the WHO's International Classification of Diseases (ICD) that also contained a mental disorder section. DSM-II (APA 1968) placed homosexuality under the heading 'certain non-psychotic disorders', and it does not refer anymore to the role of society. DSM-II is also more explicit about the medical status of homosexuality. According to DSM-II, homosexuality is a disorder. Although no reasons or arguments for this claim are given, this edition does mention that homosexuals experience a lot of distress because they feel disgusted by their sexual desires and they are generally unable to correct their own behavior.

At the end of the 1960s', however, the medicalized view of homosexuality had come under increasing scrutiny and even attack from a variety of actors, including gay activists and public intellectuals. Add to this the growing skepticism among many psychiatrists regarding the theoretical and clinical merits of psychoanalysis, many activists and psychiatrists felt that the time had come to remove homosexuality from the DSM. They got important intellectual and practical support from Judd Marmor, who was the vice-president of the American Psychiatric Association, the association that published the DSM (Marmor 1973).

Marmor had long been convinced that homosexuality was not a mental illness, and in 1972 he co-organized a symposium in 1972 to remove homosexuality from the DSM. In that same year, he helped Evelyn Hooker to prepare the report of the 'Task Force on Homosexuality' of the *National Institute of Mental Health*. In that

report, Marmor explicitly argued for the removal of homosexuality from the DSM. The main reasons Marmor and his fellow activist scientists gave for this view were the following (De Block & Adriaens 2013):

a. Homosexuality is natural because you find it many other animal species.
b. Even if it would be unnatural, it would still not follow from that that homosexuality is a disease. Celibacy is not natural either, and nobody considers it to be disease.
c. Most homosexuals do not need psychiatric help or treatment. Many homosexual individuals are as high functioning as heterosexuals, and they score as high as heterosexuals on all sorts of tests.
d. Even if the majority of homosexuals would have psychological problems, it seems strange to call homosexuality a disease, because it is very likely that the problems homosexual men and women have are largely or even exclusively due to societal norms.

Within the APA, the call for removal became louder and louder. However, two influential psychoanalytically-oriented psychiatrists, Socarides and Bieber, fiercely opposed the removal (Kutchins & Kirk 1997). A subgroup of the APA's Committee on Nomenclature researched the literature, and came up with a compromise. Homosexuality as such was to be removed from the DSM and to be replaced by 'sexual orientation disturbance', which only included those individuals troubled by their own sexual orientation. One of the important ideas behind this part of the proposal was an articulation of the definition of mental disorder. So the controversy surrounding homosexuality forced the APA to produce—for the very first time—a definition of mental disorder.

The removal met with intense protest, mainly from psychoanalysts. Nevertheless, the proposal to eliminate homosexuality from the DSM (and replace it with 'sexual orientation disturbance') was unanimously accepted by the APA's board of trustees in December 1973. Following further protest from Bieber and Socarides, the APA then organized a referendum on whether homosexuality should be in the APA nomenclature. Spitzer's proposal was eventually accepted by 58% of the APA membership, and consequently homosexuality as such was deleted from the seventh printing of DSM-II in 1974 (De Block & Adriaens 2013).

## 18.2 Gay Politics or Gay Science?

In an address Marmor gave at the University of California at Irvine in 2002, Marmor stated that the decision to remove homosexuality from the DSM was determined by science, and by science alone. Politics did not play a role, he stated: "The fact is that the decision to remove homosexuality from the DSM was not based on gay political pressure but on scientific correctness and only after a full year of exploratory hearings and study of the issue by the APA's Committee on Nomenclature" (cited in Drescher & Merlino 2007, p. 86). In Marmor's view, those who called homosexuality a disease

presented their claim as a factual judgment, while in fact it was a purely normative one. Marmor was really convinced that the solution was to replace the 'normativism in disguise' with a well-conceived naturalism about mental disorders. The adoption of such a naturalism about health and disorder would lead to the inevitable conclusion that homosexuality was not a disorder.

Not all philosophers agree with Marmor. Even after 1974, naturalists about disease/disorder have defended the conclusion that homosexuality is a disorder. In 1984, Michael Levin published a paper in *The Monist* in which he argued that homosexuality is abnormal, and that its abnormality is a scientific fact. According to Levin (1984), everybody would agree that someone who pulls all his teeth to make a necklace is using the teeth for something that the teeth are not meant for. Similarly, if a homosexual man uses his penis for homosexual acts, he is using his penis for something that the penis is not meant for. Levin argues that natural selection tends to link positive feelings to the correct or natural use of body parts, so that we can expect that those who misuse their body parts will be less happy than those who correctly use their body parts.

Even if we accept Levin's claim that natural selection tends to result in a hardwired association of positive feelings/happiness and the evolved use of body parts, one can come up with plenty of examples where the so-called misuse will not result in less happiness/positive feeling. Our fingers didn't evolve to play the piano, but many piano players are happy people, and shaving one's beard does not necessarily make people sad either. Even Scruton (1986), not exactly the most politically correct philosopher, has called Levin's argument absurd. Yet, even if we turn to more established naturalist approaches of health and disease, we still cannot be assured that such more sophisticated naturalist approaches will rule out the possibility that homosexuality is a disorder. Quite the contrary seems the case.

Take for instance how Christopher Boorse's biostatistical account deals with homosexuality. Boorse's account is probably the most influential naturalist account of health and disease. According to Boorse, to be healthy is to function normally, whereby a part of the organism's phenotype is thought to function normally if its contribution to the organism's biological goals of survival and reproduction is statistically typical. Typicality here is defined as typical with regard to a particular reference class (species, sex, age, …). Having a stable and exclusive sexual preference for mature men is statistically typical for mature women; it contributes to the reproductive fitness of mature women. For mature men, however, such a preference is not statistically typical, and the reproductive success of homosexual individuals is lower than that of heterosexual individuals. For Boorse, this suggests that homosexuality is a pathological deviation from the biological norm because "[i]t can hardly be denied that one normal function of sexual desire is to promote reproduction" (Boorse 1975, 63). In the end, Boorse concludes that even though homosexuality is a 'disease', it is no 'illness', since an illness entails being (1) incapacitating, or (2) undesirable for its bearer, neither of which are necessary for homosexuality.

Boorse's distinction between disease and illness is echoed by Jerome Wakefield's so-called hybrid account of disorder. Wakefield (1992) argues that a condition is only a disorder if it is both harmful and a dysfunction. A dysfunction requires a failure to

perform the naturally selected function (Boorse's 'disease'), but it requires a value judgment to tell whether the condition is also harmful (Wakefield 1992). An application of the harmful dysfunction analysis to homosexuality is not straightforward. Wakefield's etiological account of function seems to entail that homosexuality is a dysfunction. But is homosexuality harmful? Wakefield admits that the initial version of his analysis suggested that in societies in which homosexuality is oppressed, homosexuality is indeed harmful. Moreover, "homosexuality's purported harms justifying disorder attribution included features unrelated to oppression, such as the impossibility of having mutual biological children with the person one loves." (Wakefield 2013, 34) Still, Wakefield is not exactly eager to accept that homosexuality is—or can sometimes be—a disorder. He contends that "the social judgment that a condition is harmful may be based on misguided social values, and deeper judgments about what serves justice in the long run can override superficial harm judgments and thus negate disorder attribution" (Wakefield 2013, 34). So Wakefield wants to fix the problem by relying on 'deeper' value judgments than the 'misguided' and superficial ones of homonegative societies. According to Wakefield, that is exactly what the APA did in the early 1970s: "[p]sychiatrists avoided the incendiary issue of whether homosexuality is caused by a dysfunction and instead overrode the traditional reproductive-harm value claim, arguing that what really matters from a values perspective is capacity for loving human relationships" (ibid.).

There is much to write about Wakefield's argument, but I want to limit myself here to four points that are most relevant for the rest of this contribution. First, Wakefield's claim that psychiatrists avoided the 'incendiary issue' of homosexuality's dysfunctionality seems largely incorrect. The APA's decision to depathologize homosexuality was spurred by three leading psychiatrists (Marmor, Hooker and Spitzer), who all argued that it was *a scientific fact* that homosexuality was not a disorder, and that it was not more dysfunctional ('unnatural') than, say, celibacy. Secondly, even though homosexual people do not differ from heterosexual people in their capacity for loving human relationships, it is unclear how that would undo the purported harm of not being able to have biological children with the person one loves. Thirdly, the 'value-theory-based approach' that Wakefield advocates comes close to a kind of moral realism, and suggests that harm is only real—or at least only relevant for the attribution of disorder—when true or 'deep' values are compromised. One of the problems here is that there is room for disagreement between philosophers, psychiatrists and people in general about what the real values exactly are. Fourthly, Wakefield also suggests—even though he never really argued for it—that homosexuality is dysfunctional, at least if one takes his etiological account of function to be the correct account. This is in line with all the available studies that consistently show that homosexual men have fewer children—and lower reproductive fitness more in particular—than heterosexual men, although there are not many studies and most of them have been done in Western societies (De Block & Adriaens 2016). This fourth point is important because it underscores that the naturalistic component of Wakefield's hybrid analysis

does not save homosexuality from being a disorder. If it is saved from that label, it is through the harm-component.[1]

Of course, very few contemporary philosophers would be happy to conclude that homosexuality is a disorder. Wakefield, for example, sees it as a counterexample to an underdeveloped version of his harmful dysfunction analysis, and even Boorse seems to accept the conclusion only reluctantly. Some are willing to bite the bullet, others aren't, but for everyone it is a bullet. In the next section we will explore why most philosophical and psychiatric researchers think that it would be preferable if homosexuality wasn't a disorder.

## 18.3 Moralizing and Pathologizing

According to many sociologists and historians, three important homonegative tendencies have plagued the West: moralizing, medicalizing, and criminalizing. Yet, the relation between moralizing and the two other tendencies is complicated. Today, the ambiguous relation between moralizing and medicalizing also plays a role in discussions about the medicalization of obesity where both sides of the debate argue that the other side's position leads to a problematic form of moralizing. Historically, however, the best illustration of this ambiguous relation is probably to be found in the pathologization and depathologization of homosexuality.

For a very long time, and in many parts of the world even today, control over people's (homo)sexuality was and is exerted via religion, the criminal system, and psychiatry. Yet, we shouldn't just lump all these controlling systems and institutions together. For the individual, the type of control makes a difference. Being hanged or stoned for your homosexual behavior differs from being medically or psychotherapeutically treated for your homosexual desires. Today, we (rightfully) condemn all of these 'interventions', but for the 19th century homosexual individual, it often came as a relief that homosexuality was seen as a disease and not (or less) as a crime or a sin. As a matter of fact, this was no unintended side-effect of the medicalization of sexual deviancy. It was clearly one of Krafft-Ebing's goals to separate 'sexual deviancies' from sexual immorality.

In his excellent *Stepchildren of Nature*, Harry Oosterhuis (2000) narrates how this pathologization was welcomed by many homosexuals, and how Krafft-Ebing was proud of how he contributed to the well-being of homosexual ('inverted') people. Many homosexuals wrote letters to Krafft-Ebing, thanking him for the work he had done, and telling him they finally felt understood. They explicitly thanked him for showing them (and the whole world) that they were not alone. A homosexual physician put it as follows:

[1] Also, more recent naturalist approaches to health and disease, such as those developed by Griffiths and Matthewson (2016) and by Werkhoven (2019) can be easily interpreted as implying that homosexuality is a disease or not a healthy variant of sexuality.

> I lost all control, and thought of myself only as a monster before I myself shuddered. Then your work gave me courage again, and I was determined to get to the bottom of the matter, examine my past life, and let the results be what they might be …. After reading your work I hope that … I may still count myself among human beings who do not merely deserve to be despised. (Oosterhuis 2000, 11)

Of course, that does not alter Foucault's and Szasz' point that pathologizing and medicalizing are often also subtle forms of moralizing, and subtle forms of control can sometimes have more deplorable effects than less subtle forms, for instance because they are not easily unmasked as controlling devices. This is one of the reasons why historians are not always convinced that the medicalizing of homosexuality was really a step forward. Physicians pretended as if they only described sexual behavior, and most probably also believed it, but they also controlled sexual behavior through their descriptions (Löfström 1997). And it took a long time before the medical community also saw it that way. Only in 1974, the majority within the psychiatric community decided that homosexuality had to be removed from the psychiatric nomenclature because it had only been part of it for moral reasons. In other words, it took almost a century to unmask the medicalizing as a form of moralizing.

But if medicalizing behavior is a way to decriminalize that behavior, taking away much of the guilt and shame, then why can such medicalization still have moral overtones? If medicalizing entails that the deviancy is not intentional, then why is it still a form of moralizing? The answer is probably quite simple. The desires and behaviors are still seen as deviant, as violations of a norm. All else being equal, it is usually better not to have a disease (yes, there are exceptions). If a non-disorder is medicalized, this is problematic because it suggests that a condition is less valuable than it actually is. This may even have a pathogenic effect on those classified as disordered. After all, internalized societal norms can result in intra-psychic conflicts and serious psychiatric symptoms. For example, homonegative societal attitudes and beliefs can make the homosexual individual feel guilty and disgusted about his sexual orientation, and the self-loathing may eventually even cause a mental disorder.

So, although the medicalization of homosexuality may have been a step in the right direction (away from seeing it as a crime or a sin), it definitely was not a complete normalizing of homosexuality. And if homosexuality would be remedicalized today, this would certainly have all sorts of negative consequences for individuals, and the societal benefits would most probably be non-existent. Yet, doesn't this all assume that homosexuality is not a disorder? If homosexuality is not a disorder, then it is not just inaccurate, but also morally problematic to call it a disorder. But what if it is a disorder? Would it then still be morally problematic or even morally reprehensible to call it a disorder? This is the problem that many naturalist theories seem to struggle with. To some extent, this is related to the question whether it is a border case for naturalist accounts of mental disorders, or rather a counter example.

## 18.4 Pragmatism Against Intuitions

The purpose of conceptual analyses of disease is to analyze disease into more simple concepts. These simpler concepts provide expressions of the necessary and sufficient conditions for falling under the concept of disease. A successful analysis will explain how we tend to use the concept and how we should use it.

One of the aims of conceptual analysis is also to provide the tools to decide on particular border cases (but see Schwartz 2007), and that's probably why we need conceptual analysis the most. We obviously don't need conceptual analysis to clarify that lung cancer and schizophrenia are diseases, or that green eyes and dark hair are healthy. These are rather the 'raw material' for conceptual analysis and the stuff decisive counterexamples are made of. As Wakefield (1992, 223) puts it: "proposed accounts of a concept are tested against relatively uncontroversial and widely shared judgments about what does and does not fall under a concept." Boorse (1997, 44, italics in original) concurs: "to call pregnancy per se unhealthy would strike at the very heart of medical thought; it is the analytic equivalent of the 'Game Over' sign in a video game." So conceptual analysis is not useful because it would make us revise our most basic intuitions about disease and health, but it may help us to decide whether controversial cases such as ADHD, misophonia or obesity are genuine diseases/disorders. Some naturalists in particular are convinced that conceptual analysis can draw lines between health and disease, even in the most challenging cases (Ruse 2012).

I think that there are many problems with the philosophical research program of conceptual analysis. The most fundamental problem is that our everyday (not very theoretical) concepts probably do not have the structure that traditional conceptual analysis assumes them to have. Concepts probably do not have a definitional structure (Machery 2009), and this can explain why the track record of conceptual analysis is as poor as it is. One important issue, and the main focus of this and the next section, is what counts as a prototypical disease—Boorse (1977) calls these 'the paradigm objects of medical concern'—and as a prototypically healthy condition, and what as a border case. Wakefield and Boorse refer to shared judgements or intuitions, but it is far from clear how widely shared these intuitions should be, it is equally unclear whether they can change over time, and whether some intuitions—e.g. the intuitions of medically trained people—should count more than others. These questions are relevant because the seemingly relevant intuitions or judgments do differ, even between specialists. For example, Wakefield himself argues for his harmful dysfunction analysis by showing that there are dysfunctional but harmless conditions that are uncontroversially healthy. One of the examples he gives is 'fused toes'. The International Classification of Diseases 10, the official disease classification of the WHO, classifies fused toes as a disorder, which seems to cast some doubt on whether this condition is really uncontroversially non-disordered (De Block & Sholl *forthcoming*). At the very least, this indicates that there can be disagreement, even between epistemic peers, over whether a condition is a prototypical case of health or disease or rather a challenging border case. If it is a prototypically healthy condition,

it can be an illustration for the truth or falsehood of the analysis. If it is a border case, the results of a conceptual analysis can be applied to it.

A similar disagreement also seems present when it comes to homosexuality. Wakefield treats homosexuality as a potential counterexample and hence a straightforwardly healthy condition, Boorse as a borderline case. That is not to say that Boorse is completely at ease with the application of his biostatistical theory to homosexuality. Yet, he is willing to defend it, because.

> recent debates over homosexuality and other disputable diagnoses usually ignore at least one important issue. Besides asking whether, say, homosexuality is a disease, one should also ask what difference it makes if it is. I have suggested that biological normality is an instrumental rather than an intrinsic good. We always have the right to ask, of normality, what is in it for us that we already desire. If it were possible, then, to maximize intrinsic goods such as happiness, for ourselves and others, with a psyche full of deviant desires and unnatural acts, it is hard to see what practical significance the theoretical judgment of unhealthiness would have. (Boorse 1975, 63)

So, in Boorse's view, the disease judgment should be clearly distinguished from both a moral and a clinical judgment. Whereas the latter usually requires action, the disease judgment in itself does not. In a way, it can be perfectly fine to be unhealthy. Wakefield, on the other hand, calls it an 'incendiary issue' to consider whether or not homosexuality is (caused by) a dysfunction, and the very possibility that the specific conceptualization of the harm component in his analysis would lead to classifying homosexuality as a disorder urges him to reformulate—or even revise—that conceptualization (Wakefield 2013). Interestingly, the quote from Boorse dates from shortly after the APA's decision, while Wakefield's argument is developed in a much more recent publication. The disagreement between both may thus be explained by historical changes in our intuitions about what counts as prototypical diseases, historical changes that are partly caused by changed moral attitudes and beliefs.

Now we can also ask ourselves whether moral considerations should play a role in conceiving of a condition as a diseased or healthy condition. Can moral considerations move a case from an intermediate status—in between health and disease—to a straightforward status (health or disease)? If we would allow that, it would still be different from the situation where (non-moral) intuitions change because of moral changes. In fact, the intuitions would not change—at least not immediately—but we would just conceive of a particular condition as healthy for moral reasons, when our intuitions are unclear or conflicting. Eric Schwitzgebel (forthcoming) has argued for such a 'pragmatic' approach with regard to 'belief' that I would like to explore here for 'disease' and 'health':

> If there's more than one way to build a legitimate metaphysics or classificational scheme, you have some options. You can consider, do you want to classify the thing in question as an A? Would there be some advantage in thinking of category "A" so that it sweeps in the case? Or is it better to think of "A" in a way that excludes the case or leaves it intermediate? Such decisions can reflect, often do at least implicitly reflect, our interests and values. (…) For instance: There are lots of ways of thinking about what a person is. (…) You are a person; I am a person; this coffee mug is not a person. It wouldn't be reasonable to adopt a classificational scheme that yielded a different result than that! However, some interesting

cases appear to be antecedently open, breaking in different directions depending on what criteria are emphasized: a fetus, a human without much cortex, a hypothetical conscious robot, a hypothetical enhanced dog.

It matters to people whether we classify conditions as disorders or as healthy. The labels are important. Hence, it seems legitimate to take that 'mattering' into account when we try to prescribe how these labels should be used. But that entails that we get a clearer picture of how and why these labels matter. Do we need the labels primarily for scientific purposes, do they matter clinically, or is their moral significance what matters most?

Hesslow (1993) has argued persuasively that the distinction between heath and disease is neither clinically nor scientifically important. If it were important, Hesslow claims, medical professionals would have joined the philosophical debate. The concepts do not determine who needs medical treatment, nor do they really guide medical research. Likewise, Ereshefsky (2009) argues that the concepts health and disease are not central to medical discussions. Both Hesslow and Ereshefsky eventually draw eliminativist conclusions with regard to 'disease' and 'health'. Although I am sympathetic to their general argument, I do not want to follow their eliminativism because eliminativism about 'health' and 'disease', in more specialized contexts, will not lead to the elimination of the terms from our everyday speech. This entails that eliminativism does not offer a solution for the fact that the use of the labels impacts individuals and communities morally. Importantly, in those everyday contexts, these concepts do moral work, but not necessarily good moral work. The impact of the disease and health labels is very real, and often very problematic. For instance, cognitive scientists and ethicists have documented clear labeling effects (Mehta & Farina 1997; Rüsch et al. 2005; Goldberg 2014) showing that both pathologizing and depathologizing can reduce or increase stigma, depending on the context and the condition. If we want our concepts to do good moral work, it seems reasonable to try to curb the concepts in such a way that they fit our moral concerns better than they currently do. Again, this is no plea for a complete revision of our concepts or intuitions; it is rather a call to let moral concerns decide the controversial cases, and in such a way guide the conceptual analyses that we are after.

Because these moral effects are not always straightforward and often involve lots of stakeholders, this pragmatic or ameliorative (Haslanger 2000) proposal is not easy to implement. Moral considerations will be messy and conflicting too, and often as messy and confliction as our intuitions about disease or health judgments. Hence, implementing this proposal would not bring us much closer to a solution of what exactly a disease is, but it would shift at least part of the discussion to issues that matter more than the issues that play a central role in the philosophical debate right now. Much of the discussion would then center on the moral values that are at stake in calling border cases healthy or diseased, and in who is affected by the disease or health judgment. In a sense, that issue would have to be solved before one should try to get a theoretical grip on the line that is drawn between health and disease.

## 18.5 A Hybrid or Normativist View?

It may not be a coincidence that a naturalist like Boorse is less reluctant to call homosexuality a disorder than a hybridist like Wakefield or a normativist like Cooper. After all, naturalists think it is science and not ethics that determines what counts as a disease. Both hybridists and normativists think values can play an important role in the conceptual analysis of disease and health. In that sense, it would also be understandable if a reader would interpret the previous section as a plea for normativism or hybridism. And indeed, the pragmatic approach I propose, takes values to be central in a successful analysis of these concepts. Yet, the approach also differs substantially from traditional approaches, including the traditional hybrid or normative accounts, and that difference has to do with the role I ascribe to intuitions.

For traditional approaches (including those of Wakefield and Boorse), the fact that 'we' intuit that *d* is a disorder, should be the bedrock of conceptual analysis. This bedrock status can be unpacked as follows. Such a shared intuition that *d* is a disorder means that *d* is indeed a disorder, at least if the intuition is shared by the relevant individuals (and medical professionals are certainly among the relevant individuals). Consequently, such a shared intuition can be used as a test for the proposed conceptual analysis. If a conceptual analysis proposes to analyze disorder into the simpler concepts x and y, and *d* fulfils the conditions that are expressed by x and y, then this is evidence in favor of the conceptual analysis. But if the shared intuition is that *d* is not a disorder, and *d* fulfils x and y, the conclusion should be that the conceptual analysis has failed. The ameliorative or pragmatic approach can mostly concur with this view of what conceptual analysis should be. An important difference, however, is that the pragmatic or ameliorative approach will always demand that a condition for which it would be unethical to call it a disorder should also be seen as evidence against a conceptual analysis that entails that this condition is a disease. That would be so even when the intuition that this condition is not a disease, is not widely shared. So, whereas defenders of normative and hybrid accounts hold that values play a role in conceptual analysis because they capture—partly or completely—our intuitions about disease judgements, the pragmatic approach states that values can play a role whenever the relevant intuitions are weak or when the intuitions conflict. The values turn a case that is intuitionally controversial into a 'straightforward' case.

Now, what happens when we share the intuitions that *d* is a disorder, and there is also decisive evidence that seeing *d* as a disorder is ethically undesirable? I think that if such cases would be rife, it would be a good reason to stop traditional conceptual analyses of disease altogether, and to start engaging in more radical forms of conceptual engineering than the one I proposed here (Cappelen 2018). If such cases are (very) rare, though, it would be less clear what needs to be done philosophically. Still, it is important to answer this question, for instance because it does not seem

implausible that for almost a century many people shared the intuition that homosexuality was a disorder.[2] One option would be to choose for more radical alternatives to traditional conceptual analysis, such as conceptual engineering. Another possibility would be to try to disqualify the intuitions of the majority because they are not the relevant intuitions. As a matter of fact, this solution would not necessarily be out of line with more traditional approaches of conceptual analysis, since these analyses usually fail to make explicit whose intuitions are relevant and whose intuitions are not. Making explicit that some intuitions are irrelevant is thus complementary and not contradictory to the approach defended by traditional conceptual analysts. This solution, however, is only viable if it meets three conditions. First, it can only save conceptual analysis if not all intuitions are deemed irrelevant. So, if really everybody shares the intuition that *d* is a disorder, we have to abandon traditional conceptual analysis of disorder/disease. Furthermore, it almost goes without saying that this solution needs to be transparent and general. In other words, we need to give reasons why we should discard some intuitions. Thirdly, these reasons cannot be circular, in that we cannot simply state that we should discard intuitions that have unethical outcomes. I leave it to the reader to speculate how difficult such a rescue of conceptual analysis of disease would be.

## 18.6 Conclusion

One of the aims of a conceptual analysis of health and disease is to help decide in controversial or border cases. Yet, it is often unclear what counts as a controversial case. Traditionally, philosophers assumed that a case was controversial if intuitions diverged and/or if intuitions were vague. In this chapter, I argued that because disease and health attributions matter morally, moral considerations should (also) play a role in deciding whether a condition is a border case. I admit that this a relatively minor reform of traditional conceptual analysis.

One of the questions readers may have, is whether this proposal still has value if one would reject the traditional approach altogether. Suppose, for instance, that it would be established that most concepts really do not have a definitional structure, and that we therefore cannot analyze such concepts into simpler concepts that specify the necessary and sufficient conditions of the correct usage of the analyzed concept. Would that entail that the pragmatic approach that I developed here would become redundant? It surely would entail that the pragmatic approach loses much of its appeal. After all, the pragmatic approach would then only solve one, relatively minor problem of an approach that would in fact be irretrievably flawed because of an unrelated and more fundamental problem. That being said, parts of the pragmatic approach

[2] At the same time, it needs to be emphasized that there was least some dissensus on this issue. Even during the first decades of the 20th Century, quite some influential scholars like Freud and Havelock-Ellis did not consider homosexuality a disorder (see De Block & Adriaens 2013).

would still be valuable because they can be integrated in the philosophically viable alternatives for traditional conceptual analysis.

Clarifying concepts will always remain central to philosophy, and even the staunchest critics of traditional conceptual analysis (e.g. Machery 2017) stress that revealing the content of concepts remains an important task of philosophy. So, even if the concepts of health and disease do not have a definitional structure, it remains important to clarify the content of 'disease' and 'health' and the inferences this content underwrites. Clarifying what disease is, involves clarifying how we think about disease. What I have stressed in this contribution is that it should also consider that there are ethical aspects to how we think about disease and health, and that the clarification of concepts should take these ethical aspects into account. If the concepts of health and disease do not really matter scientifically or clinically, but do matter morally, then it should be obvious that their clarification takes that moral mattering into account, whether or not these concepts have a definitional structure. Of course, how that should be taken into account, does depend on the nature of these concepts.

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# Chapter 19
# Health in Non-human Organisms


**Henrik Lerner**

**Abstract** This chapter analyses attempts made to define health for non-human organisms. This could be done either as a bottom-up approach finding a common denominator that all organisms share, or as a top-down approach which starts with a certain valuable criterion that those organisms share. Through this chapter I will discuss both approaches. I will briefly discuss the concept of organism and why I only choose to discuss biological organisms. This chapter will also further develop a categorization of health definitions that acknowledges the variety of the different kinds of definitions. This is done as a two-level categorization consisting of categories and versions of these categories. I will go through relevant categories and versions in order to be able to say which could be fruitful to use as well as where science needs to be heading.

**Keywords** Animal health · Plant health · Definition · Categorization of health definitions · Species-specific · Levels of health

## 19.1 Introduction

In this chapter I will discuss attempts made to define health for non-human organisms. Most research has been done on animals, less on plants and fungi, but the amount of research is far less than on human health (Lerner 2017). Although there is no consensus on what human health is (Nordenfelt 2006), human health is easier to define than health for non-human organisms. When defining health in humans one only need to refer to a certain species, all individuals share a similar nervous system and all individuals are distinct entities (with the exception of Siamese twins). Defining health for non-human individuals needs to account for species-specific differences.

An underlying decision to make for such a stipulative effort is whether it is possible to find a unifying concept of health for all organisms or if one needs to define the concept of health for each species separately. I will hold the position that a unifying

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concept is worth aiming for, but we need to know the limitations and shortcomings of such a concept. In order to demarcate a unifying concept, one needs to take a stance on what an organism is, which I will do in the beginning of this chapter.

After my stance on the concept of organism, I will introduce different levels of where health can apply and discuss if a unifying concept can apply on all proposed levels. Here I will also mention some problematic cases.

Thereafter, I will turn to the different concepts of health in order to find a unifying concept. Several possible definitions of health have been proposed (see Lerner 2017, 2019; Nordenfelt 2006). These could be arranged in categories and each category can be further divided in different versions (Lerner 2019). In this chapter I will provide a tentative categorization of health definitions suitable for a unifying concept and indicate different versions of these categories. This is based on earlier research (Gunnarsson 2006; Lerner 2008, 2017, 2019; Nordenfelt 2006) but is more fully developed in this chapter. Each category and its indicated versions will be presented in separate sections below.

There are two ways of stipulating such a unifying concept, either one has a bottom-up approach finding a common denominator that all organisms share or one has a top-down approach which starts with a certain valuable criterion and then one clarifies which organisms fulfil the criterion. The bottom-up approach has the advantage that more organisms are covered but the disadvantage that health might be defined as too rudimentary to cover all aspects for organisms well above the common denominator. The top-down approach has the advantage that all health aspects of complex organisms will be covered with the cost that fewer organisms might be covered by a unifying concept (Lerner 2019). Through this chapter I will discuss both approaches.

My conclusion will be semi-normative. I state which aspects one at least needs to consider. I disregard some standpoints but I will leave several fruitful options for the reader to think about in order to strengthen the discussion in this field of philosophy of health.

## 19.2 Definition of Organism

In order to find a concept of health that apply to all organisms, one has to define what an organism is. This discussion has been extensive since the 19th Century and is interconnected with the discussion on how to define life. Despite a huge amount of definitions, no consensus exists (Jagers op Akkerhuis 2010; Pepper & Heron 2008; Pradeu 2010). I have therefore chosen a position on what an organism is in this chapter that simplifies my arguments so that I will not lose track of my main focus, which is health definitions.

In line with the analysis of the concept of organism made by Jagers op Akkerhuis (2010), I have excluded viruses and prions from this chapter. Jagers op Akkerhuis works with two criteria in order to distinguish life (which is also criteria for an organism): something needs to be an operator and the complexity of it needs to be at the level of a cellular operator or higher. An operator is defined as having

two “closures”, a membrane and autocatalysis, where autocatalysis is when a cell “autonomously creates a structural copy of its information” (Jagers op Akkerhuis 2010, p. 253). Viruses fail on the first criteria and prions fail on the second criteria according to Jagers op Akkerhuis. I deviate from Jagers op Akkerhuis’ position in that I here only will focus on biological organisms, while he also includes artefacts with artificial intelligence such as memic robots.

Biological organisms have at the highest level been divided into superkingdoms and kingdoms, and the number of kingdoms has differed through time. A recent study suggests seven kingdoms (Ruggiero et al. 2015): these are Archaea, Bacteria, Protozoa, Chromista, Fungi, Plantae and Animalia. Some of these consist mainly of unicellular organisms and others of multicellular organisms. This chapter excludes none of these kingdoms, but will mostly focus on Fungi, Plantae and Animalia.

### *19.2.1 Kingdom-Specific Limitations in Defining Health*

Will there be special implications for health when one compares each of these different kinds of organisms? Many of the biological differences that distinguishes these are irrelevant for the health concept. However, there might be kingdom-specific aspects that pose limitations in what definition of health one could choose. Some of the aspects proposed to be crucial when defining health from the top-down approach, expanding a concept primarily applied to humans, is capability of movement and/or having at least a rudimentary nervous system (Lerner 2008).

The latter one is the most central. A rudimentary nervous system seems to be a prerequisite to talk about mental health in organisms, as well as social health, at least if one defines it with cognitive aspects. The nervous system is present in all multicellular animals except sponges. There have been discussions on plants and sentience and a scientific field of plant neurobiology has been established (Calvo 2016). However, plants lack both neurons and synapses that constitute nervous system in animals. Neurotransmitters, on the other hand, are present in plants but their function has not been properly explained. The expansion of health top-down is often based on an argument of analogy, and if there is no similar nervous structure at all, the argument of analogy is hard to establish. Also, one can hardly talk about behaviour in plants, which also is something central to aspects of human health.

## 19.3 Levels of Health

After demarcating an organism, one should define where health would apply. At first glance, the individual organism seems to be the case but other ways are possible. This discussion has recently been introduced in the scientific study of One Health approaches, which are the widest global health approaches that promote health for humans, animals, plants and the environment at the same time. This discussion might

therefore be more fruitful than the discussion in philosophy of medicine whether one should define health in an individual or in a population (of humans). Lerner and Berg (2015, 2017) have found at least three levels of health that are relevant to discuss within One Health approaches, namely: individual, population, and ecosystem levels of health.

The individual level of health is the most common in plant health, veterinary medicine and human medicine. Population levels of health are used in concepts such as public health, veterinary public health and herd health. At first glance, the individual level and population level seem to be easy to distinguish but there are however blurred zones. Aphids, for example, have two forms of reproduction, one sexual and one asexual. In the asexual one, offspring have the same DNA as the parent. Reeds that grow in distinct groups in a lake might be entities that are physically separate from each other but are still clones of each other due to fragmentation, sharing similar DNA. The Portuguese Man O'War (*Physalia physalis*) is an example of a species which consists of several distinct individuals that together form what looks like an individual (Jagers op Akkerhuis 2010; Pepper & Heron 2008).

The ecosystem level of health, as in such concepts as ecosystem health, river health or forest health is mainly used by ecologists. At least two alternatives occur, where one is a proper definition of health at a system level and the other uses health in a metaphorical way with no intention to define health. In the first case, health could for example be defined as functional system processes that make the ecosystem resilient or result in a state of resilience.

## 19.4 Categories of Health

There are so many definitions of health present that there is a need for a categorization of health definitions. The traditional version of a dualistic opposition between biological definitions of health and holistic definitions of health (Kingma 2017) has nowadays been further elaborated in several attempts to construct a list of categories of health definitions (Gunnarsson 2006; Lerner 2008, 2017; Nordenfelt 2006; Tengland 2006). These have all been tentative and have tried to arrange monistic definitions, i.e. defining health with only one aspect (for example balance), in a systematic manner. Conglomerate definitions, combining two or more of the monistic aspects, have mainly been left aside. This will also be the case in this chapter. As I have elaborated at length elsewhere (Lerner 2008), conglomerate definitions have the problem that included aspects might be in conflict with each other. Then the problem arises whether an organism has health, when health is fulfilled at least in one criterion of the definition while the others show illness. Arguing for the use of conglomerate definitions implies that one also needs to specify which monistic aspect of the ones included is most influential for health. If one is able to construct a fruitful definition of health that is monistic this internal conflict can be avoided.

All categorizations need to be stringent. The concept of health has been regarded for example as a state or as a process (Medin & Alexandersson 2000; Nordenfelt

2006). In line with Rolston III's (2012) analysis of values, states and processes could both be attributed values even though they are different. The list of categories below is based on health regarded as a state.

Quite recently, I (Lerner 2019) further differentiated this way of categorization of health definitions proposing a two-layer system in a study on the category of health as balance. Within a category there is often such a wide variety of definitions that one needs to further specify the category with different versions. In my view, each version is a distinct under-category of the category and not only variants on a specific way to define.

This chapter will use the following tentative categories and versions of health definitions which are regarded as suitable for nonhuman organisms:

1. Health as balance
    a. Homeostasis
    b. Health as balance between ability and goals in an environment
2. Health as biological function
    a. Health as natural function
    b. Health as coping with pathology
    c. Health as productivity including reproduction
3. Health as well-being
4. Health as ability
    a. Health as mental and physical control
    b. Health as the ability to realize goals.

In some of these lists, a category called health as absence of disease is included. Health as absence of disease implies in this case that health is negatively defined as the opposite of disease conditions and in order to evaluate whether health occurs, one needs to go through a list of animal, plant or fungi diseases and exclude all possible diseases. Then, the individual animal, plant or fungi is considered healthy. Therefore, different classifications of diseases are important to consider in order to know whether health is present. For plants, they are mainly based on causal factors for the diseases (Agrios 2005; Kůdela 2011). For animals, besides causal factors, also the kind of tissue or organ affected or the kind of tissue change occurring is important (Broom & Kirkden 2004). I have chosen to omit this category in order to have a list only with positive characteristics of health. In Table 19.1 I have summarized categories, versions and examples of definitions.

**Table 19.1** A tentative categorization of monistic definitions of health for non-human organisms further divided into versions and exemplified by definitions mentioned in the text and organism groups that are covered. All monistic categories are based on health as a state and an individual level of health

| Category | Version | Example definition | Organism groups | Approach |
|---|---|---|---|---|
| Health as balance | Homeostasis | Lacks a full definition HHMD proposed by Dussault and Gagné-Julien is a modification to Boorse, see below | All organisms | Bottom-up |
| | Health as balance between ability and goals in an environment | Pörn stipulates that health is a balance between the person's goal profile, ability to perform actions and the environment surrounding that person | Animals able to evaluate a goal | Top-down |
| Health as biological function | Health as natural function | Christopher Boorse's biostatistical theory of health defined as: "The individual A is completely healthy if, and only if, all organs of A function normally, i.e. make their species-typical contribution to the survival of the individual and the species, given a statistically normal environment" | All organisms with organs | Bottom-up |

(continued)

### *19.4.1 Health as Balance*

Lerner (2019) analysed different versions of the category health as balance, and the two important ones are health as homeostasis and health as balance between ability and goals in an environment.

**Table 19.1** (continued)

| Category | Version | Example definition | Organism groups | Approach |
|---|---|---|---|---|
| | Health as coping with pathology | "Health refers to what is happening in body systems, including those in the brain, which combat pathogens, tissue damage or physiological disorder. Health is the state of an individual as regards its attempts to cope with pathology" | Animals | Top-down |
| | Health as productivity including reproduction | Focuses on biological growth. Productivity could be increased biomass or number of offspring | All organism groups | Bottom-up |
| Health as well-being | | "Health is a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity" | Animals (at least mammals and birds)<br>For plants and fungi only physical well-being | Top-down |
| Health as ability | Health as mental and physical control | "The animal has a mental ability to imagine a situation which could be dangerous or unpleasant and change the situation by avoiding or hindering its occurrence" | Animals with mental abilities to foresee a situation | Top-down |

(continued)

#### 19.4.1.1 Homeostasis

Health as homeostasis has been proposed as a way of defining health in homeopathic textbooks for veterinarians as well as in research studies on ecological farming (Lerner 2017). Lerner (2019), however, shows that homeostasis is not sufficient by itself to define health despite modern attempts such as the homeostatic maintenance

**Table 19.1** (continued)

| Category | Version | Example definition | Organism groups | Approach |
|---|---|---|---|---|
| | Health as the ability to realize goals | "An animal A or a plant P is healthy if, and only if, A or P has the ability to realize all its vital goals given standard circumstances" | Vertebrate animals (vital goals that promote long-time happiness) Non-vertebrate animals, plants and fungi (vital goals that promote vitality) | Top-down |

See text for definition of organism

of design (HHMD) proposed by Dussault and Gagné-Julien (2015). Health as homeostasis could however be a part of a conglomerate definition in the category of health as biological function.

#### 19.4.1.2 Health as Balance Between Ability and Goals in an Environment

The version of health as balance between ability and goals in an environment has been developed by Ingmar Pörn in philosophy of human health. Pörn (1995, 2000) stipulates that health is a balance between the person's goal profile, ability to perform actions and the environment surrounding that person. The person must be able to have goals and to evaluate whether its state is like what the person thinks it should be. All three parts of the balance can be changed. Pörn claims that this definition cannot be extended to animals or other species as a top-down approach, but Lerner (2019) has shown that this is possible within Pörn's theory. At least those non-human animals capable of having goals could have health in this way. There is a growing body of knowledge on animal minds. For example, preference and motivation tests have been developed and used to study choices made by mammals, birds and even lobsters (Fraser & Nicol 2018). In the theory behind these tests is an assumption that animals can make choices in order to get something that is better for them.

### *19.4.2 Health as Biological Function*

In the category of health as biological function one finds definitions that only deal with biological matters. Mental states are relevant only if they are explained in physiological or biomedical terms. This category has at least three different versions: normal biological function, coping, and health as productivity including reproduction. All definitions seem applicable to all groups of organisms.

#### 19.4.2.1 Health as Natural Function

In the version of health as natural function, Christopher Boorse's biostatistical theory of health is the most influential and developed in philosophy of human health (Boorse 1997). Nordenfelt has clarified Boorse's definition of health in the following words:

> The individual A is completely healthy if, and only if, all organs of A function normally, i.e. make their species-typical contribution to the survival of the individual and the species, given a statistically normal environment. (Nordenfelt 2006, p. 14)

This definition could apply to all biological species as long as it is possible to talk about organs and their function. Each individual's reference class is "an age group of a sex of a species" (Boorse 1997, p. 7).

#### 19.4.2.2 Health as Coping with Pathology

The version of health as coping with pathology has been elaborated by Donald Broom in the science of animal health and welfare and has gained influence there. His definition covers many animals, including humans.

> Health refers to what is happening in body systems, including those in the brain, which combat pathogens, tissue damage or physiological disorder. Health is the state of an individual as regards its attempts to cope with pathology. (Broom 2011, p. 133)

This definition seems to be purely physiological even though Broom talks about the brain. Using the brain as one of the body systems might imply that only vertebrates are covered by this definition. However, the critique has been raised that the definition needs further development in order to clarify when health occurs, in the process of coping or as a final state when coping is successful (Lerner 2017). Despite changes made over time by Broom in his concept of health, this main critique still exists.

#### 19.4.2.3 Health as Productivity Including Reproduction

The version of health as productivity and reproduction focuses on biological growth. Productivity could be increased biomass or number of offspring. Reproduction could be either sexual reproduction, involving at least two individuals, or asexual reproduction where only one individual is needed.

This kind of definition has been avoided within the science of animal health and welfare as being unethical, focusing on yield for humans rather than the animal itself (Lerner 2017).

### *19.4.3 Health as Well-Being*

The category of health as well-being has at its paramount definition the WHO definition of health and I have not further divided this category in versions. "Health is a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity" (WHO 1948).

Health is here seen as something positive, something to aim for, that considers the whole human (Bickenbach 2017). Although one critique has been that there is a risk of medicalizing mental and social health, the vivid discussion on this definition has shown the importance of recognizing more than one aspect of health. In philosophy of human health, this definition has influenced a rich debate on holistic normative health definitions focusing on all aspects of health, not just the objective, biological features.

In animals, this definition has been applied both at the individual and population level (Lerner 2017). In the field of animal health and welfare at present day, at least birds and mammals are considered as being able to suffer and need social relations. In plants and fungi, well-being might only be physical well-being due to the absence of a neural system.

### *19.4.4 Health as Ability*

The category of health as ability consists of two versions: health as mental and physical control, and health as the ability to realize goals.

#### 19.4.4.1 Health as Mental and Physical Control

Health as mental and physical control has been proposed in the science of animal health and welfare by Lerner (2008) after findings in an interview study. Lerner has further characterized this version as: "The animal has a mental ability to imagine a situation which could be dangerous or unpleasant and change the situation by avoiding or hindering its occurrence." (Lerner 2017, p. 295).

To be able to be ascribed this version of health, the organism needs a nervous system with the mental abilities to foresee a situation and also be able to choose between alternatives. In the science of animal health and welfare this has been accepted for animals such as birds and mammals (Lerner 2008).

#### 19.4.4.2 Health as the Ability to Realize Goals

The category of health as the ability to realize goals covers definitions that have been defined in philosophy of human health and then been further expanded to animals

and maybe plants. One of the main proponents has been Lennart Nordenfelt (2006, 2007). The main idea is that health is the ability to achieve certain, vital goals that an individual has. Nordenfelt defines a vital goal such as: "A vital goal of a person, …, is a state of affairs that is necessary for this person's minimal long-term happiness" (Nordenfelt 2006, p. 147).

Nordenfelt argues that vital goals are those that need to be fulfilled in order to reach happiness, which is the ultimate aim. According to Nordenfelt, this implies that vertebrates could be covered in this definition (Nordenfelt 2006). Nordenfelt (2007) has also tried to include plants and fungi in the definition of health in his later works: "An animal A or a plant P is healthy if, and only if, A or P has the ability to realize all its vital goals given standard circumstances" (Nordenfelt 2007, pp. 30–31).

Vital goals have here been defined as those that are needed for vitality, i.e. being able to develop or grow. For non-vertebrate animals, vital goals are also seen as those crucial for vitality (Nordenfelt 2006). Lerner (2017) questions this latter extension of his theory as reducing this category of health to a version of the category of health as biological function.

## 19.5 Suggested Further Developments

As in all kinds of research, this categorization needs to be accompanied by further research. Some examples could be stated here. The classification here is based on health as states. Definitions based on health as a process have been omitted. Further research needs to be done in order to see if these are possible to include in the same classification or whether one needs to have two lists of classifications. A fruitful area of research is health definitions developed within nursing science. Another area might be a deeper analysis of ecosystem health. Ecosystem health could be defined as a state or as a process. Here in particular health depends on relations between species, which also has implications for the understanding of disease. A bacterium that is healthy could cause disease in a human, and yet at a higher level an ecosystem could still be considered healthy.

Another area for further research is the relation between different levels of health, barely mentioned in this text. Is it possible to define health in a manner that meets all three levels at the same time? Even here, a more thorough analysis of whether health should be defined as a state or a process might be fruitful. In order to manage this task, one needs to use at least those species examples already mentioned above in the section of levels of health.

## 19.6 Bottom-Up and Top-Down Approaches Analyzed

As has been shown, although still tentative, several possible definitions exist (Table 19.1). A unifying definition for all organisms (including humans) would simplify

research a lot. There are, however, several obstacles to bear in mind. One is that philosophy of human health, mainly analysing health for one particular species, hasn't reached consensus on a definition of health. Another is that having a unifying definition could fool us to treat the different species to be more alike than they are. Lerner (2008) and Derrida (2008) raised the issue that animals have been falsely treated on the group level and not on a species or individual level, both in animal ethics as well as in the science of animal health and welfare.

To stipulate a definition of health along with a bottom-up approach means that one tries to find a common denominator at the lowest level of organism kingdoms. In order to cover all proposed seven kingdoms, one needs to start with Bacteria or Archae. The categories available for this approach are health as biological function or the version of health as homeostasis in the category of health as balance (if someone could develop a monistic version of this). A bottom-up approach avoids kingdom-specific and species-specific limitations. For the kingdom-specific limitations even organisms that lack mental or social aspects of health tied to cognitive skills are included. However, we end up in a definition of health which is only based on physical health.

If one, on the other hand, stipulates a definition of health with a top-down approach, one often starts with the species that are most developed on the kingdom-specific aspects that might cause limitations in the definition. A starting point is a definition developed for human health and then one either extrapolates or re-stipulates it in order to cover most of the kingdoms. Nordenfelt's definition in the version of health as ability to realize goals is an example of this. The WHO definition in the category of health as well-being is another example showing kingdom-specific limitations excluding kingdoms that lack mental or social aspects of health tied to cognitive skills.

Depending on what one strives for, choosing a definition of health that covers all organisms or with the ability to cover a wider range of organisms than just human health, one needs to choose either a bottom-up or top-down-approach. Both these approaches need to take into account kingdom-specific as well as species-specific aspects.

## 19.7 Conclusion

In this chapter I have discussed attempts made to define health for non-human organisms. The chapter covers all proposed biological seven kingdoms of organisms, although most emphasis is placed on animals, plants and fungi. A tentative categorization of different health definitions is proposed that considers monistic health definitions based on health as a state. Each category has also been divided further in different versions of the category, creating a finer grid in order to differentiate between different definitions of health. Top-down and bottom-up approaches to defining health are discussed in order to show that kingdom-specific and species-specific aspects are

important to consider. Still, no consensus exists on what definition of health to choose, although this chapter provides a richer grid of distinctions that could be helpful in the aim of reaching a unifying definition.

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# Chapter 20
# Healthy Worms


**Rikke Hindsgaul Harders, Katrine Vogt Møller, Maria Grymer Metz Mørch, Matthew S. Gill, and Anders Olsen**

**Abstract** Health is often seen as the attractive opposite to disease but what are the molecular mechanisms that underpin health and can we target these pathways to improve health? Model organisms have been instrumental in defining the molecular genetics of complex biological processes, including longevity, and now they are increasingly being used to investigate health. In this chapter, we review some of the insights that have been gained by studying health and healthspan in the soil nematode *Caenorhabditis elegans*. Interestingly, several gene mutations and interventions have been shown to improve health in *C. elegans* offering possibilities of translation to humans.

**Keywords** Health · Healthspan · Lifespan · *C. elegans* · Ageing · Stress resistance · Mobility · Reproduction

## 20.1 Introduction

Model organisms have been instrumental in defining the molecular genetics of complex biological processes, including longevity. But can they also teach us about health? We often think about our health, particularly as we get older. The media constantly bombards us with strategies and solutions purporting to improve our health, while public health policies are aimed at saving us from ourselves. What are we trying to achieve when we say we want to become healthier? In the short-term, this is a straightforward and simple question for most of us, as we typically want to exercise more, eat better and generally feel better. What about the long term? Here, most people are concerned with staving off age-associated illness in order to stay active and disease-free. In recent years, this concept has been encapsulated by

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geroscience (the science of ageing) which has provided us with the new goal of improving "healthspan". So, what do we mean by health and healthspan?

Healthspan has been defined as the period of life that is free from debilitating disease (Rowe and Kahn 1987). While it is hard to measure average healthspan, the World Health Organization (WHO) has been measuring something similar with an indicator called HALE: Healthy life expectancy (Sullivan 1971). HALE estimates how many years a person can expect to live in a healthy state. Estimates generated by the WHO in 2016 found that global life expectancy was 72.0 years and healthy life expectancy was 63.3 years. The lowest and highest HALE in 2018 were observed in Sierra Leone (44.4 years) and in Sri Lanka (67.0 years), respectively (Islam et al. 2018). One goal of healthspan research is to minimize the discrepancy between life expectancy and health expectancy. Despite large national differences, there is clearly a potential for increasing healthspan both at the level of the individual and society.

In this chapter we will address health and age-related changes from the point of view of the popular model organism *Caenorhabditis elegans* (*C. elegans*). Health is officially defined by the WHO as "a state of complete physical, mental, and social well-being, not merely the absence of disease or infirmity" (Jadad and O'Grady 2008; WHO 2002). Since we do not yet have the tools to study mental health and social well-being in the worm, we will mainly discuss physical health and focus on the molecular and physiological mechanisms that may be at play. Having well described measures of health could perhaps in many instances provide a more operational definition of health.

## 20.2 What is a Healthy Organism?

From a Darwinian point of view, one component of a healthy organism is its ability to successfully reproduce and thus continue the survival of the species. Evolutionary theories of ageing elaborate on this concept and suggest that the trade-off between investing in reproduction versus maintaining the soma is the underlying reason for ageing and eventually declining health (Lithgow and Kirkwood 1996). From this line of thinking comes the premise that if we can identify the molecular mechanisms that cause ageing, we will simultaneously identify molecular mechanisms that maintain health. Studies in small genetic model organisms such as yeast, fruit flies and the soil nematode *C. elegans* have revolutionized our understanding of the molecular pathways that drive ageing and longevity. More recently, attention has turned to whether the same molecular pathways also improve healthspan and whether genetic approaches can be utilized to identify new mechanisms involved in health and healthspan (Hansen and Kennedy 2016). To do so, we need to define health in simple, multicellular organisms such as *C. elegans*.

## 20.3 *C. elegans* as a Model Organism

*C. elegans* is a small nematode found in the soil and was established as laboratory model organism by Sydney Brenner in the 1960s (Brenner 1974). *C. elegans* can be cultured inexpensively on agar plates or in liquid cultures with *E. coli* bacteria as food source. These worms are typically maintained as self-fertilizing hermaphrodites, developing from egg through four larval stages (L1–L4) into adults within 3 days, which are then capable of producing approximately 300 genetically identical progeny. The adult hermaphrodite consists of 959 cells and the entire cell lineage has been mapped (Sulston and Horvitz 1977; Sulston et al. 1983). Brenner established the model to facilitate genetic analysis of complex traits in a simple multicellular organism and, in this respect, the rare presence of males in the population can be exploited for genetic crosses and makes epistasis analysis fast. Over subsequent years, a robust set of genetic tools has been developed including, but not limited to, transgenic gene expression, RNAi, CRISPR based genome editing, and unbiased random mutagenesis protocols (Corsi 2006; Nance and Frokjaer-Jensen 2019). The entire *C. elegans* genome was fully sequenced in 1998 (CSC 1998). It encodes approximately 18,000 genes, many of which have high homology to human genes. Indeed, it is estimated that 56% of human genes have an orthologue in the worm (Kim et al. 2018). Several seminal discoveries over the years have established *C. elegans* as one of the premier model systems, particularly for ageing research, complementing other established models such as yeast and fruit flies.

### *20.3.1 Genetic Analysis of Ageing in* C. elegans

The discovery that single gene mutations could dramatically increase lifespan in *C. elegans* was a turning point in ageing research (Johnson and Wood 1982; Kenyon et al. 1993; Klass 1983). Since then, nearly 4 decades of ageing studies in worms have had a profound impact on our understanding of the molecular mechanisms underlying the ageing process and helped identify interventions and compounds that increase lifespan (Olsen and Gill 2017). Molecular mechanisms of ageing that have been studied in the worm include insulin signalling, dietary restriction, mitochondrial function, TOR signalling and autophagy, to name a few of the better characterized (Fig. 20.1).

These studies have been thoroughly reviewed elsewhere (Olsen and Gill 2017) and only a few of the identified pathways will be discussed in this chapter, as these have been studied in the context of health.

One of the best-described pathways affecting ageing and longevity is the insulin/IGF-1 signalling pathway (Fig. 20.2). The insulin signalling pathway is particularly interesting because the effect on ageing is also observed in flies, mice and likely humans, suggesting evolutionarily conservation (Katic and Kahn 2005). The effect of insulin signalling on healthspan has also been extensively studied and will

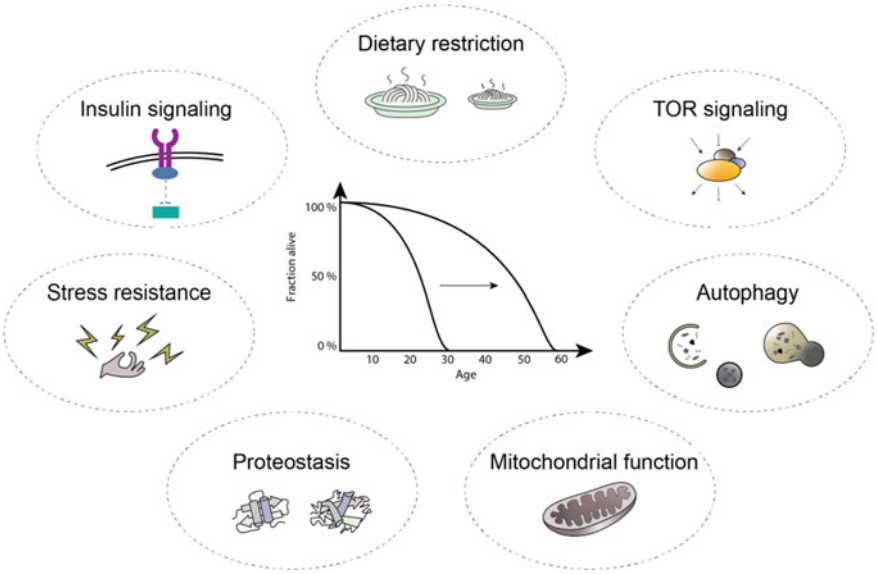


**Fig. 20.1** Mechanisms involved in longevity in *C. elegans*. Studies of long-lived mutants have revealed many of the underlying molecular mechanisms required for longevity. These include but are not limited to increased stress resistance, reduced insulin signalling, altered nutrient sensing (dietary restriction and TOR signalling), increased autophagy, altered mitochondrial function and enhanced proteostasis

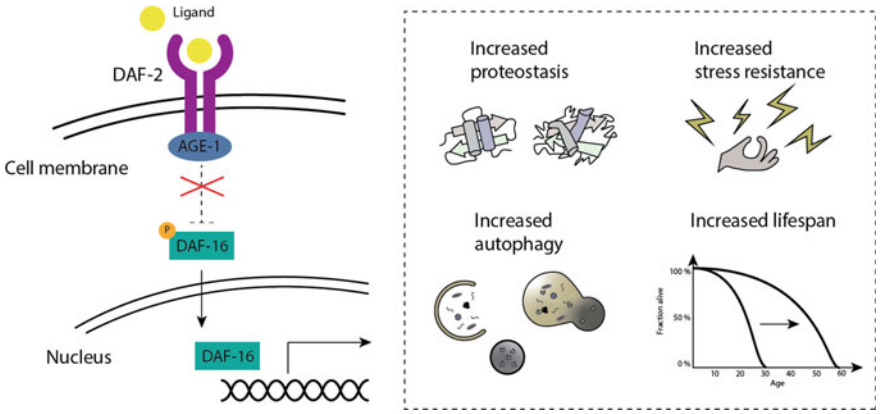


**Fig. 20.2** Schematic representation of the insulin/IGF-1 signalling pathway in *C. elegans*. Insulin-like peptides (ligands) activate DAF-2, which result in recruitment and activation of AGE-1. In turn, a signalling cascade is activated resulting in phosphorylation of DAF-16 and its retention in the cytosol. When insulin signalling is reduced, the transcription factor DAF-16 is dephosphorylated and translocates to the nucleus where it induces or represses target gene expression, leading to increased organismal stress resistance and longevity

be discussed in the following sections. In *C. elegans* mutation or reduced levels of DAF-2, the insulin/IGF-1 receptor, or the downstream PI3-kinase AGE-1 increase lifespan typically by more than 50% and sometimes up to a striking 500–1000% depending on the allele and genetic background (Ayyadevara et al. 2008; Chen et al. 2013b; Kenyon et al. 1993). This increase in longevity is fully dependent on the FOXO transcription factor DAF-16 (Kenyon et al. 1993; Lin et al. 1997; Paradis and Ruvkun 1998) which coordinates gene expression programs involved in stress resistance, proteostasis and autophagy amongst others (Fig. 20.2).

Autophagy is an evolutionarily conserved process by which cellular material is encapsulated by a double-membrane vesicle (autophagosome) and delivered to the lysosome for degradation and recycling (Cadwell 2013). As such, autophagy has an essential role in maintaining energy homeostasis and in protecting cells against stress. Autophagy is also emerging as one of the most important cellular mechanisms involved in health (Tables 20.1 and 20.2). Most, if not all, long-lived mutants have increased autophagy (Hansen et al. 2018; Kumsta et al. 2019; Mosbech et al. 2013; Seo et al. 2018) and several compounds and interventions that increase lifespan are dependent on autophagy, including for example supplementation with ω-6 polyunsaturated fatty acids (O'Rourke et al. 2013) and dietary restriction (Mosbech et al. 2013). Furthermore, since autophagy is often disturbed in age-related diseases such as cancer, diabetes and neurogenerative diseases (Dikic and Elazar 2018; Huang and Klionsky 2007) increased autophagy has been associated with improved health.

The early focus of ageing research in *C. elegans* was on identifying genes that increase lifespan (Olsen and Gill 2017). Typically, researchers reported summary measures of survival, including median, mean and maximum lifespan when analysing longevity mutants (Fig. 20.3).

An underlying assumption that was made in many ageing studies was that health and lifespan would be correlated. Hence, if lifespan is increased the animal would also have an extended period of health compared with animals with regular lifespan. Subsequently, this view has been challenged and researchers have started investigating whether increased survival really equates to prolonged health. In simple terms, an animal that is immobile and decrepit but lives a long time may have increased survival but likely exhibits poor health and ageing. In contrast, an animal that is able to maintain movement and feeding as well as living longer could be considered to have aged more successfully (and thus to be healthier). In a different scenario, maximum lifespan is not altered, but median lifespan is increased (curve A vs. curve B, Fig. 20.3). This "squaring of the curve" is considered to be an indicator of improved healthspan as more animals reach their maximum lifespan potential. These issues become more relevant when considering which interventions might be translatable into improving human healthspan. As it turns out this is a rather complicated matter.

**Table 20.1** Selected studies of healthspan genes in *C. elegans*. Some genes have both positive and negative (designated by *) effects on healthspan depending on the assay used

| Genes | Healthspan effect | Lifespan effect | References |
|---|---|---|---|
| *age-1*<br>*PI-3 kinase* | Extended fast body movement[1]<br>Extended pharyngeal pumping span[1]<br>Increased thermotolerance[2]<br>Increased resistance to oxidative stress[3,4]<br>Reduced brood size*[5] | ~40 | [1]Huang et al. (2004)<br>[2]Lithgow et al. (1994)<br>[3]Vanfleteren (1993)<br>[4]Larsen (1993)<br>[5]Friedman and Johnson (1988) |
| *daf-2*<br>Insulin/IGF-1 receptor | Extended movement ability[6, 7, 8]<br>Extended fast body movement[9]<br>Increased maximum velocity[10]<br>Slowed deterioration[11]<br>Extended pharyngeal pumping span[9]<br>Increased resistance to colonization[6, 11, 12]<br>Increased thermotolerance[7]<br>Increased resistance to oxidative stress[7, 16]<br>Extended self and mated reproductive span[13, 14, 15]<br>Reduced brood size*[13, 14]<br>Prolonged frail state*[1, 6, 7] | ~60% | [6]Podshivalova et al. (2017)<br>[7]Bansal et al. (2015)<br>[8]Newell Stamper et al. (2018)<br>[9]Huang et al. (2004)<br>[10]Hahm et al. (2015)<br>[11]Garigan et al. (2002)<br>[12]Portal-Celhay et al. (2012)<br>[13]Gems et al. (1998)<br>[14]Hughes et al. (2007)<br>[15]Luo et al. (2010)<br>[16]Barsyte et al. (2001) |
| *elo-1* and *elo-2*<br>Elongation fatty acids | Increased resistance to oxidative stress[17] | 11% for *elo-1*<br>8% for *elo-2* | [17]Shmookler Reis et al. (2011) |
| *fat-4*<br>Fatty acid desaturase | Increased resistance to oxidative stress[17] | 25% | [17]Shmookler Reis et al. (2011) |
| *faah-1*<br>Fatty acid amide hydrolase | Increased thermotolerance[18]<br>Reduced levels of N-acylethanolanimes[18] | 9.1–60% | [18]Lucanic et al. (2011) |
| *gsy-1*<br>Glycogen synthase | Increased locomotion (liquid and solid)[19]<br>Lower levels of AGEs[19]<br>Increased thermotolerance[19]<br>Increased resistance to oxidative stress[19]<br>Increased oxidative stress*[20] | ~20% | [19]Seo et al. (2018)<br>[20]Gusarov et al. (2017) |

(continued)

**Table 20.1** (continued)

| Genes | Healthspan effect | Lifespan effect | References |
|---|---|---|---|
| *hpa-1* and *hpa-2* | Extended locomotory capacity[21]<br>Lower levels of AGEs (*hpa-1*)[21]<br>Increased pharyngeal pumping rate[21] | 16% *hpa-1*<br>10% *hpa-2* | [21]Iwasa et al. (2010) |
| *hyl-1* and *lagr-1* Ceramide synthases | Increased thermotolerance[22]<br>Reduced feeding[22]<br>Increased # of autophagosomes[22]<br>Reduced brood size*[22] | 21.4% | [22]Mosbech et al. (2013) |
| *ife-2* Initiation factor 4E | Reduced age-associated lipofucsin granules[7]<br>Increased thermotolerance after 15 days[7]<br>Prolonged frail state*[7] | 40% | [7]Bansal et al. (2015) |
| *lipl-4* Lysosomal lipase | Increased lipid hydrolysis (lean worms)[23] | 24% | [23]Wang et al. (2008) |
| *phm-2* SAFB protein | Extended reproductive span[24]<br>Increased thermotolerance[24]<br>Increased pharygeal pumping[24]<br>Reduced brood size*[24] | 34% | [24]Kumar et al. (2019) |
| *sgst-1* (oe) Autophagy receptor | Increased autophagy[25]<br>Improved neuronal and intestinal proteostasis upon proteotoxic conditions[25] | 30% | [25]Kumsta et al. (2019) |

## 20.4 Evaluating Health and Healthspan in *C. elegans*

The significant challenge in *C. elegans* has been defining the metric(s) that can be used to infer health and most studies have attempted to define this in the context of healthy ageing. Over the last 20 years there has been considerable interest in identifying biomarkers of ageing that can predict animals/populations that will exhibit increased longevity (Collins et al. 2008). Many of these have been repurposed with a view to providing an index of health and healthspan (Tables 20.1 and 20.2). These assays monitor different aspects of physiology including stress resistance, neuronal health, gut health, immune health, muscular health, and reproductive health (Fig. 20.4). In the following sections we discuss some of the results from these studies.

**Table 20.2** Selected studies of interventions in *C. elegans*. Some interventions have both positive and negative (designated by *) effects on healthspan depending on the assay used

| Intervention | Healthspan effect | Lifespan effect | References |
|---|---|---|---|
| Trehalose supplementation | Extended the reproductive span[1]<br>Increased pharygeal pumping rate[1]<br>Retarded accumulation of lipofuscin autofluorescence[1]<br>Increased thermotolerance[1]<br>Reduced proteotoxicity[1] | ~30% | [1]Honda et al. (2010) |
| Proline and tryptophan supplementation | Increased thermotolerance[2] | 14–20% | [2]Edwards et al. (2015) |
| α-lipoic acid supplementation | Enhanced chemotaxis (day 5) worms[3]<br>Attenuated hydrogen peroxide levels[3]<br>Increased thermotolerance[4] | 21–24.2% | [3]Brown et al. (2006)<br>[4]Benedetti et al. (2008) |
| Ketone body s-hydroxybutyrate supplementation | Increased thermotolerance[5] | ~20% | [5]Edwards et al. (2014) |
| Phosphatidylcholine supplementation | Increased resistance to oxidative stress[6]<br>Delayed decline in age-related motility[6]<br>Decreased proteotoxicity[6]<br>Reduced fertility*[6] | 28.8% | [6]Kim et al. (2019) |
| Indole supplementation | Increased motility (thrashing) after day 15[7]<br>Increased pharyngeal pumping after day 15[7]<br>Delayed onset of paralysis after day 15[7]<br>Increased fecundity[7]<br>Extends reproductive span[7] | Increased | [7]Sonowal et al. (2017) |
| Probiotics | Increased resistance to pathogen infections[8, 9]<br>Improved intestinal barrier[10]<br>Increased resistance to oxidative stress[11] | Increased—strain specific response | [8]Ikeda et al. (2007)<br>[9]Park et al. (2014)<br>[10]Kim and Moon (2019)<br>[11]Grompone et al. (2012) |

(continued)

**Table 20.2** (continued)

| Intervention | Healthspan effect | Lifespan effect | References |
|---|---|---|---|
| Dietary restriction | Increased self-fertile reproductive span[12, 13, 14]<br>Increased fast body movement span[13]<br>Increased pharyngeal pumping span[13]<br>Maintenance of long-term memory[15]<br>Increased autophagy[16]<br>Decreased proteotoxicity[17]<br>Increased resistance to oxidative stress[18]<br>Increased thermotolerance[18, 19]<br>Reduced brood size*[12, 14]<br>Reduced thermotolerance*[20]<br>Impairment of young adult memory*[15] | Increased—depends on DR method | [12]Hughes et al. (2007)<br>[13]Huang et al. (2004)<br>[14]Klass (1977)<br>[15]Kauffman et al. (2010)<br>[16]Hansen et al. (2008)<br>[17]Steinkraus et al. (2008)<br>[18]Lee et al. (2006)<br>[19]Kaeberlein et al. (2006)<br>[20]Bansal et al. (2015) |
| Swim exercise | Retained body wall muscle and improved performance[21]<br>Morphological and functional mitochondria function improvements[21]<br>Improved neuronal health and learning[21]<br>Increased pharyngeal pumping after day 11[21]<br>Improved intestinal barrier function[21]<br>Improved locomotive vigor[21] | ~15% | [21]Laranjeiro et al. (2019) |

## 1. **Reproductive Health**

Reproductive health is of obvious importance for the species to survive. In *C. elegans* fertility and fecundity are often used as measures of reproductive health (Hughes et al. 2011; Keith et al. 2014). These assays involve counting the number of offspring (brood size) and assessing their ability to reproduce. These measures are heavily influenced by external factors that compromise the health of the animals, such as temperature, starvation or exposure to toxins, resulting in animals that lay fewer eggs and sometimes their progeny are unable to reproduce.

Interestingly, mutants that live longer often have a compromised ability to reproduce. In many cases the effect on fertility is overt and linked to the nature of the mutation. For example, long-lived *eat-2* and *phm-2* mutants have defects linked to

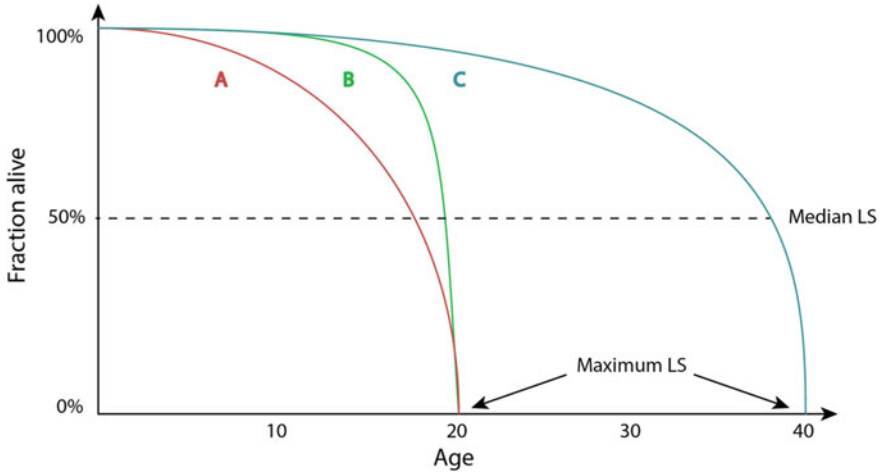


**Fig. 20.3** Lifespan of three different populations. Median, mean and maximum lifespan are often calculated and used to describe the populations. Population A has the same maximum lifespan as population B but population A has shorter median lifespan than B. Population C has increased mean and maximum lifespan

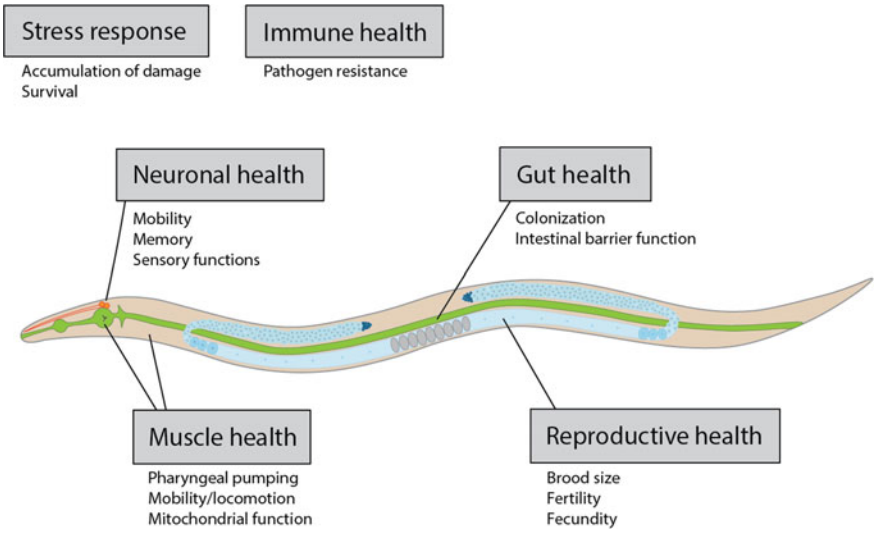


**Fig. 20.4** Overview of different health parameters and common assays used to measure health in *C. elegans*

feeding behaviour and thus their reduced brood sizes relate to decreased food intake (Kumar et al. 2019). In other cases, the fertility differences might seem negligible or even absent at the level of the individual, but have a profound effect on the fitness of the population, in agreement with evolutionary theories of ageing. An elegant example of this came from studies of insulin signalling mutants. A specific mutant allele of *age-1* has identical total fertility compared with wild-type animals, but when co-cultured with cycles of starvation, the *age-1* allele becomes extinct within 10 generations, due to a delay in time to first egg lay upon re-feeding (Walker et al. 2000). In contrast, *daf-2* mutants are lost after only a few rounds of reproduction without any starvation cycle (Jenkins et al. 2004). In this case, the long-lived mutants can be considered to be less healthy than control worms, due to their compromised reproductive fitness. Interestingly, certain long-lived *daf-2* mutants have longer reproductive lifespans (Gems et al. 1998; Mendenhall et al. 2011), meaning that they are able to self-reproduce at much older ages than wild-type, although total fertility remains reduced. Hence, if the ability of an individual to reproduce in late life is taken as a measure of health, these *daf-2* mutants would be considered to have an extended healthspan despite having smaller brood size. Thus, depending on the health measure employed one could equally argue for and against these *daf-2* mutants being more or less healthy.

Some would argue that reproduction is the ultimate measure of health of a species. However, in the context of longevity, if an anti-ageing intervention were to be applied after reproduction one could overcome the inherent health problems associated with reduced or late reproduction. Moreover, when considering manipulating human healthspan, it is likely that ageing interventions would target the post-reproductive period to avoid any such trade-offs. Thus, for the remaining part of this chapter, we will be referring only to post-reproductive health.

Although not directly linked to reproduction per se, age-associated vulval integrity defects (a phenotype called Avid) has been proposed as a marker of healthspan in worms (Leiser et al. 2016). This phenotype is often seen in aged populations and is manifest as an extrusion of internal body material through the vulva. As Avid leads to premature death that is unrelated to ageing, animals that exhibit this phenotype are usually censored from the analysis. However, in a careful study of how this Avid phenotype correlated with factors related to lifespan and health it has been proposed as an additional method of assessing healthspan in the worm.

### 2. **Activity and Mobility**

In older people with failing health, loss of muscle mass (sarcopenia) severely impacts many physiological processes and behaviours such as mobility and grip strength (Fisher 2004). Similarly, sarcopenia and a decline in movement can be observed in ageing populations of *C. elegans* (Herndon et al. 2002; Hosono et al. 1980). Measurement of spontaneous and induced movement was one of the first metrics of healthspan in the worm to be evaluated and involves simply classifying the motility of animals throughout life and then correlating it with survival (Hosono et al. 1980). This was further employed by Herndon et al., who noted that time spent in a state with no touch-provoked movement was highly predictive of subsequent death (Herndon

et al. 2002). Midlife measures of mobility have been shown in a different study to be a better predictor of lifespan than measurements early in life (Newell Stamper et al. 2018).

Since then, movement assays have been refined to include measuring how much and how fast the worms are moving on the agar plates or by measuring the number of body bends/thrashes if the worms are cultured in liquid (Keith et al. 2014). These relatively simple mobility assays actually monitor several health parameters including muscle integrity, neuronal function, and energy metabolism. Hence, it is generally accepted that healthy animals are more active than sick animals.

In humans, an age-related decline in balance and gait is observed which is associated with an increased risk of falls (Osoba et al. 2019). In fact, physical ability, assessed by means of a short physical performance battery, correlates well with health during ageing and can even predict short-term mortality and nursing home admission (Guralnik et al. 1994). In *C. elegans* it was recently shown that maximum velocity is an accurate measure of movement ability that is predictive of maximal lifespan if measured in mid-life (Hahm et al. 2015). From a health point of view, it is interesting to note that if healthspan is defined as the period of life where worms have maintained at least 50% of maximum velocity, then *daf-2*/insulin signalling mutant worms have more than doubled their healthspan compared to wild-type. Using a machine vision approach, others have demonstrated that the rate of motor decline with age correlates better with lifespan rather than the absolute motor activity in early to mid-life of individual worms (Hsu et al. 2009).

## 3. **Pharyngeal Pumping**

*C. elegans* feeds by taking up bacteria into the buccal cavity and passing them through the pharynx, a neuromuscular organ that undergoes rhythmic contractions called pumping. In the posterior bulb of the pharynx is a grinder that macerates bacteria before they are passed into the intestinal lumen. The contractions of the grinder in the terminal bulb can easily be visualized under low magnification and is used as an indicator of feeding rate. Like mobility, pharyngeal pumping requires muscular activity in *C. elegans* and it has been used to assess health during ageing and following various interventions. Evaluation of pharyngeal pumping with age in normal animals shows an age-related decline (Hosono et al. 1980) that has been shown to correlate with time of death (Huang et al. 2004).

The decline in pumping rate has been attributed to sarcopenia due to mechanical stress (Chow et al. 2006). Although the pharyngeal pumping rate can be used as an indicator of expected lifespan, can it also be used as a healthspan measure? One argument against this is the fact that there is little difference in pumping rate between wild-type and long-lived mutants after day 15, despite large differences in subsequent survival (Bansal et al. 2015). Another issue is plugging of the pharynx by bacteria, which has been hypothesized to reduce the pumping rate (Steger and Avery 2004). However, slow pumping is also observed in animals without bacterial plugging of the pharynx (Chow et al. 2006). Mechanical stress due to a high pumping rate in young adults decreases the efficiency of grinding and increases the risk of proliferating

bacteria infecting the pharynx, which has been suggested to cause early death (Zhao et al. 2017). Thus, pumping rate in early life might indirectly be linked to health status later in life.

### 4. **Gut Health**

Under laboratory settings *C. elegans* normally feeds on a single bacteria strain, namely the *E. coli* strain OP50. As in humans, the intestine digests and absorbs nutrients, synthesizes enzymes and stores energy, while also serving as a first line of defence against pathogens. Thus, intestinal function is critical for maintaining homeostasis and is thereby closely implicated in the health state of an organism. Health parameters of the *C. elegans* gut that have been used in assessment of healthspan are: the bacterial colonization level, the barrier and the morphology of the intestine.

(i) *Bacterial Colonization in the Gut*

Several studies have shown a significant accumulation of *E. coli* in the intestine during ageing (Fernando et al. 2012; Garigan et al. 2002; Portal-Celhay et al. 2012), which is thought to arise from the combination of functional decline of the grinder and the innate immune system, as well as changes in gut morphology with increasing age. The colonization level can be determined either by measuring bacterial colony forming units (CFU) from the intestine of lysed animals (Portal-Celhay et al. 2012) or by feeding the worms a GFP-expressing bacteria strain (Podshivalova et al. 2017; Virk et al. 2016).

It has been suggested that proliferating bacteria in the gut may result in a dysbiotic state causing severe constipation and failing gut health, potentially leading to death (Cabreiro and Gems 2013; Revtovich et al. 2019). This model is supported by several studies. Using UV-irradiation or antibiotics to stop the proliferation of *E. coli* increases the lifespan (Garigan et al. 2002; Gems and Riddle 2000; Podshivalova et al. 2017). In addition, some long-lived mutants have fewer bacteria in their intestine (Podshivalova et al. 2017; Portal-Celhay et al. 2012) suggesting that intestinal colonization could influence aging in a more general manner. Nevertheless, other studies find that bacterial growth in the intestine does not correlate with the survival of *C. elegans*, as not all dead animals have accumulation of bacteria in the intestine (Virk et al. 2016). Accumulation of bacteria can also have a beneficial effect by activating the innate immune system (Kumar et al. 2019). Thus, the role of bacterial colonization during ageing is complex and not yet fully understood. In terms of health, it seems as the intestine is healthy until the point that it becomes colonized to a dysbiotic level, at which point the immune response could be induced or impair body movement, sensation or susceptibility towards pathogens. Hence, the colonization degree can be used as a health parameter.

(ii) *Intestinal Barrier*

As the intestine serves as a first line of defence against invasion of bacteria to adjacent tissues, the effectiveness of the gut epithelial barrier function has been used as a measure of gut health. In animals with compromised barrier function, feeding with

dyes like erioglaucine disodium (FD&C blue) leads to an accumulation of blue dye in intestinal cells ("Smurf assay") (Gelino et al. 2016). Interestingly, in terms of health, one study has found that worms that have undergone swim exercise for 4 days in early life have a less leaky barrier later in life (Laranjeiro et al. 2019). The intestinal barrier can also be improved by feeding the worm the *E. coli* probiotic strain Nissle 1917 which confers an increased tolerance towards enterotoxigenic *E. coli* infection (Kim and Moon 2019). Conversely, mutants that have a compromised intestinal barrier are more susceptible to environmental toxins (Qu et al. 2018). Pathways known to impact ageing and healthspan also influence intestinal barrier function. For example, inhibition of intestinal autophagy in *eat-2* mutants impairs intestinal barrier function (Gelino et al. 2016), while inhibition of intestinal autophagy leads to a decrease in motility with age (Hsu et al. 2009).

(iii) *Intestinal Morphology*

Loss of nuclei, changes in shape and size of the intestinal lumen, and loss of microvilli are some of the changes seen as the worm ages (McGee et al. 2011). As the cell lineage is defined for every cell and the worm is transparent, it is relatively easy to quantify the number of cells and nuclei. However, to assess morphological changes of the intestinal brush border, it is necessary to use electron microscopy, which is more technically challenging. Shape and size of the lumen can be visualized through confocal microscopy and 3D volumetric reconstruction (McGee et al. 2011). Some of these morphological changes have also been observed after feeding the worm an *E. coli* strain expressing a fungal lectin, which is toxic to *C. elegans*, including loss of microvilli and gaps in the terminal web causing invaginations of the apical membrane (Stutz et al. 2015). This type of intestinal pathology is therefore also involved in health and could be a beneficial parameter to use in assessing healthspan of the animal.

## 5. **Stress Resistance**

With increasing age and declining health, humans are more susceptible to both intrinsic and extrinsic stressors. This can be explained by a shrinking of our homeodynamic space, which is a theoretical framework collectively describing a number of different stress response pathways including wound healing, immune responses, DNA repair systems, antioxidant enzymes (Rattan 2018). Using stress resistance as surrogate for longevity has proven a successful strategy for identifying novel longevity genes in multiple model organisms (Fabrizio et al. 2001; Olsen et al. 2006a; Wang et al. 2004). Most of the long-lived *C. elegans* mutants tested are also resistant to various types of stress. Consequently, it is appealing to conclude that being able to mount a proper stress response is essential to be healthy. As a result, various measures of stress response are being used as indicators of healthspan. These assays often have survival as endpoints and include thermotolerance (Olsen et al. 2006a), resistance to oxidative damage (Sampayo et al. 2003), resistance to heavy metals (Barsyte et al. 2001) and pathogen resistance assays (Garsin et al. 2003).

Single (or multiple) exposures to mild stress can result in beneficial health effects through a phenomenon known as hormesis (Rattan 2018). In *C. elegans,* both increased lifespan and healthspan have been reported due to hormesis (Olsen et al. 2006b; Sun et al. 2020). The causal mechanisms depend on the type of stress and include increased levels of heat shock proteins and chaperones (Cypser et al. 2006; Olsen et al. 2006b), increased autophagy (Kumsta and Hansen 2017), elevated mitophagy and increased antioxidants (Ristow and Schmeisser 2011; Ristow and Zarse 2010) and innate immune system activation (Leroy et al. 2012).

6. **Other Measures of Health in *C. elegans***

(i) *Neuronal Health*

*C. elegans* has a relatively simple nervous system, consisting of 302 neurons, that controls surprisingly complex behaviours such as motility, foraging, touch response, thermotaxis, chemotaxis, and pathogen avoidance (Hobert and Hobart 2003). These behaviours are important to keep the organism healthy and to avoid danger. Several morphological methods, as well as behavioural assays, have been developed to evaluate the health of the *C. elegans* nervous system. Fluorescently tagged proteins, various dyes and electron microscopy have been used to assess morphological changes of the individual neurons. Despite being relatively well conserved, there are age-dependent morphological changes including neurite branching, axon swelling, synapse deterioration, lesions in processes and misshaped somas (Pan et al. 2011; Tank et al. 2011; Toth et al. 2012). Interestingly, as in humans, *C. elegans* experiences a functional decline of the nervous system with increasing age (Chen et al. 2013a). For example, chemotaxis and thermotaxis are impaired with increasing age and the change can be ameliorated by reduced insulin signalling (Kauffman et al. 2010; Murakami et al. 2005). One learning paradigm in *C. elegans* associates food with specific odorants and upon conditioning a learning index can be calculated. Interestingly, swim exercise can enhance this learning ability (Laranjeiro et al. 2019) suggesting that learning is a good marker for neuronal health.

(ii) *Disease Models*

Misfolded proteins or aggregates of damaged proteins are thought to be causally involved with numerous diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Dugger and Dickson 2017). Thus, the maintenance of protein homeostasis, or proteostasis, is essential to health. In *C. elegans*, transgenic models of protein homeostasis have been used to model specific diseases but also to address health. Interestingly, many mutations, compounds and interventions that increase lifespan also delay the onset of proteotoxicity in these models (Alavez et al. 2011; Morley et al. 2002; van Ham et al. 2008), suggesting that they might be promoting health as well.

(iii) *Accumulation of Autofluorescent Material*

As *C. elegans* age there is an accumulation of autofluorescent material, particularly in the intestine, that produces broad spectrum emission. The accumulation of this autofluorescent material has long been investigated as a biomarker of ageing (Davis et al. 1982; Forge and Macguidwin 1989; Klass 1977), although its utility remains inconclusive. The Driscoll lab demonstrated that the emission spectrum could act as a molecular fingerprint for the ageing state of the animal (Gerstbrein et al. 2005). Furthermore, ageing interventions such as dietary restriction caused a shift in the spectrum that was characteristic of the longevity mechanism. Others have suggested that autofluorescence does not correlate well with longevity (Coburn et al. 2013). More recently it has been suggested that consideration of autofluorescence at different wavelengths is more informative, with red fluorescence correlating better with lifespan than blue or green (Pincus et al. 2016).

## 20.5 Genes and Interventions that Regulate Healthspan

Given the historical evaluation of healthspan in the context of longevity, the majority of genes that have been shown to influence healthspan also increase lifespan (Table 20.1). Various interventions have also been reported to increase healthspan in *C. elegans* including dietary restriction, swim exercise, hormesis, compound treatments and probiotic diets (Table 20.2). Like most of the genes that improve healthspan, these interventions often increase stress resistance, autophagy and lifespan. Interestingly, these interventions have all been proposed as health-promoting across multiple species, suggesting evolutionary conservation. One simple explanation for this enrichment of longevity pathways could simply be selection bias, as healthspan increases have most often been looked at in the context of longevity interventions. Alternatively, if healthspan and lifespan are causally linked by the underlying biology, then it may also be the case that the chances of increasing healthspan are truly higher if your mutation of interest or intervention also increases lifespan. This is not unreasonable considering ideas like the homeodynamic space and appropriate stress responses as drivers of healthy ageing.

However, there are a number of instances where lifespan and healthspan can be uncoupled. For example, the *hpa* (for high performance in advanced age) mutants have increased swimming capacity, yet do not have a greatly extended lifespan (Iwasa et al. 2010). On the other hand, long-lived mutants do not always show increased healthspan, although sometimes this uncoupling is only observed for very particular measures of health. This is nicely illustrated by looking at the long-lived *daf-2* mutants. While many studies have found that *daf-2* mutants remain active into late adulthood, others have suggested that as a fraction of total lifespan they may actually have more inactive days than wild-type worms (Bansal et al. 2015; Huang et al. 2004). Does that mean that the *daf-2* mutants are unhealthy? Not necessarily, two different studies argue. Podshivalova et al. find that the *daf-2* mutants experience prolonged

decrepitude because they are actually more resistant toward bacterial infections that kill wild-type worms much sooner (Podshivalova et al. 2017). This complicates our health assessment of these mutants, because if our health definition also includes pathogen resistance, then *daf-2* animals are in fact healthier than wild-type worms. Resistance towards bacterial infection may not be the sole reason for *daf-2* mutants having a fractionally extended inactive state. Another study has made the interesting observation that the *daf-2* mutants have elevated levels of the odorant receptor ODR-10 and that this causes the worms to prefer food over exploration (Hahm et al. 2015). In other words, the *daf-2* mutant worms actually have the capacity to move in late life but choose not to do so. These studies highlight the need for a comprehensive assessment of healthspan across of range of interventions that lead to enhanced longevity to carefully examine the relationship between healthspan and lifespan in *C. elegans*.

Despite the interest in recent years in examining healthspan in *C. elegans*, there have been relatively few attempts to identify genes that specifically increase healthspan. The key to these endeavors is deciding the best suitable end-point. Most ageing research has focused on identifying long-lived rather than short-lived mutants, with the rationale that it is easier to make an animal sick than make it more robust. A similar approach would seem practical in the context of healthspan screens. Interventions that compromise healthspan could be genuine modifiers of health but are also likely to be targeting the mechanics of the process itself. While none of the healthspan measures in worms are perfect, age-dependent motility appears to be the most robust indicator (Hahm et al. 2015; Hsu et al. 2009). Thus, a screen for interventions that increase maximal speed or slow the rate of movement decline could be a fruitful approach to identifying novel mechanisms that influence healthspan. In fact, this approach has been evaluated on a small scale to identify genes that extend the locomotory healthspan. The genes *hpa-1* and *hpa-2* act through the EGF pathway to reduce lipofuscin and AGE pigments, maintain pharyngeal pumping and locomotion with increasing age without increasing maximum lifespan (Iwasa et al. 2010).

Measures of healthspan in *C. elegans* tend to involve characterization of behavioral phenotypes, often longitudinally, and as such they are often both time-consuming and labor-intensive. However, the development of automated lifespan and behavioral systems, such as The Lifespan Machine (Stroustrup et al. 2013), WormBot (Pitt et al. 2019) and WorMotel (Churgin et al. 2017) to name a few, offers new prospects to screen for healthspan modifiers on a much larger scale. For example, the Aging with Elegans (AwE) initiative proposed to utilize the WorMotel system to facilitate RNAi and compound screens to comprehensively characterize healthspan modifiers in *C. elegans* and examine their relevance to human health (Luyten et al. 2016).

## 20.6 Conclusion

In contrast to the wealth of data on the genetic determinants of lifespan in *C. elegans*, our understanding of the molecular determinants of healthspan is in its infancy. To date, a number of life history traits and behavioural phenotypes that show age-related

changes have been used to assess health in worms. Although these measures are informative, it is not clear whether there is a single measurement that can robustly capture healthspan in *C. elegans*. Of the existing measures, activity and motility are perhaps the best as they provide an integrated measure of the function of a number of physiological processes. However, more work is required to validate the utility of existing measures and to identify new metrics.

It is important to remember that *C. elegans* is a model system and as such its utility is in discovering genes and pathways in a simple system that have relevance to more complex organisms such as humans. While the discovery of longevity mutants in worms has been invaluable in defining the molecular genetics of ageing in mammals, it remains to be seen whether the same will be true for health and healthspan interventions. However, with the development of new technologies for characterising these complex behavioural phenotypes with age, there is reason to be optimistic that the nematode model will continue to provide important insights into ageing, disease and health in humans.

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# Chapter 21
# An Environmental Perspective on Health


**Evgenios Agathokleous and Edward J. Calabrese**

**Abstract** This chapter examines the concept of what may constitute a healthy environment. It discusses current understandings of adaptation and acquired resilience across both lifespan and generations. This analysis will be framed within an evolutionarily-based dose response evaluative setting of biological adaptation and its quantitative dose response features which are typically hormetic-like biphasic dose responses. Moreover, using this evolutionary adaptive response-hormetic dose response approach, this chapter illustrates how modest environmental stresses can often enhance biological resiliency, protect organismal health via the upregulation of adaptive mechanisms and act as a vehicle for enhancing health from a holistic (i.e., physical, psychological, and social) point of view across lifespans and generations. However, the concept of a healthy environment is not a static one, since there is considerable interindividual variation in response to environmental and other health stressors and that susceptibility will markedly vary over the lifespan. This creates an enormous challenge for both governmental regulatory agencies and individuals attempting to reduce risks from environmental contamination as well as trying to optimize both public and individual health.

**Keywords** Disease · Environmental changes · Healthy people · Hormesis · Mental well-being · Organismal stress · Physical well-being · Social well-being · *U*-shape curve · Wellness

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## 21.1 Introduction

Before attempting to examine the question of what constitutes a "healthy" environment, this chapter will address the question of "what is environment?" The environment concept is all encompassing, ranging from micro- to macro-scales. Environment is our selves, the home, the job, the soil, the air (outdoor and indoor), the sea, the plants, the animals, the microbes, the biota, the Earth, the Space. For the programmer, environment is the interface which (s)he uses to program; so is the room where he is programming and the conditions within it (e.g. light, humidity, volatile organic compounds, particulates, etc.). For those working in a mine at a certain point of time, environment is anything existing in that mine. For the tapeworm *Taenia saginata* in the body of an infected animal, environment is the body, and everything else that may affect it (e.g. what the infected animal is eating, what medicines it is receiving, etc.). For the soil nematode, environment is the soil and anything existing therein. For the plant, environment is anything existing in the space surrounding it. For the ecologist, environment is the entire biosphere, i.e. the sum of the global ecosystems. For us, in the framework of this chapter, environment is anything that can interact with and potentially affect living organisms at any point in time and space throughout the lifespan, unless specified otherwise.

The constitution of World Health Organization (WHO; established in 1948) defines health as "*a state of complete physical, mental and social well-being, not just the absence of disease or infirmity*" (United Nations Environment Programme 2016). In 1986, WHO also clarified that "health is *a resource for everyday life, not the objective of living*. Health is *a positive concept emphasizing social and personal resources, as well as physical capacities*" (https://www.who.int/healthpromotion/conferences/previous/ottawa/en/). Hence, this chapter will be guided by the WHO's definitions to examine health as a state of holistic well-being, beyond the absence of disease or infirmity.

This chapter aims at providing an environmental perspective on health. It discusses how the environment has the potential to affect organismal health as well as what a healthy environment might be for living organisms.

## 21.2 How Does the Environment Affect Organisms?

To understand what a healthy environment might be for living organisms, it is essential to understand how environmental challenges can affect living organisms and potentially affect their health.

### *21.2.1 The LNT Fallacy: We Got It Wrong*

Research in the 1920s showed that very high doses of radiation could induce transgenerational phenotypic changes (claimed to be caused by heritable point mutations) in fruit flies, and that the radiation-induced negative effects increase in magnitude with increasing radiation (Muller 1927a, b, 1928). This proportionality between dose and response translates to what is now called linear-non-threshold (LNT) dose-response model (Fig. 21.1), and assumes that a single "hit" of an organism with an exposure can lead to cancer or that multiple hits cumulate additively over time (Golden et al. 2019). Furthermore, the LNT suggests that any hit by any genotoxic environmental agent is harmful, with the situation becoming more damaging as multiple hits of single agents or many challenges together cumulate over time. Hence, in general, the LNT perspective suggests that any environment on Earth is theoretically unhealthy for living organisms and that all living organisms will accumulate molecular damage over time leading to its demise.

The LNT has provided a controversial element to the history of toxicology and regulatory risk assessment (Calabrese 2017a, 2018, 2019a; Calabrese and Golden 2019). The US Environmental Protection Agency (EPA), which was established in 1970, has been guided by questionable information and biased decisions and policies over a series of events that occurred in the mid-late decades of the twentieth century, allowing the LNT to become the central cornerstone of cancer risk assessment (Calabrese 2017a, 2018, 2019a; Calabrese and Golden 2019). This ideologically-based policy decision to recommend LNT by the US NAS was at the expense of the threshold (and hormesis) models, which assume that, before linearly increasing adverse effects start occurring, there is a dose range at which there is no significant biological response (Fig. 21.1). This would mean that environmental stress, up to a certain level, does not induce any harmful organismic response, whereas above a certain level adverse effects on organisms would increase with increasing environmental stress. This suggests that only some environments are unhealthy, i.e. those capable of inducing biological stress greater than toxic thresholds. While the LNT was assumed true by default and adopted in regulatory procedures, recent examinations have revealed significant errors that have undermined its scientific credibility (Calabrese 2017a, 2018, 2019a; Calabrese and Golden 2019).

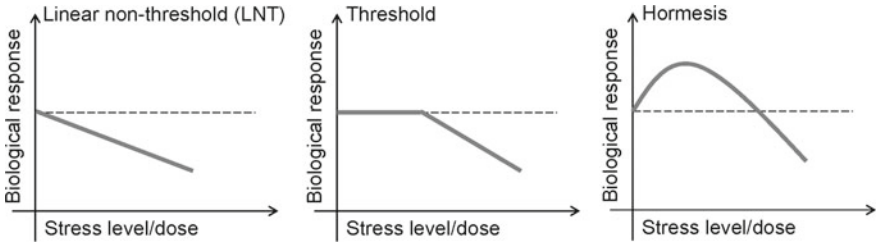


**Fig. 21.1** Hypothetical linear-non-threshold (LNT), threshold and hormetic dose-response models

### 21.2.2 The Hormesis Resurgence: From Marginalization to the Mainstream

Research efforts have recently shed considerable light on the scientific foundation of hormesis (Agathokleous and Calabrese 2019). Hormesis is a paradigm of dual action of chemical/physical stressor (Fig. 21.1). Such stressor agents can induce positive effects on an organism and enhance its fitness when doses/concentrations are low, while inhibiting organism performance and/or deteriorating its fitness at higher doses/concentrations (Agathokleous et al. 2018). Hormesis was marginalized during the twentieth century, yet there was evidence for its occurrence some 150 years ago. However, it was incorrectly linked with homeopathy leading to its rejection by the medical community (Calabrese and Baldwin 2000; Calabrese 2004, 2005).

Massive documentation of hormesis in the recent years now suggests that hormesis is a general phenomenon occurring across biological systems, stressors, and response endpoints (Calabrese and Blain 2011; Poschenrieder et al. 2013; Agathokleous et al. 2019d, f; Arnao and Hernandez-Ruiz 2019; Calabrese and Agathokleous 2019; Martel et al. 2019; Li et al. 2019; Agathokleous et al. 2019c; Carvalho et al. 2020), and is constrained by the limits of biological plasticity, with its maximum stimulation, as a rule of thumb, below two-fold the control response (Calabrese 2017b; Agathokleous 2018; Agathokleous et al. 2019a, d, g; Calabrese et al. 2019a).

In plants, low-level/dose challenges can enhance gas exchange processes (and thus photosynthesis) and capacity for antioxidative defense, and stimulate plant growth and productivity (Poschenrieder et al. 2013; Agathokleous et al. 2019a, d, f; Arnao and Hernandez-Ruiz 2019; Carvalho et al. 2020). In animals, low-level challenges can also enhance detoxification capacities and metabolism, stimulate neuronal functioning and cognition, and extend the lifespan (Lamming et al. 2004; Mattson and Magnus 2006; Rattan 2006, 2008; Ristow and Zarse 2010; Agathokleous et al. 2018, 2019h; Calabrese et al. 2019b). In microbes, positive low-level effects can be seen as stimulation of diploid/disomic meiotic products, growth, luminescence and migration (Calabrese 2017b; Liu et al. 2018; Yao et al. 2019; Xu et al. 2019). These observations are in agreement with the recent recognition that low levels of stress from biological products (especially reactive chemical species), induced by low-level environmental challenges as well, have positive health effects and are essential for normal cellular functioning, effective stress signalling and organismal success in highly interactive environments (Ristow and Zarse 2010; Baxter et al. 2014; Koyama 2014; Mittler 2017; Czarnocka and Karpiński 2018; Arnao and Hernandez-Ruiz 2019).

The most recent developments in dose-response research suggest that organisms have the ability to intelligently utilize the information perceived from the environment to equip the system with the necessary "tools" for defending against predicted forthcoming environmental challenges that are potentially health-threatening. This is a type of "predictive" preconditioning where low-level stimuli precondition organisms for potential forthcoming adverse challenges (Calabrese 2016; Calabrese and Mattson 2017; Agathokleous et al. 2019b). Preconditioning by low-level stimuli enhances organismal "coping skills" and creates biological shields against severe

oxidative stress, neurodegenerative diseases and other ageing-related pathological conditions in plants and animals (Son et al. 2008; Rattan 2008; Calabrese 2016; Calabrese and Agathokleous 2019) and against severe oxidative stress, environmental pollution and other environmental challenges (Agathokleous et al. 2009b, d, g, h).

Hormesis suggests that not all the environments are unhealthy for biota (Calabrese 2017c, 2019b; Costantini and Borremans 2019). More precisely, hormesis suggests that environments can promote health, i.e. those inducing "little" stress (at stress levels/doses lower than the non-observed-adverse-effects-level, NOAEL), whereas other environmental conditions may be unhealthy, i.e. those inducing excessive "severe" stress (at stress levels/doses higher than toxic thresholds) (Costantini and Borremans 2019). The current understanding of genetic and phenotypic organismal responses to low-level stress suggests that hormesis affects acclimation as well as phenotypic plasticity and is supported by ecological and evolutionary theory (Costantini et al. 2010; Costantini 2019). It is within an evolutionary based hormetic framework that stress biology permits organisms to adjust to changing environments (Costantini et al. 2010) instead of undergoing adverse effects at ever low levels of stress.

### *21.2.3 A "Little" Stress Can Be Good*

Stimulation of organisms by low-level stress has been demonstrated in numerous species, various forms of life and functional groups of species, with the quantitative characteristics of stimulation being independent of biological mechanisms (Calabrese and Blain 2011; Calabrese 2017b; Calabrese and Mattson 2017; Agathokleous 2018; Agathokleous et al. 2019a, d; Calabrese et al. 2019a). These observations were found for a vast range of stress-inducing chemical and physical agents, including emerging environmental contaminants and worldwide pollutants (Agathokleous et al. 2019d, a, i, e; Agathokleous and Calabrese 2020). The unambiguous generality of these phenomena suggests that organisms have evolved in a way that permits sustaining normal functioning, and fitness-reproduction balance, in environments that are continuously changing. Notably, in contrast to the LNT assumption that each hit of radiation is harmful, contemporary biology has revealed that removal of background radiation can have negative effects on organisms (Agathokleous et al. 2018; Agathokleous and Calabrese 2020). Such new developments in biology suggest that living organisms depend on a basal level of stress for normal functioning and health. This hypothesis is also supported by the recent understanding that a basal level of reactive chemical species supports normal functioning and health (Ristow and Zarse 2010; Dietz et al. 2016; Mittler 2017).

### *21.2.4 Wellness or Only Disease and Infirmity?*

If human health is "*a state of complete physical, mental and social well-being, not just the absence of disease or infirmity*" (United Nations Environment Programme 2016) (see also previous chapters in this book), then the research focus should also be on health and well-being, not just on disease. Well-being (or wellness) can be used to describe "diverse and interconnected dimensions of physical, mental, and social well-being that extend beyond the traditional definition of health" (Naci and Ioannidis 2015). Therefore, it is clear that being healthy is not lacking a disease but having sustainable physical, mental, and social well-being. However, it is necessary to add the preconditioning hormesis component to the definition. That is, optimal health involves the capacity to anticipate biological, chemical and physical stresses and to be able to recover successfully from such challenges. However, most biomedical research focuses on disease (Naci and Ioannidis 2015), and this might have contributed to the marginalization of hormesis throughout the twentieth century as well as the resultant preclusion of the understanding of positive effects of low-level stress (Calabrese 2004; Agathokleous and Calabrese 2019, 2020).

## 21.3 What is a Healthy Environment for Living Organisms?

The natural environment is a critical factor for the 2030 Agenda for Sustainable Development (United Nations Environment Programme 2016). The United Nations Environment Programme (2016) concluded that "in 2012, an estimated 12.6 million deaths globally were attributable to the environment. The air we breathe, the food we eat, the water we drink, and the ecosystems which sustain us are estimated to be responsible for 23% of all deaths worldwide." The concept of a healthy environment must consider the fact that all people will die and that public health/medical scientists will make estimates of the causation of death. Thus, even in a "healthy" environment, eventually death will occur. Within this context, it is evident from the hormesis literature that what may constitute an optimal environment (i.e., healthy stress) for the average segment of the population may be non-optimal and/or even harmful for those at increased risk. Furthermore, it is recognized that the capacity to enhance resilience via hormetic preconditioning activities can decrease significantly with age, especially in the elderly, and due to other medical conditions (e.g., obesity, diabetes), potentially significantly affecting one's capacity to respond to the challenges of normal aging as well as numerous other conditions that affect health and survival.

It is true that a healthy environment associates with healthy people (United Nations Environment Programme 2016). A closer examination of the factors humans are exposed to reveals that health is significantly affected by the environment (Fig. 21.2). Hormesis suggests that low-level stress can enhance physical and mental well-being, and is essential for optimum health (Mattson and Magnus 2006; Gomez-Pinilla

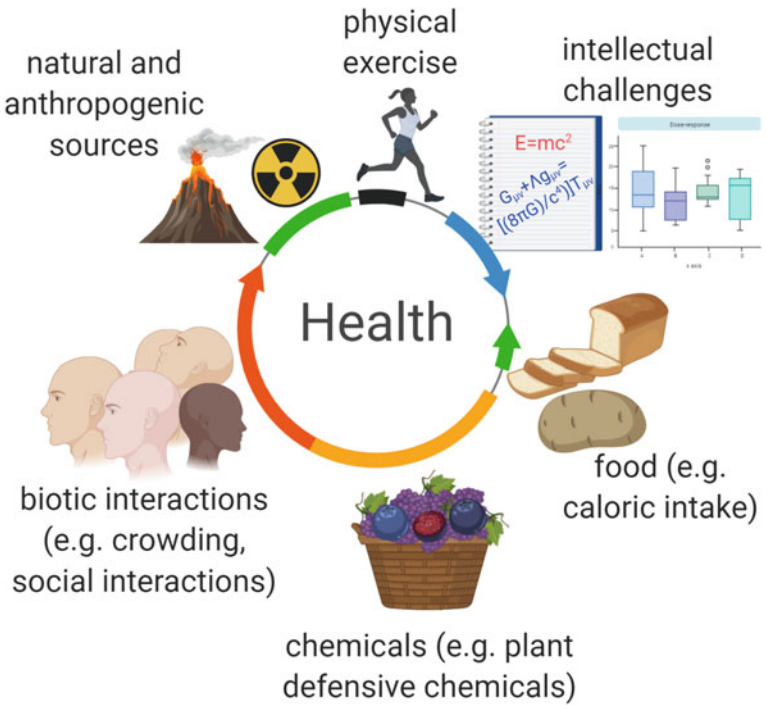


**Fig. 21.2** Health is "*a state of complete physical, mental and social well-being, not just the absence of disease or infirmity*" (United Nations Environment Programme 2016). Physical, mental and social well-being are influenced by various factors, such as human physical activity (e.g. exercise) (Ristow and Zarse 2010; Koyama 2014; Peake et al. 2015; Lee and Jacobs 2015; Gradari et al. 2016), natural and anthropogenic sources (e.g. radiation, volcanoes, etc.) (Luckey 1980; Agathokleous 2018; Agathokleous et al. 2019d, b, g; Agathokleous and Calabrese 2020), brain activity (intellectual challenges) (Calabrese and Agathokleous 2019), biotic interactions (e.g. crowding and social interactions) (Saitanis and Agathokleous 2019), food (e.g. amount of calories ingested) (Masoro 2007; Mesquita et al. 2010; Ludovico and Burhans 2014; Colman et al. 2014; Martel et al. 2019), and chemical intake (e.g. plant defensive chemicals in fruits) (Son et al. 2008; Wang et al. 2018; Calabrese et al. 2019b). All these factors influence health at various degrees and in a mixture of some or all of these. The degree of influence (level/dose of stress) of each of these separately and in combination as well as the components of the cocktail of stresses vary across spatiotemporal scales and for each individual

2008; Rattan et al. 2009; Ristow and Schmeisser 2011; Stranahan and Mattson 2012; Calabrese et al. 2012, 2015, 2018; Cornelius et al. 2013; Agathokleous et al. 2018; Saitanis and Agathokleous 2019). Among other health positive effects, low-level stress can also enhance psychological characters, such as emotional stability, anxiety and impulsivity, which can apparently affect social well-being (Boyce and Ellis 2005). Both physical and mental health can affect social interactions and thus all together define well-being (Anderson and Jané-Llopis 2011). When exposed to a cocktail of influential factors (Fig. 21.2), such health positive effects occur at low levels of some or all the components of the cocktail, and can be cancelled when

the levels of some or all the components exceed some individual-specific particular thresholds (beyond the threshold). This suggests that a variety of influential environmental factors can have antagonistic, additive, or synergistic effects under certain conditions (Agathokleous and Calabrese 2020), suggesting that some environmental factors may negate others or that too many hormetic exposures may become overwhelming or damaging to living organisms. It is practically challenging to control the environment at this level of detail, and more research is needed to advance the understanding of the effects of cocktails of influential factors all occurring at stimulatory doses (Agathokleous and Calabrese 2020). However, it is clear that for an environment to be considered healthy for living organisms it would provide conditions that permit normal cellular functioning, enhanced physical and mental performance, and resilient social well-being (or in general resilient biotic interactions for non-social organisms). An environment with some or all conditions harsh enough to generate adverse effects chronically or acutely and repeatedly would not be a healthy environment. Likewise, a too "comfortable" environment that is incapable to generate any low-level stress, e.g. with the "modern 'couch potato' lifestyle" (Mattson 2014), would not be a healthy environment (Tipton 2018).

## 21.4 Conclusions

We conclude that an environment that is too "comfortable" or too harsh is unhealthy for organisms. An environment to be considered healthy for organisms would be the environment with continuous challenges that induce low-level biological stress, which can permit normal cellular functioning, enhance the physiological and mental (for animals) performance and induce resilience to support biological and social well-being (for humans and other social animals). Such an environment provides a perspective for enhanced health.

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# Chapter 22
# Social Relations and Health


**Robert Zachariae**

**Abstract** In humans, relationships are of the utmost importance for their physical, psychological, and social functioning and well-being. As reviewed in this chapter, there is considerable evidence to suggest that (a) social relations that provide instrumental and emotional support may (b) buffer negative health-related consequences of stress, by (c) protecting against stress and stimulating positive emotions and health-promoting behaviors, that (d) stimulate adaptive immune function and reduce inflammation, thereby (e) reducing the risk and prognosis of cardiovascular disease, Alzheimer's disease, and other inflammatory conditions, and (f) promoting longevity. Not only do people benefit from receiving social support from others, but there is also promising research suggesting that altruistic behaviors, i.e., providing social support to others, may be associated with improved health outcomes. Future research is needed to disentangle the complex associations between the societal context, social relations, biological mechanisms, health-related behaviors, and health outcomes, which, if they can be identified, could translate into effective preventions and treatments.

**Keywords** Biopsychosocial model · Social support · Social integration · Stress buffering hypothesis · Altruism · Inflammation

## 22.1 Introduction

> Man is by nature a social animal.
>
> *Aristotle, the Politics*

In humans, relationships with others are important—perhaps even crucial—for psychological well-being and physical health. Regardless of educational, cultural, and other socio-demographic differences, humans express the need for stable and

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positive relationships with other people (Diener 2000), and the level of social integration and sense of belonging has been shown to be important to emotional well-being and overall quality of life. In contrast, lack of social network and feelings of loneliness have negative consequences for mental and physical health (Holt-Lunstad et al. 2010; Karelina and DeVries 2011). The importance of social interactions are reflected in the World Health Organization's definition of health as a "*state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (World Health Organization 1958).

In spite of this early (1948) attempt at a positive definition of health, Western medicine has long predominantly based itself on a negatively defined concept of health. Historically, the biomedical approach has, in close collaboration with the pharmaceutical industry, focused on the diagnosis and treatment of the individual symptom or disease of the individual patient by identifying and repairing the hypothesized underlying pathophysiological mechanism, i.e., the breakdown of the biological machine. As argued in an early seminal paper (Engel 1977), this biomechanical approach to disease has been very successful in many areas, but at a cost. By ignoring the behavioral and psychosocial aspects, we are limited in our ability to understand, prevent, and treat the complex, multifactorial, lifestyle-related chronic diseases that dominate modern societies. Today, there is—at least theoretical—consensus that a broader biopsychosocial approach is needed. The present chapter expands the traditional biomedical model of health by moving beyond the health of the individual and examining available theories and empirical findings concerning the role of social relations in well-being and physical health.

## 22.2 Defining Social Relations

While there is general consensus that social relations are robust statistical predictors of a broad range of physical health outcomes (House et al. 1988; Uchino et al. 2018), the causal relationships are far from clear. It is, e.g., not yet clear which types of relationships and interpersonal events have a positive impact and which have a negative impact on people's mental and physical health. Likewise, the available knowledge of the affective, cognitive, and psychophysiological mechanisms that might explain these associations remains limited. While there are several decades of research on the role of social relations in health, the field is challenged by lack of methodological clarity. This applies to both the more general theoretical framework and the concrete operational definitions of the various aspects of social relations used in the existing research.

One of the challenges has been the considerable variation in approaches to assessing social relationships. Terms such as "social integration", "social ties", "social networks", and "social support" have been used interchangeably for many different operational definitions, with resulting difficulties in interpreting the results across studies (Berkman et al. 2000). In recent decades, more clear conceptualizations have emerged. There is, for example, consensus that research on social relations

should distinguish between *structural* and *functional* aspects. The structural aspects can generally be divided into formal and informal relationships, with formal relationships referring to the role and status of an individual in society, e.g., spouse, parent, colleague, etc., whereas the term social network usually covers more informal relationships, e.g., friends, relatives, etc. Both formal and informal relationships can be quantified in several ways, e.g., number, frequency, and duration of contacts, together with aggregated measures such as the diversity in the types of relationships an individual may have.

The functional aspects, on the other hand, refer to the function and quality of the interactions that take place in the social network, with social support being the most frequently researched functional aspect (Cohen and Syme 2007). Social support is defined as resources provided by other individuals in the individual's network, and can be assessed both as actual support provided and the experienced support. There are several forms of support, including practical support, information, emotional support, and recognition. While the structural aspects of social relationships may be considered as relatively neutral, the functional dimension includes not only positive but also negative aspects. Social relationships can involve demands and conflicts and thereby be a source of practical, financial, and emotional stress. The concepts described above are neither exhaustive nor completely consistent. E.g., the concept of social integration can be based on structural aspects assumed to predict the quality of an individual's social network, but can also be based on the individual's subjective experience of recognition and affiliation. Examples of operational definitions of social relationships used in research on social relations and health are shown in Fig. 22.1.

## 22.3 Social Relations and Health Outcomes

### *22.3.1 Structural Aspects*

Associations between structural aspects of social relationships and health are generally well-researched, and several major studies over the last 30 years have been able to confirm that a number of positive and negative associations exist between various measures of social relations and mortality. In an early review of a number of large population surveys from the United States, Sweden, and Finland (House et al. 1988), the evidence indicated increased mortality among people with weak social networks. As seen in Table 22.1, these findings are confirmed by the results of more recent systematic reviews with meta-analyses showing that negative social characteristics such as living alone and social isolation have generally been found associated with approximately 30% increased risk of all-cause mortality, whereas positive aspects such as larger social networks and greater social integration appear to be protective, reducing the risk of mortality by—again—approximately 30%. In general, the negative impact of factors such as social isolation on health appears to

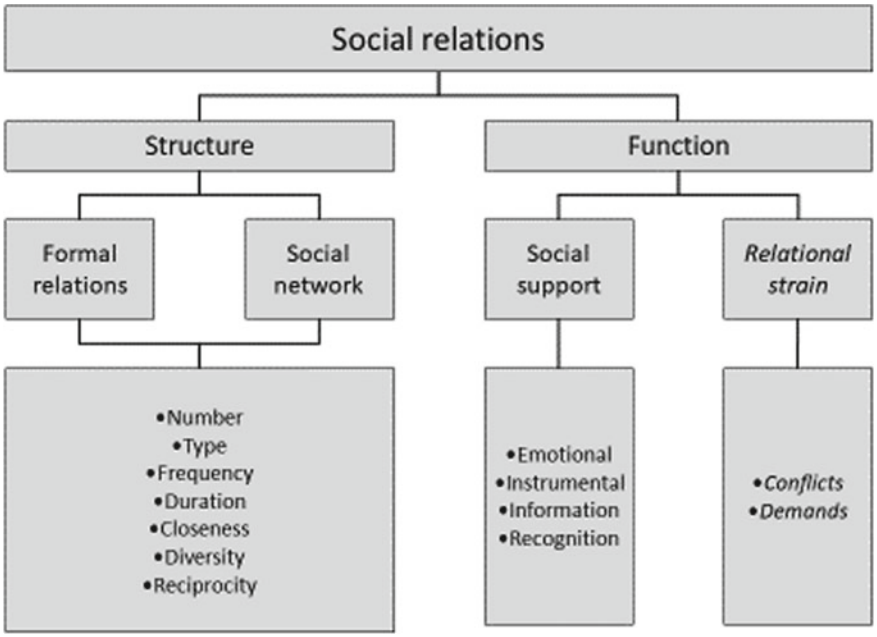


**Fig. 22.1** Operational definitions of social relations. Adapted from Due et al. (1999)

be of at least the same magnitude as other known risk factors such as high blood pressure, obesity, sedentary lifestyle, and smoking.

As seen in Table 22.1, the presence or absence of a partner is among the most frequently studied social network characteristics, which is likely due to the high availability of information on marital status in various registries. Generally, being married or living with a partner appears to be protective with a meta-analysis suggesting that being married is associated with a 25% reduced overall mortality (Holt-Lunstad et al. 2010). The protective role of having a partner is supported by a large number of studies showing that marital dissolution, i.e., separation and divorce, is associated with poorer health, with a meta-analysis of 104 studies providing data on more than 600 million persons showing that divorce/separation is associated with a 30% increase in mortality (Shor et al. 2012). Similar effects are found for widowhood, with an overall increased risk of mortality of 23% found across 124 studies (Roelfs et al. 2012). It is worth noting that the increased risk of poorer health and increased mortality is particularly strong among single men, whether they are divorced, never married or widowed (Robards et al. 2012). The reasons for the gender differences in the effects of marital status are not yet clear. Among the suggested explanations are that women may be more likely than men to seek to influence their spouses' health-related behaviors, which could mean that married men are more likely to stop smoking, have a healthier diet, exercise more, and seek medical attention when needed than single men (Umberson 1992), while women's health behaviors are more

**Table 22.1** Results of systematic reviews with meta-analyses examining the associations between measures of social relations and risk of all-cause mortality

| Category | Author, year | Number of studies | Predictor[a] | Effect (95%CI)[b,c] |
|---|---|---|---|---|
| Structural (quantitative) | Holt-Lunstad et al. (2015) | 25 | Living alone | OR = 1.32 (1.14–1.53) |
| | Holt-Lunstad et al. (2015) | 14 | Social isolation | OR = 1.29 (1.06–1.56) |
| | Holt-Lunstad et al. (2010) | 45 | Social integration | OR = 0.66 (0.59–0.73) |
| | Holt-Lunstad et al. (2010) | 71 | Social networks | OR = 0.69 (0.63–0.76) |
| | Holt-Lunstad et al. (2010) | 62 | Marital status | OR = 0.75 (0.68–0.73) |
| | Shor and Roelfs (2015) | 91 | Contact frequency (excluding marital status) | HR = 0.90 (0.88–0.93) |
| | Shor et al. (2012) | 104 | Divorce (all)<br>Divorce (men)<br>Divorce (women) | HR = 1.30 (1.23–1.37)<br>HR = 1.37 (1.27–1.49)<br>HR = 1.22 (1.13–1.32) |
| | Roelfs et al. (2012) | 124 | Widowhood (all)<br>Widowhood (men)<br>Widowhood (women) | HR = 1.23 (1.19–1.28)<br>HR = 1.27 (1.19–1.35)<br>HR = 1.15 (1.08–1.22) |
| Functional (qualitative) | Holt-Lunstad et al. (2015) | 13 | Loneliness | OR = 1.26 (1.04–1.46) |
| | Holt-Lunstad et al. (2010) | 9 | Received social support | OR = 0.82 (0.61–1.10) ns |
| | Holt-Lunstad et al. (2010) | 73 | Perceived social support | OR = 0.74 (0.67–0.82) |
| | Robles et al. (2014) | 126 | Marital quality | OR = 0.67 (0.51–0.86) |
| | Gilbert et al. (2013) | 39 | Social capital (trust, reciprocity, participation) | OR = 0.85 (0.75–0.98) |

*Notes* (a) Operational definitions: *Living alone*: Living alone versus living with others; *Social isolation*: Lack of social contact, communication, participation in social activities or confidant; *Social integration*: Participation in a range of social activities or relationships, sense of community; *Social networks*: Network size or number of contacts; *Marital status*: Married versus other; *Contact frequency:* Number of contacts per time unit; *Loneliness*: Self-reported feelings of isolation, disconnectedness, not belonging; *Received social support*: Self-reported receipt of emotional, informational, practical, financial, and other support; *Perceived social support*: Perceived availability of emotional, informational, practical, financial, and other support if needed. (b) When authors provide results for both unadjusted and adjusted data, results for adjusted data are presented. (c) Some of the reported effect sizes have been inversed so as to make effects comparable. Abbreviations: OR—Odds ratio, HR—Hazard ratio

independent of their marital status. It could also be that when distressed, men are more likely to seek emotional support and confide in their female partner, whereas women may be more prone to seek emotional support from others, e.g., female friends, than from their male spouse (Phillipson 1997).

In addition to examining the impact on overall mortality, several studies have explored the possible associations of social relations with the risk of developing various diseases and their prognosis, including heart disease, cancer, dementia, and infections.

For example, in a large cohort study of more than 76,000 US women followed for 22 years, the most socially integrated women were found to have 45% lower risk of developing coronary heart disease (Chang, Glymour et al. 2017). In another example, a cohort study of 13,686 US community-dwelling men and women with no history of stroke followed for a median of 18.6 years revealed that those with a small social network had a 44% increased risk of stroke after adjusting for sociodemographic variables, marital status, and behavioral and major stroke risk factors (Nagayoshi et al. 2014). In addition to being a risk factor for developing heart disease, social network characteristics also appear to play a prognostic role. For example, in a prospective study of 1019 patients with stable coronary heart disease, the risk of mortality was 50% higher in socially isolated patients compared to non-isolated patients after adjusting for demographic and disease-relevant factors (Kreibig et al. 2014). In the studies on heart disease, the associations between social network characteristics and mortality were to a large degree explained by health-related behaviors, with those with poorer social networks also displaying more negative health behaviors such as smoking.

A wide range of studies have examined the role of social relations in cancer. A systematic review and meta-analysis of 87 studies has investigated the associations of various social network characteristics with cancer-related mortality (Pinquart and Duberstein 2010). The results revealed that studies that had adjusted for various demographic, health-behavioral, and disease-related variables found statistically significant lower risk of mortality in those cancer patients who were married and those with larger social networks, with reductions in mortality ranging from 12 to 20%. Likewise, compared with married cancer patients, those who were widowed, those who were divorced or separated, and those who had never been married, all had increased cancer-related mortality with increases in risk ranging from 14 to 23%.

Cognitive function plays an important role in determining functional abilities, independence, and quality of life in the aging population, and while some age-related changes in cognitive function, e.g., processing speed and episodic memory, are considered normal, cognitive decline is not a part of healthy aging (Klimova et al. 2017). Social relationships provide access to social networks and promote engagement in social activities that may protect against cognitive decline. In a systematic review of 39 studies, the authors found that six out of the nine studies that had examined social network size and contact frequency found positive associations with measures of global cognitive function at follow-up (Kelly et al. 2017). These findings suggest that social relations could perhaps also be protective of the development of dementias such as Alzheimer's disease, a hypothesis which finds support

in a systematic review and meta-analysis of 31 cohort and two case-control studies of a total of 2,370,452 participants (Penninkilampi et al. 2018). The results indicated that being unmarried (eight studies) and having a poor social network (six studies) were associated with 63 and 59% increased dementia risk. Likewise, having many social contacts (eight studies) and a high level of social activity (six studies) reduced the risk of developing dementia by 15% and 38%, respectively.

While diverse social networks thus generally appear to be associated with better physical and cognitive health, there may also be exceptions. For example, there is evidence to suggest that a large and diverse network with many contacts can increase exposure to infectious agents, resulting in increased risk of upper respiratory infections such as the common cold (Hamrick et al. 2002). On the other hand, a large network may also be protective by reducing stress and health behaviors associated with weakened immune responses to infections (Zachariae 2009). This is supported by the results of an experimental study of volunteers infected with the common cold under controlled conditions, which revealed that participants with a more diverse social network were less susceptible to the experimentally induced infection (Cohen et al. 1997). A subsequent epidemiological study by the same group of researchers indicated that stress and diversity of social networks interacted such that social network diversity was associated with more illnesses among those with more stressful life events and slightly fewer illnesses among those with fewer stressful life events (Hamrick et al. 2002).

### *22.3.2 Functional Aspects*

While there is considerable evidence, as shown above, that various structural aspects of social relationships, including marital status, network size, network diversity, and contact frequency are associated with a number of health outcomes, including mortality, it is difficult to imagine how these *quantitative* measures in themselves can influence health. It is more likely that these measures are proxies of underlying *qualitative* aspects of direct or indirect importance to an individual's health.

A possible consequence of living alone, having a small social network and few social contacts, and being involved in few formal and informal social activities, is the subjective feeling of loneliness. As shown in Table 22.1, self-reported loneliness has been found associated with a 26% increase in mortality. With respect to specific diseases, while there a several studies showing associations between cardiovascular disease and the structural measure of social isolation, the evidence base is modest for the associations between the subjective measure of loneliness and cardiovascular disease with only very few available studies (Courtin and Knapp 2017; Leigh-Hunt et al. 2017). However, as seen in Table 22.1, the effect magnitudes found for social isolation and loneliness are similar (29% and 26% increased risk of mortality, respectively), which could suggest that the differences between the objective and subjective measures of social isolation may be minimal. However, the results are mixed, and there are studies reporting that groups of older people who are isolated or lonely

only partly overlap, and that both social isolation and loneliness are independent risk factors for a range of health outcomes (Courtin and Knapp 2017).

The most frequently studied functional aspect of social relations is social support, in particular the subcategory of perceived social support. As seen in Table 22.1, a total of 73 studies reviewed in 2010 (Holt-Lunstad et al. 2010) had examined the association between perceived social support and mortality finding an overall reduction in mortality of 26%. In a meta-analysis of a subset of 21 studies of the association of social support with cancer survival which had controlled for a number of potential demographic, clinical, and health-behavioral confounders, the results revealed a similar (25%) reduction in cancer mortality (Pinquart and Duberstein 2010). An earlier review of 15 studies published between 1974 and 2004 on social relationships and breast cancer prognosis (Zachariae and Christensen 2004) suggested that when social relations were assessed with structural measures, e.g., network size, frequency of contacts, or number of friends and family members, or with non-emotional functional measures, e.g., practical support or other people's ratings of received support, no associations with prognosis were found. In contrast, all studies that had used some measure of perceived *emotional* support found support for the association with breast cancer prognosis.

While there is overwhelming evidence that married people—on average—have better physical health and live longer, the simple presence of a spouse is not necessarily protective in itself (Kiecolt-Glaser and Wilson 2017). Relative to non-cohabiting social network members, married couples share space, time, investments, and resources, creating not only opportunities for support but also for conflict, and the degree to which marital status is protective is likely to depend on the quality of the relationship. Marital quality can be defined as a global evaluation of the marriage on several dimensions, and a high-quality marital relationship can be operationalized as high self-reported satisfaction with the relationship, together with positive feelings and attitudes towards the partner and low levels of hostile and other negative behaviors (Robles et al. 2014). A meta-analysis of 128 studies of a total of 72,674 participants, greater marital quality was found to be correlated with a number of health-related outcomes, including better self-reported health ($r = 0.14$), healthier cardiovascular reactivity measures (heart rate and blood pressure) ($r = -0.13$), and an on average 33% reduced mortality ($r = -0.11 \approx$ odds ratio $= 0.67$) (Robles et al. 2014).

One of the important resources that partners and other social network members can provide is the opportunity for emotional disclosure. Emotional inhibition and non-expression are generally believed to be associated with ineffective coping skills and adverse outcomes in the face of stress (Nyklicek et al. 2004). Conversely, the ability and opportunity to express thoughts and feelings about traumatic or stressful life events, e.g., a cancer diagnosis or spousal bereavement, are believed to be important for successful adjustment to such events (Pennebaker 1995; Zachariae and Jensen-Johansen 2011). However, social networks are not equally responsive to the needs of their members and may represent high levels of social constraints. Social constraints refers to the perception that partners, friends, and others in one's social network are unsupportive, e.g., unreceptive to attempts to talk about health-related concerns

and other problems (Lepore 2001). For example, in a study of 238 bereaved individuals, social constraints were associated with poor psychological adjustment and more perceived stress, more mental and somatic symptoms, and poorer self-reported overall health. It is important to note that a relationship, e.g., a marital relationship, characterized by high levels of social constraints does not necessarily represent negative intentions on behalf of the partner. It could also mean that the partner is unaware of the needs of his or her spouse or lacks the social, communicative skills to meet their spouse's needs.

### *22.3.3 Ask Not (Only) What Others Can Do for You …*

While most studies on social support, well-being, and health have focused on the effects of *receiving* social support or the lack thereof, more recently, researchers have also begun to explore the potential benefits of providing help to others (Post 2005). The potential benefits of helping others, e.g., exploring the motivations for and the benefits of participating in volunteer work (Clary and Snyder 1999), can be viewed in the light of altruism, where we, from an evolutionary perspective, would expect a selection for altruistic behaviors within groups as this confers a competitive advantage against other groups (Kurzban et al. 2015). Altruistic behaviors are believed to go beyond just helping those who carry one's own genes, as those who help others—even those who are not closely related—may stand to receive both direct and indirect long-term benefits.

From an evolutionary perspective, selection for helping behaviors would require these behaviors to be associated with reinforcing positive emotions, a hypothesis that has been supported by experimental studies providing evidence that individuals who are given the opportunity to help others, e.g., helping participants avoid unpleasant electric shocks, experience more positive emotions (Batson et al. 1991). In addition, it has been demonstrated that being involved in volunteer work is associated with lower levels of depression and increased well-being (Piliavin and Callero 1991; Borgonovi 2008). However, most studies are cross-sectional, making it difficult to determine the direction of a possible causal relationship. The results of a large longitudinal study suggests bidirectional causality: not only were people who were happier, more satisfied with life, and less depressed more likely to engage in volunteer work, but increases in the number of hours volunteering over time were also associated with increased quality of life (Thoits and Hewitt 2001). That evolution appears to have hardwired humans to engage in helpful behaviors finds further support in studies showing that subcortical "pleasure centers" in the brain involved in reinforcing behaviors, e.g. the septal area and amygdala, are activated when one is engaged in supportive behaviors (Inagaki 2018).

While the studies are still relatively few, the available research suggests significant associations between kindly emotions and helping behaviors on the one hand, and well-being, health, and longevity on the other (Post 2005). For example, in a study of a group of women interviewed in 1956 and in 1986, 30 years later, it was

found that the women who had been engaged in various types of volunteer work lived longer than the remaining women (Moen et al. 1995). In addition, among the surviving women, a correlation was found between how much volunteer work they had been engaged in over the years and their current self-reported well-being and physical functioning. In another prospective study of 1972 older people, the 15% "high volunteers" who volunteered for more than one organization had 63% lower mortality than non-volunteers, even when possible confounders such as health behaviors, physical functioning, and their received social support were taken into account (Oman et al. 1999). The association between volunteering and health benefits is unlikely to be linear, as demonstrated by data from a national sample of 3617 older non-institutionalized US citizens collected over an eight-year period, showing that a moderate involvement in volunteer work, i.e., less than 40 h, over the past year, was associated with 54% reduction in mortality, whereas several hours beyond this number had no further protective effect (Musick et al. 1999). The results further indicated that the protective effect was strongest in participants with limited informal social networks, measured in terms of how often they spoke with friends, neighbors or relatives during a typical week.

The available results thus generally suggest that giving support is good for health. However, helping others may not be equally beneficial in all situations—and could perhaps even be costly under certain circumstances. It has thus been suggested that people will experience the greatest health benefits from helping others when they are providing the support of their own free will and experience that the support given is effective and appreciated by the recipients (Inagaki 2018). For example, in a longitudinal study of a large sample of US adults involved in volunteer work, those who felt more respect for their work from others were more likely to continue volunteering and had higher levels of daily positive affect, lower levels of daily negative affect, and higher levels of well-being over a 20-year period (Tse 2018). A special case of supportive behavior is that provided by informal caregivers, including spouses and others, of, e.g., people with Alzheimer's disease or cancer. In a landmark prospective study of 392 caregivers and 427 non-caregivers who were living with their spouses, those who provided care and experienced caregiver strain were found to have 63% higher risk of mortality than non-caregivers, whereas caregivers who provided care but did not experience strain did not differ significantly in mortality risk from non-caregivers (Schulz and Beach 1999).

## 22.4 Mechanisms

While there is overwhelming evidence of the potential influence of social relationships on well-being and physical health, our knowledge about the psychological, behavioral, and biological mechanisms that explain the links between social relationships and health is still relatively limited. Identifying the mechanisms by which social relations promote the beneficial—and sometimes adverse—effects on health

are important, not only for theoretical reasons, but also for applied reasons, as they will inform the development of efficacious preventive measures and interventions.

### 22.4.1 Direct or Indirect Effects?

One question concerns whether the associations of social relations with health are explained by direct main effects, or whether they are more likely to be due to indirect mechanisms (Cohen 1991; Uchino et al. 2012). The *direct effect* model suggests that the social network may have direct effects on health, more or less independent of the person's current situation (Cohen et al. 2001). First, informational and practical support from others in the network may assist the person in avoiding or minimizing potentially stressful situations. Second, social support and recognition from others may be directly associated with fewer negative emotions and increased self-efficacy, perceived control, self-esteem, and other positive emotions that may have a direct impact on biological processes of relevance to health, e.g., the immune system (Zachariae 2009). The social network may also act as health-promoting by influencing the person's health behaviors, e.g., smoking, through social control. Finally, it is also possible that practical and financial assistance may increase the availability of healthcare, e.g., by driving a physically constrained person to a doctor's appointment. The *indirect* effect model suggests that social relations may have a positive impact on health by providing protection against the negative health consequences of stressful events and negative life circumstances. This so-called stress-buffer hypothesis (Cohen 1985) suggests that having a network of people who provide relevant informational, practical, and emotional support, and who promote feelings of being loved, respected, and valued, may influence the person's ability to cope with stress and thereby protect him or her against negative health consequences of stress. There appears to be relatively good evidence for the stress buffering hypothesis (Cohen 1985), with the most consistent effects found for perceived availability of support, primarily emotional support. However, the support found for the indirect model does not necessarily preclude direct health-related effects of social support.

### 22.4.2 Biological Pathways

One of the biological mechanisms which could potentially explain the connections between social relations and health-related outcomes is the immune system (Zachariae 2009). Humans have evolved as social beings, and living in large social groups offers many advantages, e.g., by reducing the risk of predation, improving food production, and rationalizing the care of offspring. There are, however, also costs, including increased risk of infections through social contact and sharing food. From an evolutionary perspective, to counter these costs, increased social interaction thus necessitates protection against pathogen exposure through increased antiviral

immunity. Lack of social connection, on the other hand, has led to increased vulnerability to physical attacks, increasing the risk of wounding. When the social network is insufficient, inflammatory processes, which promote wound healing and protect against subsequent infection, are more likely to be needed (Leschak and Eisenberger 2019). Empirically, one would therefore expect to find more effective adaptive immune responses and lower levels of inflammation in people with larger social networks and higher levels of social support, and, conversely, evidence of suppressed immunity and increased inflammation after social disruption in chronically socially isolated and lonely individuals.

Some of the earliest studies on social relations and immunity explored the effects of social disruption such as the death of a spouse, demonstrating weakened immune responses, e.g., reduced lymphocyte proliferative responses or lower natural killer cell activity, in bereaved persons compared to non-bereaved controls (Bartrop et al. 1977; Stein 1985). Similar effects have been observed in divorced and separated people (Kiecolt-Glaser et al. 1987) and in married couples with multiple marital conflicts (Kiecolt-Glaser 1988, 1993). When examining the influence of psychosocial factors on immunity, researchers have often turned to assessing responses to vaccination, e.g., for influenza, as a model of immuno-competency. A series of studies have thus documented that various types of stress, including stressful life events and chronic stressors such as being an informal caregiver of patients with Alzheimer's disease, are generally associated with weaker antibody responses to influenza vaccines (Pedersen et al. 2009). Some of these studies have included measures of social support. For example, results from a group of medical students who had been inoculated with hepatitis-B vaccine showed that those who reported greater social support and lower levels of anxiety and stress had higher antibody responses and more vigorous T-cell responses to hepatitis antigen (Glaser et al. 1998). In another study of antibody responses to influenza vaccination in a group of healthy university freshmen, high levels of loneliness and small social networks were found to be independently associated with lower antibody responses (Pressman et al. 2005). Those with both high levels of loneliness and small social networks had the weakest antibody response.

Associations with suppressed cellular immuno-competency may explain some aspects of the influence of social relations on health, mainly susceptibility to infectious diseases, but perhaps also cancer. Given their importance across a variety of diseases, including cardiovascular disease, cancer, and a wide range of inflammatory and autoimmune conditions (Hunter 2012), inflammatory pathways between weak social relations and poor health are also likely to be of central importance. While short-term inflammatory responses, e.g., to injury and infection, are generally adaptive by removing the sources of injury or infection and promoting tissue repair, long-term or chronic inflammation characterized by elevated levels of proinflammatory cytokines, e.g., interleukin 1, 6, 8, and 12, and tumor necrosis factor alpha (TNF-α), can be detrimental to health by increasing oxidative stress, promoting DNA damage, increasing telomere shortening, causing death of neurons, and numerous other known disease-promoting factors. Given the evidence for increased risk of

mortality and diseases associated with chronic inflammation in people with insufficient social networks and low levels of social support, one would expect poor social relations to be associated with higher levels of various proinflammatory markers. Overall, this has found support in the results of a large meta-analysis of 41 studies with a total of 73,037 participants (Uchino et al. 2018). The majority of studies had investigated associations with levels of CRP, IL-6, TNF-α, and fibrinogen finding—on average—similar small, but statistically significant, overall effect size correlations ranging from –0.6 to –0.8 across the various inflammatory markers and social relationship measures of social integration, received and perceived social support.

While the majority of research has focused on the "top-down" associations between social relations and the immune system, another line of research has focused on the "bottom-up" pathways, i.e., how the immune system may influence social behaviors of relevance to health (Dantzer 1999). The *behavioral immune system* is believed to have evolved as a first line defense against infections and includes behaviors that serve to minimize the contacts between infected and uninfected individuals (Shakhar 2019). Several biobehavioral mechanisms are thought to have developed to facilitate these processes. One example is *sickness behavior*, an evolutionarily conserved biobehavioral syndrome induced by proinflammatory cytokines released by innate immune cells in response to an infection acting on the brain, with the well-known physical, psychological, and behavioral changes including fever, nausea, fatigue, muscle pain, loss of appetite, changes in cognition, depressed mood, and social withdrawal (Dantzer et al. 2008).

Sickness is a normal response to infection which induces a motivational state that promotes adaptive responses that are believed to serve several purposes. First, it reorganizes perceptions and cognitions that will help the individual cope better with the infection, e.g., by conserving energy and avoiding external threats in a vulnerable situation. For example, after an experimentally induced inflammatory challenge, individuals feel more socially disconnected and lonely, display deficits in social cognition, and are more sensitive to negative social stimuli, which may serve to motivate them to withdraw socially and avoid potential harm from unfamiliar others (Moieni et al. 2015; Muscatell et al. 2016). Second, the sickness behavior syndrome may serve to protect the group by reducing the risk of transmitting the pathogen to uninfected hosts. This can happen in two ways. First, the reduced motivation for social interaction of the infected individual will serve to reduce the risk of infecting others. Animals deficient in adaptive immunity have been found to exhibit social deficits (Filiano et al. 2016). For example, mice deficient in interferon gamma (IFN-γ), a cytokine that plays an important role in the cellular immune response to viral infections (Chesler and Reiss 2002), show no preference for social stimuli, a response that appears to be completely restored after injections of IFN-γ in their cerebrospinal fluid. Second, the biological immune system of the infected individual may also activate the behavioral immune system of the group by increasing the likelihood that uninfected individuals will respond with disease-avoidant behaviors to infected individuals. For example, in a double-blind, placebo-controlled, cross-over experiment (Regenbogen et al. 2017), the immune systems of volunteers were transiently activated with injections of lipopolysaccharide (LPS). Pictures and body odor samples

were taken from the participants both when temporarily "sick" and "healthy", i.e., injected with saline. A second group rated the faces and odors as less likable when sick and displayed activation of face- and odor-perception neural networks.

### *22.4.3 Behavioral Pathways*

When examining the role of social relations in health, researchers often do their best to adjust for the influence of possible confounders, including health-related behaviors such as smoking, alcohol consumption, physical activity, dietary habits, delay in seeking medical attention, and adherence to treatments. Rather than treating such factors as "confounders", the influence of social relations on health behaviors may represent important—and possibly malleable—behavioral pathways through which social relations may influence health outcomes. However, as indicated by several reviews of the literature, the results are mixed, suggesting that the associations between social relations and health behaviors are complex. It could thus be that while some social relations may promote healthy behaviors, others may have no effect or even be harmful to health behaviors and overall health.

For example, in the Framingham Heart Study, a large population-based cohort (Mahmood et al. 2014), it was found that the almost 50% reduced risk of dying seen among married men could not be explained by either cholesterol, smoking or diabetes (Eaker et al. 2007), and overall, differences in health behaviors may explain only a relatively limited proportion of the covariation in social network characteristics, e.g., marital status, and health outcomes (Cacioppo and Hawkley 2003). This conclusion is supported by systematic reviews of the literature. For example, in a meta-analysis of 32 studies of the associations between measures of social relations and adherence to healthy lifestyles and medication in patients with hypertension, the authors found no support for an association between marital status—a core structural social relationship characteristic—and overall adherence (Magrin et al. 2015). In contrast, significant associations were found between functional support, e.g., from family and friends, and adherence to medication.

The lack of clear findings concerning associations between structural social relationship characteristics and adherence to treatments has found further support in an overview of seven systematic reviews (Mathes et al. 2014). The associations may be further moderated by other factors, e.g., population characteristics such as age and disease, and the type of health behavior examined. For example, in a systematic review of 27 studies examining the role of social support in physical activity (Lindsay Smith et al. 2017), positive associations were generally found between social support specifically directed at physical activity and physical activity levels in older adults, especially when the social support is provided by family members, whereas there were no clear associations between physical activity levels and general social support, social support for physical activity from friends, or loneliness. In contrast, in a large study of cancer survivors, those who received higher levels of social support were

less likely to be smokers than those who experienced low levels of social support (Poghosyan et al. 2016).

Taken together, while there appear to be some associations between at least some health behaviors and functional aspects, e.g., social support, the associations with structural social network characteristics, with marital status being the most frequently investigated, appear to be limited. Behind the null-findings may lie effects in opposite directions. Spouses' daily lives are intertwined, and each partner's personal attributes such as moods, attitudes, behaviors, health, stresses, and lifestyle affect both spouses. Couples' health and health behaviors are thus often similar and tend to converge over time (Kiecolt-Glaser and Wilson 2017). An early review of the literature suggested that family relations are associated with the adoption and maintenance of unhealthy behaviors such as smoking, unhealthy dietary habits, and levels of physical activity (Burg and Seeman 1994), indicating that couples' mutual influence may thus not only be beneficial but could also have a negative effect on health behaviors and health.

Sleep, one behavior of potential importance to well-being and health, has been given particular attention in recent years. A growing literature reports finding associations between various measures of sleep, including self-reported sleep quality, sleep duration, and sleep disturbances, and a number of health-related outcomes, including risk of cardiovascular disease (Javaheri and Redline 2017), Alzheimer's disease (Shi et al. 2017), cancer (Erren et al. 2016), and all-cause mortality (Gallicchio and Kalesan 2009). From an evolutionary perspective, higher levels of social support would be expected to be associated with better sleep by providing increased safety from predators, conspecific enemies, and other dangers (Faria et al. 2019). This hypothesis is supported by findings from a growing number of studies. For example, in a large British cohort of people who had their positive and negative social support assessed at ages 53, 60–64, and 68 years, greater cumulated exposure to positive support and lower exposure to negative social support was associated with better sleep quality at age 68 (Stafford et al. 2017). Furthermore, those who indicated at age 53 that their spouse was their closest person, but not at age 68, an indicator of deteriorated marital relationship, had poorer sleep quality than those who nominated their spouse on both occasions. In another prospective study, a national probability sample of US citizens completed measures of social support and social strain together with later measures of subjective sleep quality. They also completed sleep diaries and had their sleep efficiency, total sleep time, and night-to-night variability in total sleep time assessed with actigraphy (Chung 2017). The results showed that higher levels of social support predicted better self-reported sleep, whereas social strain was only associated with objective sleep parameters. These findings are further supported by the results of a recent systematic review and meta-analysis of 61 studies which had included a total of 105,437 participants (Kent de Grey et al. 2018). Across all 61 studies, social support was associated with more favorable sleep outcomes, the association corresponding to an effect size of $r = 0.15$. Further moderator analyses showed that the strongest associations between social relations and sleep were found for measures of social integration, perceived social support, and self-reported sleep in samples of participants without chronic conditions.

While studies directly examining sleep as a potential mediator of the associations between social relations and health outcomes are still lacking, two lines of evidence suggest that inflammation could be the biological mechanism linking effects of social relations on health outcomes with their influence on sleep. As described above, inflammatory processes are involved in many of the adverse health outcomes associated with low levels of social support. Furthermore, both experimental and observational studies have demonstrated that disturbed sleep is associated with dysregulation of the immune system with subsequent downregulation of adaptive cellular immune responses and increased release of proinflammatory cytokines (Irwin 2019).

## 22.5 Conclusions and Societal Perspectives

As reviewed above, there appears to be overwhelming evidence that social relations play a role in well-being and health, with the present chapter focusing primarily on the available evidence for associations with physical health outcomes. There is ample evidence of correlations between various structural social relationship characteristics, e.g., marital status, social network size and diversity, and frequency of contacts, and a range of health outcomes, including mortality. However, the true drivers of these effects are more likely to be the qualitative, functional aspects, e.g., various types of practical, informational, and emotional social support—or lack thereof—together with the possible strains, e.g., relational conflicts or social constraints, one may also experience in social relations. In addition, there is limited but promising research working to establish the possible bidirectional benefits of not only receiving but also providing social support. As summarized in Fig. 22.2, there are many possible psychological, biological, and behavioral pathways linking social relations with health outcomes.

Among the limitations of the available research, is that most research has focused on social relations from the individual's perspective, i.e., how the individual benefits (or is harmed) by his or her social network and the support received from individuals in this network. However, from a systems perspective, individuals are embedded in social networks that by themselves are embedded in larger social structures, e.g., organizations, communities, and nations, the characteristics of which may provide additional benefit—or harm—to the health of the members of these social structures.

The concept of *social capital* represents an analytic approach that attempts to grasp these extra-individual qualities and effects, with social capital having been defined as "features of social organizations, such as networks, norms and trust that facilitate action and cooperation for mutual benefit" (Putnam 1993). Social capital includes not only aspects of *bonding*, the relationships with family and friends in one's network, but also *bridging*, which is used to characterize the quality of relationship between different groups, e.g., ethnic or socioeconomic groups. The third concept of *linking* represents the relations between individuals and groups, and between organizations and institutions, e.g., government institutions. In a meta-analysis of 39 studies, the authors had evaluated the bivariate associations between various social

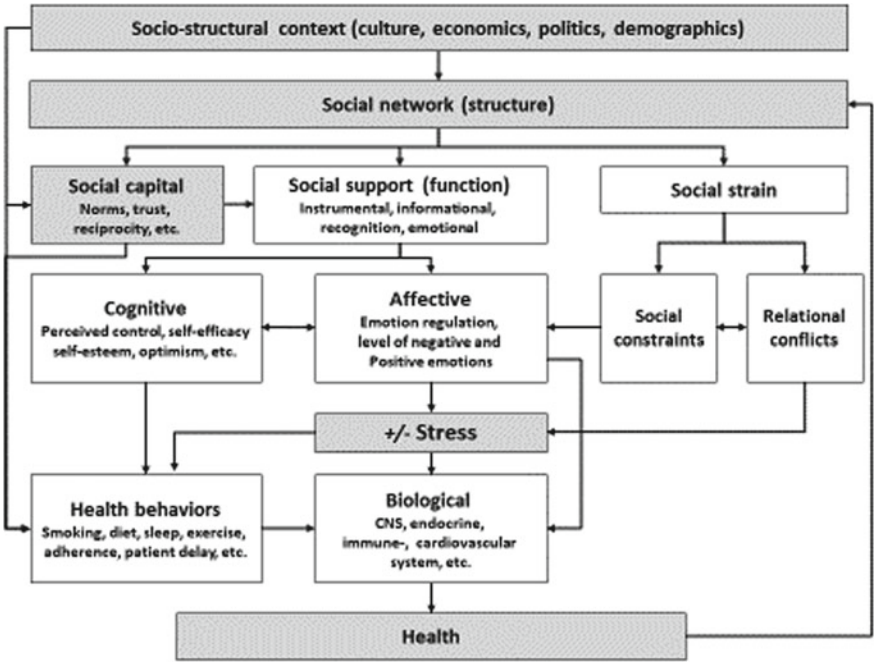


**Fig. 22.2** Possible pathways linking social relations and health outcomes

capital constructs and self-reported health and all-cause mortality (Gilbert et al. 2013). Overall associations between social capital variables and health showed that the presence of social capital, operationalized as trust, reciprocity, and participation at different levels, reduced the risk of mortality by approx. 15% and increased the odds of good self-reported health by 27%. When examining the individual constructs, *sense of community*, defined as perceptions of neighborhood safety, social cohesion, and friendliness of neighbors, every one-unit increase in sense of community increased the odds of having good self-reported health by 28%. Similar positive effects were found for studies of *reciprocity*, defined as willingness to help others, altruistic activities, and giving, which increased the odds of having good health by 39%. The idea that the relations, not only with those in a person's own network, but also with those in different groups may influence a person's health is further supported by studies showing that perceived racism and discrimination are associated with negative physical health-related outcomes. This was demonstrated in a meta-analysis of 134 studies showing that perceived discrimination was associated with poorer mental and physical health as well as increased stress responses and poorer health behaviors (Pascoe and Smart 2009).

Taken together, further research is clearly needed to disentangle the complex, presumably bi-directional associations between the societal context, social relations, biological mechanisms, health-related behaviors, and health outcomes. If the salient

moderators ("for whom does it work?") and mediating mechanisms ("how does it work?") can be identified, this knowledge could translate into effective preventions and treatments. In a wider perspective, the growing evidence of the role of social relations in health challenges the dominant narrow biomechanical concept of health and suggests a broader systemic approach that goes beyond the health of an individual defined as the presence or absence of disease.

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# Chapter 23
# Kinds of Explanation in Public Health Policy


**Alex Broadbent and Benjamin Smart**

**Abstract** Making public health policy in the Southern African region is challenging because public health policy tends to be informed by a Western perspective, and as a consequence is prone to ignore local social and cultural factors that may be important, practically and ethically (Kagawa-Singer and Kassim-Lakha in Acad Med 78:577–587, 2003). Contact between medical traditions has been considerably delayed by the separationist policies characteristic of the region (e.g. apartheid). From epidemiological research to population-scale medical decision making, traditions outside of what has been called "Mainstream Medicine" (Broadbent in Philosophy of medicine. Oxford University Press, New York, 2019) are systematically ignored. In this chapter, we argue that ignoring local social and cultural factors is a mistake. Whether a policy works depends on culture (we use this word in a broad, catch-all sense, to capture all local social norms and practices, societal organization, power relations, economic arrangements, and so forth). That is not a constitutive claim, leading to a strong relativism, on which facts about whether something works depend on culture. Medical relativism is rejected. Rather, it is a causal claim: features of the cultural context may affect the efficacy of a given measure. We contrast two cases, that of the development of Tenovir gel for use against HIV infection rates in Southern Africa, and the campaign to circumcise African men, with the same objective. We argue that the former takes culture into account, while the latter does not, and is objectionable for this reason.

**Keywords** Explanation · Causation · HIV · Circumcision · Philosophy of epidemiology · Prediction

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## 23.1 Introduction

Health is of near-universal concern to individuals, and public health ought to be of universal concern to governments. Public health relies on medical ideas about the nature of health, disease-explanation, and effective means of prevention and cure. Medicine is an ancient human practice that has developed in completely different ways in different times and places. Thus, while public health is a universal concern, the medical ideas it invokes are imbued with local culture.

There is much debate on the nature of health and disease in the western philosophy literature, but the most prominent analyses e.g. (Boorse 1975; Schwartz 2007; Wakefield 1992) agree that disease concerns physiological part-function; that is to say, it is organs, tissues and cells that can be diseased. However, many non-Western perspectives have a broader concept of disease, whereby health and disease are viewed holistically (Gordon 2019). The accompanying explanations for poor health reflect those differences. Whereas the western psychiatrist might reach for the SSRIs to raise serotonin levels in the depressed patient's brain (to redress the 'chemical imbalance' explanation for the condition), depression in Uganda is "regarded [by the Bantu people] as a "clan illness" (eByekika), arising from poor relationships between the living and the dead". The Bantu explanation does not call for Western medication, but "culturally accepted corrective traditional therapies" (Okello and Ekblad 2006). Clearly one cannot expect western-trained medics to accept that one's relationship with the dead is a plausible explanation for any pathology (although perhaps there are naturalistic resonances in Freudian psychodynamic theory). Nevertheless, understanding the cultural norms is fundamental to effective public health interventions. This begs the question: How should public health policy proceed in any given region, in a way that is both respectful of local culture, and responsible to the universal demand for effective public health measures?

In Sect. 23.2 we outline the "Inquiry Thesis" advanced by Broadbent (2019), with a particular focus on "explanation in medicine". In Sects. 23.3 and 23.4, we explore and contrast two cases of public health policy formulation and action in the region, both targeted at reducing HIV infection rates. In Sect. 23.3 we present Case 1, the development of Tenovir gel to reduce infection rates among women in Kwa-Zulu Natal. In multiple respects this is an exemplary piece of research, resulting in a firm empirical foundation for policy, and yielding policy that is empowering, and that respects the social and cultural pressures on the target population. In Sect. 23.4, we present Case 2, the case of male circumcision campaigns as a means to reduce male HIV infection rates. We argue that this is multiply problematic, being inadequately supported by evidence, as well as morally objectionable. We argue that the problems are explicable in terms of the Inquiry Thesis, which not only describes the nature of medicine more generally, but provides guidelines as to what counts as good medical and public health practices. We conclude by highlighting the importance of holistic, "illness causation" explanations in public health policy decision-making.

## 23.2 The Inquiry Thesis

We start with the assumption that the goal of medicine is cure. This is a non-trivial assumption, but it is one that has been defended (Broadbent 2019), and in the present chapter we wish to focus on other matters.

According to the Inquiry Thesis, even if the goal of medicine is cure, it is misguided to claim that cure is the core-business of medicine (Broadbent 2019). Much of the time, "good" medical practice does not involve any form of cure whatsoever. What good medical practice always involves, however, is investigation into whatever symptoms a patient may be experiencing, with a view to *explaining* why those symptoms are experienced. From this explanation is borne proper diagnosis, prognosis (prediction of disease course), and potentially (but not necessarily) an appropriate intervention.

Despite the fact that even now, modern medicine does not have curative or preventative interventions for many diseases, an explanation (in one form or another) for the disease is commonly offered. According to the Inquiry Thesis, it is the ability to offer an explanation (or, more fully, to engage this case with the larger project of discovering one) that is the hallmark of medical expertise—and is accepted as such even in the absence of the ability to cure.

Of course, sometimes a doctor will misdiagnose, which occurs most frequently when very similar sets of symptoms are compatible with multiple pathologies. The misdiagnosis (an incorrect explanation for a set of symptoms) is acknowledged as further data rules out the original decision, leaving alternative diagnoses compatible with all the available data to choose from. Ultimately, good medical practice occurs when proper investigation allows one to infer the best explanation for a clinical disease. Cure is great; but the inability to cure does not necessarily imply medical malpractice, while misdiagnosis does.

Doctors are often confronted with myriad possible explanations for their patient's illness (and the corresponding prognosis and treatment plan, if available), and they must choose between them. The abductive strategy of identifying possible explanations and choosing the most likely is (obviously) not a deductive process (Lipton 2004), which explains the prevalence of misdiagnoses and the ineffectiveness of at least some prescribed interventions. However, our ability to make good abductive inferences in medicine has radically improved over the last 100 years or so; in other words, we are increasingly good at practicing the core business of medicine. Our curative abilities have also substantially increased, but in a stepwise fashion, and more so in some areas than in others. Cancer remains resilient against our efforts to find effective interventions. But our comprehension of cancer has grown dramatically, and so too has the medical specialism of oncology. To be a medical specialist is to understand a lot about a condition, not necessarily to be able to cure it.

This captures only half the story, however. Explanations in medicine and public health are more often than not "causal explanations", but the etiology of illness (the causation process) is essentially a two-part process. The first is known as "illness causation", and the second "pathomechanism". Illness causation refers to the

(causally relevant) external sequence of events prior to the somatic response that marks the onset of the disease process. Pathomechanism (or "pathogenetic mechanisms"), on the other hand, "consists of subsequent mechanisms within the body leading from the initial response to the characteristic manifestations of the disease" (MacMahon and Pugh 1970, 27). Consider the following example:

Sam visits a surgery to see a GP about his sore ankle, and the woman sat next to him, who is suffering from bacterial bronchitis, coughs. As a result, Sam contracts bronchitis. The process of Sam attending the surgery (and more specifically, being coughed on) constitutes the illness causation. The sick woman's cough subsequently induces the disease course, beginning with the pathomechanism: a string of pathophysiological processes caused by the bacteria, culminating in the manifestation of the clinical disease with its characteristic symptoms.

Interventions are possible on both the illness causation and the pathogenetic mechanisms. In the first instance, Sam might have not visited the doctor for a minor ankle injury, and thus never sat next to a woman with bronchitis. Alternatively, he might be more careful about whom he sits next to, in an environment where it is common for infectious individuals to hang around (airports, buses, waiting rooms, and so forth). In the second instance (once Sam becomes aware of his illness) he can take antibiotics. The antibiotics put an end to the pathomechanisms by killing the pathogens responsible. Intervening with illness causation is clearly preferable, since successful intervention at that stage prevents Sam from getting sick in first place! Both the illness causation (being coughed on by someone with bronchitis) and pathomechanism (the spread of the infection) are genuine explanations of the clinical disease that follows (Dammann 2015; Dammann and Smart 2019).

In the following sections we outline two case studies. As we shall see, in the first case the team paid close attention to both parts of the disease etiology; that is, those causally relevant events occurring prior to the pathomechanism, as well as the pathogenetic mechanisms preceding clinical disease. In the second case, however, only the pathomechanistic explanations were considered in any detail. Ignoring important aspects of the illness etiology, we argue, is highly problematic when trying to identify effective public health measures.

## 23.3 Case 1: Tenovir Gel

In this section and the next, we set out two contrasting cases of public health policy formation, targeted at reducing rates of female and male HIV infection respectively. In this section, we set out the first case, which led to the development of the vaginal gel Tenovir (Abdool Karim et al. 2010; Mbali 2013).

The South African epidemiologist Quarraisha Abdool Karim set out to identify means to reduce the rate of HIV infection in women in rural Kwa-Zulu Natal. She made socio-behavioral studies of the target population (Mbali 2013), and identified some relevant factors.

For instance, HIV infection peaks 10 years earlier in women than men: in the 15–19 age bracket for women, and 25–29 for men. This implies a corresponding age differential in coupling patterns, which further suggests that there will be a power differential between the men and the women at the highest risk of infection. For the team, this meant that any method requiring cooperation on the part of the man was subject to his agreement. If a man refuses to wear a condom, there is little that the woman can do to change this, given the power differential implicit in these coupling patterns.

Another important point is that many of the men in this context are migrant workers, returning home perhaps once a month. Abdool Karim found that women were not generally having sexual relations in the absence of their husbands or partners. This suggested that an effective measure would not be one that required constant adherence on the part of the woman—a daily pill, for example. Women typically knew when they would be having sex, and this was on a several-weekly rather than daily basis, so a daily intervention might well be ineffective due to non-adherence. The team discovered this the hard way, by developing a pill that was effective in preventing infection in trials—but failed when tested in this context, because women did not take it with sufficient consistency.

The team ultimately developed an anti-retroviral gel, marketed as Tenovir (Abdool Karim et al. 2010), that needed to be applied vaginally within a window of a couple of days both before and after sex. Compliance with this protocol was found to be much higher than for a daily anti-retroviral pill.

Abdool Karim's work has been praised (e.g. Mbali 2013) both for its effectiveness, and for the fact that it empowers a vulnerable group—young women and teenage girls. It empowers them in the sense that it gives them a real choice about what level of risk to take, within the confines of a social world that otherwise provides them with few and difficult choices.

The success of the project is attributable in an obvious and direct way to its "explanatory" approach. It began with socio-behavioral studies of HIV infection in rural Kwa-Zulu Natal, and it tested its proposed interventions, not simply for their "in the lab", "in the clinic", or "biomedical" effectiveness, but for their effectiveness "in the wild"; that is, in the social and cultural context in which they are intended to make a difference. Abdool Karim searched for explanations for the high morbidity rates beyond the lab, and more specifically, *prior to* the lab. By explaining high HIV infection-rates through illness causation: the social dynamics of power-differentials; patterns of sexual behaviour; working conditions of sexual partners, and so on, the team was able to develop an intervention that pre-empts the disease course.

A pathomechanistic/pathogenetic explanation for the transmission of the virus may be sufficient to develop an intervention and test its efficacy, but significant differences between an intervention's efficacy and effectiveness can clearly be seen in Abdool Karim's work. The daily pill was ineffective because although the pathomechanistic explanations were understood, the team took insufficient notice of the larger explanatory story for the transmission of HIV, which included facts about coupling patterns, power relations, migration, treatment adherence, and many more besides.

The team rejected the initial approaches (e.g. daily pills and condoms), inspired only by pathomechanistic explanations for HIV, since they were effective *only* in the clinic. The Tenovir Gel, which was developed with illness causation as the primary explanatory factor in mind, turned out to have a strong basis for policy-making. We know that the treatment actually works in the target community—not that *under certain conditions* it reduces infection rate, but that it does so *under the conditions prevalent in the target population.* It is thus both effective and efficacious. Abdool Karim shows that it reduces infection rates in the conditions in which it is intended to do so, including the social conditions. When made available to the target group, they use it, and when they use it, it works.

### *23.3.1 The Ethical Dimension*

In addition to the effectiveness improvements admitted by illness causation explanations, there is a clear ethical dimension to Abdool Karim's work, which also derives from its explanatory approach. It *empowers a vulnerable group*: it gives them a choice, which is a feasible one within the scope of their social and cultural context, and which may even remain private if they so wish. A woman wishing to use the gel may do so without disrupting her relationship or the social or cultural world she inhabits. She may even do so in secret. Conversely, a woman wishing not to use Tenovir, or wishing to stop using it, may do so at her own discretion, and nobody would be any the wiser—including scientists conducting studies (she could continue collecting the gel and secretly dispose of it).

Nor does any of this prevent a woman who *does* want to challenge the social order that disempowers her from doing so. She may protect herself, while still seeking to force a reluctant and senior partner to use a condom, for example. If she fails, she is still at lower risk of infection. The approach does not assume that behaviours or societies cannot change. It merely takes account of the empirical findings that (i) power differentials exist in couples where women are most at risk of HIV infection, and (ii) that where a population comprises primarily migrant workers, prescribing pills that must be taken daily is less effective than an "only when needed" alternative. Interventions that focus on pathomechanistic explanations do not admit of this form of empowerment. Vulnerable groups can only be empowered through their own free decision-making, and these can only be situated within the social and cultural contexts ignored by pathomechanistic intervention strategies.

In subsequent sections we draw out the conceptual elements of this approach to construct a theoretical framework to form the basis for approaching health policy research in the region. Before that, however, we want to contrast another case, which we argue fails in various respects in which Abdool Karim's approach succeeds.

## 23.4 Case 2: Male Circumcision Campaigns

This second case is the attempt to reduce male infection rates through male circumcision, which has given rise to a widespread campaign in the region to persuade men to be circumcised (Williams et al. 2006). The motivation for this intervention is not an "illness causation explanation" of HIV in males, but rather a pathomechanistic explanation. It takes little account of the social and cultural behaviours within the target group, focusing only on the pathogenetic mechanisms involved in HIV transmission.

We shall argue that this campaign has an unconvincing empirical base, and regardless that it suffers from ethical problems. Both the ethical and empirical problems arise from a lack of concern for social and cultural explanations for the morbidity rate, and it is this link that we wish to establish in this section. The recommendation is a bonus.

The empirical uncertainty arises from four factors. First, although it is often asserted that the effectiveness of circumcision for reducing infection rates in heterosexual males is supported by clinical trials (Siegfried et al. 2009), despite claims to the contrary, there are in fact no randomized trials of circumcision. It is impossible to achieve true randomization with an intervention of this nature. Because there are obvious ethical concerns in randomly determining who will be circumcised, a wish to be circumcised is an inclusion criterion in such trials (Auvert et al. 2005), introducing selection bias and defeating randomization. And the obvious impossibility of blinding makes it difficult to interpret the results of the trials. Circumcision may lead to behavioural changes. Since the incidence of HIV infection in the region appears to be primarily driven by sexual behaviour, evidence that does not rule out behavioural confounders must be treated skeptically, especially in the absence of reliable information on the motivation, sexual habits, relative income levels, incentivization or persuasion techniques, exposure to advertising for the trial (which may appeal to specific insecurities or aspirations), or other residual differences between those who do and do not consent to circumcision.

Second, while clinical trials of circumcision do tend to show positive effect on HIV transmission reduction, the *degree* of effect shows little statistical homogeneity between different trials (Siegfried et al. 2009). This strongly suggests that there indeed are some residual confounders at work. One might respond that the effects are positive, so it doesn't matter; but this is to miss the point. So long as there are residual confounders, we cannot confidently conclude anything about the effect, including that it is positive. We have no reason to rule out the possibility that the residual confounders may be responsible for the entire effect; we cannot honestly claim to have the causal explanations necessary to justify this public health campaign.

It is thus not the case that there is an evidence base for the public health campaign to circumcise African males.

The third reason to doubt the effectiveness of this intervention is the lack of evidence that it works for men who have sex with men (MSM) (Wiysonge et al. 2011). This appears to run counter to one theory about how the intervention might work,

which is that the virus enters through the skin of the inner foreskin, whose removal thus removes a point of entry. By undermining the pathomechanistic hypothesis explaining the effectiveness of the apparent effect observed in male-female relations, it favours the view that the effect observed in male-female trials is due to an unidentified confounder, specific to some social or behavioural feature of male-female sexual relations.

In short, no "illness causation explanation" for male HIV infection is available to warrant male circumcision, and the pathomechanistic explanation for the high morbidity rate assumed by those purporting male circumcision conflicts with evidence from trials on men who have sex with men. These empirical problems arise from a lack of the kind of detailed socio-behavioural approach that Abdool Karim employed.

We now turn to the ethical problems, which must be considered in light of the limited degree of confidence in the benefits.

### *23.4.1 The Ethical Dimension*

Male circumcision is the removal of the foreskin. Removing a body part without consent is a violation of human rights in most situations, the main exception being pressing medical circumstances in which life is at risk and the patient is unable to give consent (is unconscious, for example); in such cases, consent is presumed. Circumcision is an ancient practice with cultural significance, and males who were circumcised in infancy do not as a rule complain about it; so this is, perhaps, a nice example of an instance when a consequentialist approach is, by general consensus, more reasonable than a strictly deontological rights-based approach. Stepping back further, the notion of a right, and especially a human right, is fairly specific to recent Euro-American thought, and this is an instance of the tension that arises when the inherently universal nature of such rights is brought to bear in other regions and cultures. Thus circumcision as a cultural practice is generally not legislated against, nor understood as a violation of national or international human rights violations, even though there is a compelling case that it is in fact a violation.

Regardless, *encouraging* someone to be circumcised is not covered by any exemption that might apply to culturally-practiced circumcision. It is generally not permissible to encourage any mutilation, or any act that might be a bodily harm. Where a person is not already circumcised as the result of a practice in the culture to which that person belongs, there is clearly no defense available from the suggestion that this is a practice in some other cultures, any more than it is reasonable to suggest abandoning any element of one's cultural heritage. It may be chosen, but for powerful, privileged, wealthy people to seek to persuade strangers in a different part of the world to be circumcised is wrong. It is of course wrong on an additional count if the persuasion is based on false claims about the empirical evidence for effectiveness and efficacy.

Thus, even if circumcision is not mutilation in the context of a cultural practice, it clearly *is* mutilation outside such a practice, since outside a cultural context there

is nothing to distinguish it from the removal of any other body part. It is thus wrong to encourage circumcision to the extent that it is wrong to encourage any other form of mutilation. This is the first ethical problem with the campaign to promote circumcision.

The natural reply is that circumcision is medically warranted as a preventive measure, and thus falls within the ambit of exceptions such as pre-emptive mastectomy among women with the BRCA1 gene. A physician may reasonably encourage such a procedure, one might maintain. In fact, physicians would exercise enormous caution in making any such recommendation, much more than is implied by, for example, a leaflet encouraging young men to "do the right thing" and get circumcised. Moreover, the power relations between a Western physician in a one-on-one consultation with a Western patient in the West are markedly different from those between an NGO worker (who may well be Euro-American) and an illiterate man in Swaziland, for example (Gwandure 2011). Even if medical grounds for recommendation of mutilation are available, they require informed consent, which, we suggest, is not compatible with the approaches in fact used in these campaigns and associated advertising.

One might of course argue that the same is true of the Tenovir gel intervention—but the nature of the treatments are different in several important ways. First, circumcision is irreversible, whereas one can stop using the gel at any point. Second, although the power-relations still hold at consultation, and the illiterate woman in Swaziland may feel compelled to consent, the application of the gel is up to her, and she can secretly rebel even if she has consented. There may still be ethical concerns in this case (it is rare that they are entirely absent in medical trials), but they are considerably less serious, and the evidence base is considerably stronger.

Third, the cultural significance of circumcision means that it is wrong to promote it, to just the same extent that it would be wrong to seek to prohibit it. If there are arguments to the effect that the cultural significance of circumcision is such as to exempt it from what would otherwise be its status as a gratuitous mutilation inflicted upon persons who are usually too young to consent, then the same arguments show that the *lack* of circumcision is likewise culturally significant. To promote circumcision is to attack a cultural precept. If it is wrong to attack a cultural precept that endorses circumcision, it is just as wrong to attack one that rejects it.

Finally, the underlying assumption of the campaign is that educational approaches cannot be effective. While it is true that sex education campaigns are not especially successful in this regard, many studies have shown a strong inverse correlation between female education level and HIV infection risk. The program of circumcising African men suggests a set of assumptions about the potential for influencing coupling patterns in the region, both in relation to male sexual behavior and female empowerment. These assumptions are not warranted.

The root cause of these objections is that Case 2, the circumcision campaign, arises in a fundamentally different way from Case 1, the Tenovir case. Fundamentally, Case 2 is a matter of identifying a measure that is thought to be effective in reducing HIV infection, by interfering with the relevant pathomechanisms, and then seeking to roll it out. Case 1 was fundamentally a matter of seeking to understand the illness

causation of HIV infection in a particular group, and then identifying a measure that would prevent it within the existing socio-cultural context. If Abdool Karim had adopted the approach of circumcision activists, she would have stopped with daily anti-retroviral pills, and launched a campaign to promote their use. The excellence of her approach is that she did not do this, but instead identified an intervention that fitted within the existing social context, without necessitating a behavior that was in tension with it. It was an *empowering* intervention in that it *increased* choice, while circumcision obviously does not change any decision space. The latter is also not reversible, while the use of Tenovir may easily be discontinued. And empirically it is far better grounded; that is, we have quality evidence supporting both its efficacy and effectiveness.

## 23.5 Conclusion

In this article we have focused on HIV, but these principles generalize. The WHO response of 'washing hands' and 'social distancing' to the 2020 COVID-19 pandemic is a prime example of how illness causation explanations are used. We understand (roughly) how the disease spreads (the illness causation), and thus know that staying away from others and washing one's hands will slow morbidity rates. The global implementation of these measures in 2020 will unquestionably prevent millions of COVID-19 deaths. However, we also know that not all countries and/or regions are the same. Social distancing in an African township or Indian slum is significantly more challenging than in wealthy suburbs, and this must be fully considered when forming public health policy—all too often a "one-size-fits-all approach" is employed, and this can be deadly (Broadbent and Smart 2020). Social distancing measures that are effective in a wealthy British suburb may not be effective in a rural South African township. The more detailed and specific one's understanding of a disease's illness causation, the better tailored-to-circumstance preventative public health advice can be, and the more effective it will prove.

### *23.5.1 Holistic Explanations*

There is a simple difference between the Tenovir and circumcision cases. In the Tenovir case, the researchers sought a measure that was grounded in knowledge of social context as well as pathogenesis. This resulted in a measure whose use is warranted by an explanation that is *holistic*, in the sense that it considers every relevant factor, regardless of type. By contrast, male circumcision promotion is grounded in pathogenetic knowledge, deriving from biological evidence and evidence from trials, which yield idealized circumstances (although in these particular trials, the circumstances are not ideal, as we have argued). The resulting method is not warranted by a holistic explanation since there is no consideration of the various social factors that

may interact with, affect, or be affected by circumcision. Given this lack of evidential warrant, the serious ethical problems identified in relation to circumcision become very pressing. Thus, the presence of a holistic explanation of the way in which a proposed public health measure is meant to work is not merely "nice to have". It can make the difference not only between success and failure, but also between moral right and wrong.

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# Chapter 24
# Shaking off the Linear Regulatory Constraints on Human Health


**Jaap C. Hanekamp and Edward J. Calabrese**

**Abstract** Humans are exposed to a plethora of chemicals each day. As governments across the globe heavily invest into the regulation of chemicals, we need to consider if the right choices are made, how these are made, and what our scientific understanding is telling us now. Regulating chemical exposure requires a feasible perspective on the effects of exposure and how to measure those. The orthodox regulatory perspective incorporates a linear non-threshold (LNT) model to estimate risks for especially carcinogenic compounds. This model fails to appreciate the biphasic nature of chemical dose–response relationships and as a result neglects the limited intervention possibilities posed by the default finality of resources. We want to challenge this regulatory perspective, both theoretically and empirically. This chapter proposes a new perspective that is innovative in terms of insights into risks, health, and safety in our inevitable and invaluable exposure to chemicals.

**Keywords** Chemicals · Human health · Toxicology · Dose–response models · Regulation · Cost-induced fatalities · Value of statistical life · Precaution

## 24.1 Bridging the Natural-Synthetic Divide–A Prolegomenon

Regulation of chemicals contains a certain perspective on the understanding of effects of exposure and how to gauge them, both through experimental data and theoretical deliberations (models). We want to challenge the orthodox regulatory perspective, both theoretically and empirically, and build up a new perspective that is innovative

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in terms of insights into risks, health, and safety in our inevitable *and* invaluable exposure to 'chemicals'.

The way humans are exposed to the wealth of chemicals is mostly through the diet that varies widely across countries and continents. Just to give an idea of how much food is consumed: an individual eats, during his or her lifetime, on average, some 30 tons of food. That food consists of many thousands of different chemicals: macronutrients (fats, protein, carbohydrates), micronutrients (vitamins, minerals), non-nutrients including anti-nutrients[1] and natural toxins, anti-oxidants, man-made contaminants such as antibiotics and pesticides, but also chemical pollutants such as dioxins and PCBs, and additives such as preservatives and colouring agents. This immense smorgasbord of chemicals that make up our food impacts our health in many different ways.

The question then immediately arises as to how to assess and manage this diverse chemical world to which we are to a large degree unwittingly but also willingly exposed. Cramer et al., already in 1978 sum up this 'circle of frustration' and societies' call for ever-increasing safety as follows (p. 255):

> Toxicology … bears a double burden. We demand ever greater safety in an environment that many people fear – not necessarily correctly – is increasingly hazardous. At the same time, the notably rapid advance of analytical chemistry has continued to alert us to the presence of previously unsuspected toxicants and to a host of substances we have not yet begun to evaluate. It is clear even to a casual observer that the sensitivity and precision of analytical chemistry are far ahead of toxicology. Even less happily, toxicologists find it far easier to produce an adverse effect in laboratory animals than to interpret with assurance the meaning of such an effect for human safety.
>
> Our response to this situation has customarily been simply to demand more testing on virtually every substance that has recently been evaluated. No one denies that we would be better off with more data. Our universal problem has been that the demand for data has grown faster than the supply. …

Our quest is to define human health from a public perspective using the latest scientific knowledge available. As governments across the globe heavily invest into the control of 'chemicals', we need to consider if the right choices are made, how these are made, and what our scientific understanding is telling us now.

Put differently, there are essentially two ways in which regulatory efforts can interfere—either positively or negatively—with the protection and improvement of human health. Firstly, regulatory sciences can use models that either capture the dose–response continuum more or less accurately *or* (much) less so. Secondly, regulatory efforts controlling chemicals exposure, rooted in the first principle, can be cost-effective *or* (much) less so, the latter potentially even inducing cost-induced fatalities when wide off the mark. We will try to fathom both below.

[1] Anti–nutrients are food components that induce toxic effects by causing nutritional deficiencies by interference with the functioning and utilisation of nutrients. Examples are lectins, phytic acid, and oxalic acid.

## 24.2 Human Health

Before we can say how and why regulation and models can interfere with human health, defining what health is, is essential. The classical WHO definition of health, as found in the Constitution of the organization (1946), is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." This definition seems woefully wide off the mark, as it is idealistic and in fact impossible to implement. That is, it imagines human beings in some sort of stasis of healthy bliss. And that makes very little sense in the dynamic world we live in. That fact alone implies change, and change implies adaptation. The latter—adaptation—is the principle driver of life's evolutionary processes.

Considering the many different conditions humans live and thrive under, health is better described in terms of *the ability to adapt* (see Canguilhem 1991). The multitude of effects generated by food alone explicitly reveals that ability to adapt (Bast and Hanekamp 2013).

## 24.3 Toxicological Models

When confronted with what seems like overwhelming complexity, scientists and regulatory agencies have a tendency towards simplification, which has become a standard procedure in science. Understanding reality in the fullness of its complexity is (almost always) impossible. The subsequent precision, or lack thereof, obtained from this common and necessary procedure is conditional on the evidence gained and the applicability thereof in its translation into regulatory standards.

In order for regulatory standards to be at least *effective* and *efficient*, the *quality* of the scientifically gained evidence must be *objective* (*reliable*), *have utility* as in being *adequate* and *relevant, and be robust*. Here, we understand *objectivity* as rational; that is the state of having accurate epistemic access to the thing itself. This entails that if one has rational objectivity regarding some topic, then one can discern the difference between genuinely good and bad reasons/evidence for a belief about that topic and one can hold the belief for genuinely good reasons/evidence. Operationalised, (standardized) methodology of experimental procedures are transparently reported that subsequently give evidence of the precision and plausibility of the findings. The term *utility* seems straightforward enough as to the focus of the research done and evidence gained being suited, adequate and relevant, for the purpose of regulatory standardisation. *Robustness* indicates data to be encompassing enough to do the regulatory job properly.

Now, in order to apply, in terms of regulation, scientific knowledge gained from toxicological research, models need to be in place that can effectively translate the latter into the former. Thus, the question whether toxicological models successfully *capture reality* in terms of exposure-levels,—duration, and, most importantly,—effects is quite an important one. The inevitable reductionist aspects of modelling

come into view here. These models are typically used to fill gaps where data is limited or even non-existent. For example, we might have evidence about the health effects in rodents (mice, rats) that were exposed to (very) high doses of a chemical, but if we want to know what happens to humans at much lower exposure levels, there might not be much information available, for both practical and ethical reasons.

In toxicology, reductionism would approximately reason as follows: a complex system (whole organism) is nothing but the sum of its parts (e.g. metabolic pathways) whereby a toxicological effect, induced by some compound at a certain concentration over a certain amount of time experimentally expressed in vitro or in vivo, is a sufficient indicator for the whole of the target-organism, e.g. human beings. This reasoning in all its technical intricacies—e.g. the applied reductionism is multi-facetted as not only metabolic pathways function as a marker for the whole, but also one organism is regarded to stand as a model for another—has tremendous societal importance. Although this kind of conceptual reductionism is well known for its success in physics—the use of the kinetic theory of gases to accurately reduce the concept of temperature, whereby the thermodynamics of bulk matter is reduced to the average kinetic energy of the molecules of the gas—its limits are also evident. Individual water molecules, for instance, do not possess the property of what we as humans experience as 'wetness'. This is a conceptually irreducible aspect of the behaviour of a multitude of water molecules, which together generate inter-molecular forces that are the source of the bulk property called surface tension.

Obviously, this is not the whole story. The European REACH regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals), for instance, requires that on tens of thousands of industrially produced chemical compounds, biological, chemical, physical, and toxicological data need to be gathered and reported as a means to protect human health and the environment. The precursory 'Strategy for a future Chemicals Policy' whitepaper of the European Commission in 2001 even posited the "protection of human health and promotion of a non-toxic environment" as one of the key elements of REACH. By implication, the toxicological models "need" to be precautionary so as to translate scientific data into a regulatory context that is ostensibly protective for the general public. Hazard, instead of risk, plays a key role here.

Real-life exposures are usually the result of acute or routine exposures that are either unavoidable because of a natural (ecological) presence of chemicals or the result of human activities. The extrapolative strength of existing toxicological data, which, again, are usually derived from high-dose exposures to rodents, is assumed without much discussion despite the fact that there are 'too many rodent carcinogens' (Ames and Gold 1990a). Not to mention the current developments in the field of epigenetics we cannot discuss here in any detail, or indeed the increasingly important dose–response findings, which we can best define as biphasic (model C; see Fig. 24.1).

Traditionally, there have been two dose-response models that have dominated the field of regulatory toxicology: the threshold dose-response model (B) that is applied to non-carcinogen endpoints and the linear non-threshold (LNT) model (A) that is used to estimate cancer risks (Fig. 24.1). These models were first developed for

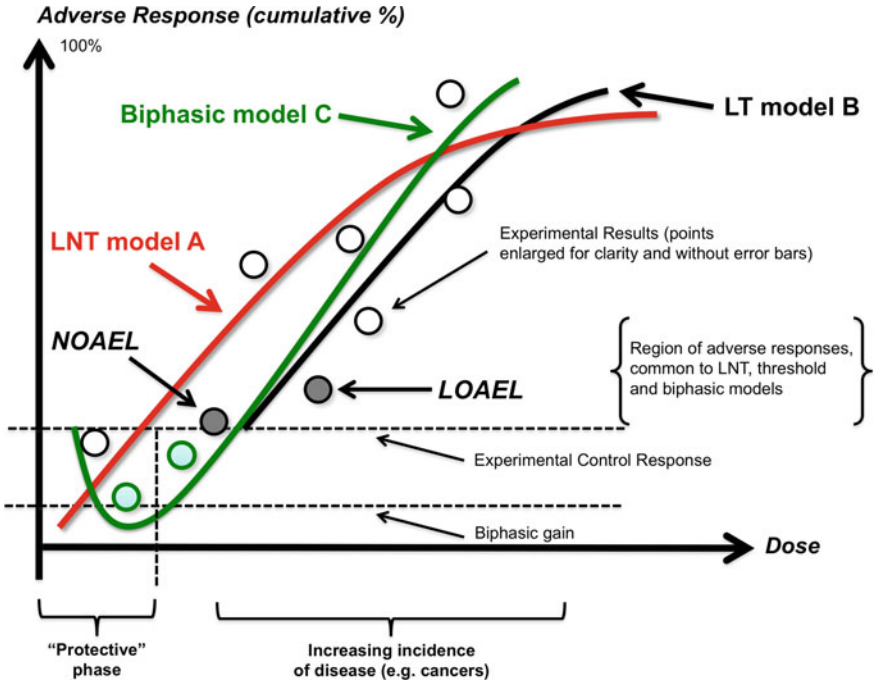


**Fig. 24.1** Three toxicological models

possible regulatory use during the 1920s, especially with respect to the emerging concerns to protect workers from chemical and radiation hazards. The dominating threshold dose-response model was challenged during the 1940s by members of the radiation geneticist community who believed that there was no safe level of exposure to ionizing radiation-induced mutations. This view would eventually become accepted by the regulatory community and was applied to the process of carcinogenesis for assessing cancer risks from ionizing radiation and chemicals deemed to be carcinogenic.

The U.S. Environmental Protection Agency (US EPA) adopted low-dose linearity for cancer risk assessment during the mid-1970s with its first application to the regulation of total trihalomethanes resulting principally from the chlorination of surface drinking water in 1979, using the multi-stage cancer risk assessment model which was also linear at low dose.

Over the subsequent decades and to the present time, cancer risk assessment has been the dominant issue within the environmental regulatory community. Cancer risk assessment has been especially challenging since the levels of acceptable risk (e.g. <1/100,000/1,000,000 (the latter being called the MTR-level—Maximum Tolerable Risk) over a >70–80-year lifetime) cannot be practically validated and implementing regulations usually has major societal and financial costs.

In all this, one should keep in mind that "low dose behavior of any agent acting on any medical end point can only be indirectly derived and is to that extent an unproven assumption not a fact." (Heitzmann and Wilson 1997). In fact, empirically showing that the LNT model would entail that 2 "carcinogenic" molecules induce twice the amount of genetic harm compared to one molecule seems impossible. No experiment would actually be feasible to *causally* connect the perturbation of some part of the DNA by one molecule that subsequently would develop, over the organism's lifetime, into some disorder such as cancer. Also, considering the second law of thermodynamics, each individual interaction between molecules does *not* produce a chemical reaction and, therefore, a biological effect (see Koch 1983). Molecules must have a minimum activation energy to react with receptor molecules. So, only a percentage of the total amount of molecules present in an organism has the required activation energy to react. Obviously, for a reaction to occur at all, the molecules must collide with the receptor molecules. But, not any collision will do: the molecules must have the proper orientation to react. To make matters even more complicated, in view of the fact that chemical damage can induce (cellular) protection, using models like the LNT would not represent potential damage done; quite the contrary.

Since the adoption of the LNT model for cancer risk assessment, scientific discoveries/developments that have emerged involving the recognition that essentially all somatic cells can repair DNA mutations efficiently and have a plethora of other adaptive mechanisms than can affect the process of carcinogenesis. These developments suggest that the assumption of low-dose linearity leads to significant over-estimates of actual cancer risks (Goldman 1996).

Indeed, as the experimental dose of a chemical is increased, different saturable or inducible toxicokinetic (e.g., metabolism, uptake, excretion) and toxicodynamic (e.g., homeostasis, receptor interactions, protein binding, repair mechanisms) processes involved in chemical toxicity (e.g., tumorigenicity) can be involved, which may not be engaged at environmental exposures. It seems that the high doses used *were triggering different mechanisms* which lead to the development of neoplasms in laboratory animals. *Determining which mechanisms are operative along the dose–response curve has important implications for interpreting bioassay data for the purposes of predicting human risk* (Boobis et al. 2016; italics added; see further Calabrese 2018).

Those different mechanisms at low-dose exposure, roughly defined as damage as the instigator of cellular repair and subsequent protection, is on sound empirical footing nowadays. This is depicted in Model C (Fig. 24.1) as already mentioned briefly above: the biphasic/hormetic dose-response model. The fundamental conceptual facets of hormesis are respectively: (1) the disruption of homeostasis; (2) the moderate overcompensation; (3) the re-establishment of homeostasis; (4) the adaptive nature of the overall process (see e.g. Bast and Hanekamp 2017; Calabrese and Baldwin 2003; Calabrese 2011; Kaiser 2003).

Hormesis is defined in a continuum of the dose–response curve. There are low-dose effects and high-dose effects of exposed organisms. Low doses could be stimulatory or inhibitory, in either case prompting living organisms to be dissociated from

the homeostatic equilibrium that in turn leads to (over)compensation. For example, heavy metals such as mercury prompt synthesis of enzymes called metallothioneins that remove toxic metals from circulation and probably also protect cells against potentially DNA-damaging free radicals produced through normal metabolism. Conversely, low doses of anti-tumor agents commonly enhance the proliferation of the human tumour cells in a manner that is fully consistent with the hormetic dose–response relationship.

High doses push the organism beyond the limits of kinetic (distribution, biotransformation, or excretion) or dynamic (adaptation, repair, or reversibility) recovery. This is the classical toxicological object of research usually required as a result of public and regulatory concerns, whereby hormetic responses are by default regarded as irrelevant, or even contrary to policy interests, and therefore remain overlooked. Public concern about synthetic chemicals exposure seems to infuse public reluctance to view hormesis as a viable empirical description of toxicological reality. Policymakers, similarly, are eager to address this concern and see no room for exploring hormesis and the possibilities of regulatory implementation.

Nevertheless, many researchers have found, for instance, that there is a decrease in tumour rates at some sites when rodents are exposed to some chemicals (Gray et al. 2002). This makes perfect sense to view chemical 'insults', up to a certain exposure, as additive to the overall adaptive capabilities as a central feature of health. This is for instance made clear in the study by Ina and Sakai (2004), who found that chronic low-dose-rate $\gamma$-irradiation at 0.35 or 1.2 mGy/h prolonged the life span of mice carrying a deletion in the apoptosis-regulating Fas gene that markedly shortens life due to a severe autoimmune disease. Obviously, much more research is needed to elucidate the hormetic aspects of adaptive responses to chemical or electromagnetic perturbations.

## 24.4 Safety Standards

Standards of safety are borne out of the models used and the assessment (uncertainty) factors applied. Assessment factors (AF) are numbers reflecting the estimated degree of uncertainty when experimental data from model systems (e.g. animal testing or tests done with cells) are extrapolated via some model to humans. These AFs usually lie in the range of 10–10,000. The conceptual basis for the application of AFs is that chemical toxicity usually follows a predictable pattern with increasing dose: from no significant or measurable effects, to minimal effects (not necessarily adverse) within the range of biological compensation, to clearly toxic effects, and finally to overt disease and/or death. The use of AFs is predicated on the assumption that sufficiently reducing exposure from levels known to be toxic will yield an exposure level that is safe for at least the great majority of the exposed population, including vulnerable subgroups (Dankovic et al. 2015). Obviously, in view of the biphasic dose-response model we discussed above (model C), AFs might work counterproductively (see further Calabrese et al. 2016).

An important uncertainty we already discussed above, which is the dose used in experiments and the extrapolative potential of found results. Uncertainties also lie in exposure routes. Humans are usually exposed through the inhalation, oral and dermal routes. Animals can be exposed via other routes as well such as injections or implanted minipumps. That might make animal results not directly applicable to the human situation.

Other uncertainties are the result of interspecies differences in biological responses to chemical exposures. These include differences in, for example, physiology, genotype, phenotype and metabolism, making it difficult to carry over the results obtained in one species to another species. The central issue is to what extent in vivo and in vitro models are predictive of human responses to a chemical exposure. Although the predictive value of animal models is limited (see e.g. Bracken 2008; Shanks et al. 2009), it is often assumed that results from animal models are *prima facia* extrapolative to humans. This assumption is not always valid, for instance if human physiology and disease formation are not adequately represented by animal models. Nevertheless, results that are consistently reproduced in different species using different methodologies might be regarded as indicative of the human situation (Ioannidis 2012).

In vitro models have their own limitations generating uncertainties, such as: (i) they are artificial and non-physiological as they lack total organism integration; (ii) the number of cells used is in general <1% of the cells found in actual tissue whereby intracellular signalling is impaired; (iii) usually only one cell type is used, it is often monoclonal in origin and is further degenerated during maintenance culture, and lacks cell–cell interactions; (iv) when primary cells are used, preparations require animal or human tissue, introducing variability between different cell preparations; (v) culture conditions are not homeostatic because of the sudden exchange of media, continuous depletion of nutrients, and accumulation of waste products; and (vi) dissolved oxygen is consumed during the first hours of an experiment following which oxygen is available to the cells only through diffusion from the surrounding atmosphere into the solution, potentially resulting in anaerobic culture conditions (Anadón et al. 2014). Also, the availability of the tested chemical to the exposed cells is immediate and continuous for the duration of the experiment, and this exposure inherently circumvents the usual physiological processes of absorption, distribution and excretion.

With these uncertainties being part and parcel of toxicology, threshold model B (see Fig. 24.1) proceeds to identify a no adverse effect level (NOEL) or lowest observed effect level (LOEL) derived via statistical evaluation of the hazard assessment data (see above). These terms became more refined when the "effect" identified is seen as adverse or not (i.e., NOAEL and LOAEL). The NOAEL has been defined as the highest dose that does not differ from the control group in a statistically significant manner. The LOAEL is the lowest dose that differs from the control in a statistically significant manner. The LOAEL/NOAEL scheme has been applied in establishing a reference dose (RfD) concentration value, acceptable/tolerable dietary intake (A/TDI) and occupational exposure limits (OEL) as well as threshold limit values (TLVs). These various approaches typically identify the most sensitive

endpoint in the key study and use it as a point of departure (POD) when applying various AFs based on interspecies and inter-individual variation.

The use of the NOAEL/LOAEL has been criticized since they are very dependent on dose selection, sample size, and statistical significance. Since the key factor in their determination relies on a single dose (e.g., NOAEL), it does not explicitly make use of the entire dose–response relationship and its potential for biomathematical extrapolation to lower doses. Based on these limitations, a benchmark dose (BMD) was proposed over three decades ago to provide an alternative to the NOAEL/LOAEL method. While its acceptance has been slow, there has been a growing interest in the BMD approach in the U.S. and Europe.

The BMD is defined as a dose of an agent that induces a specific quantitative benchmark response (BMR). This is a response that typically exceeds the control response by only 1–10% (n% in Fig. 24.2). Thus, the modest increase over control values tends to approximate the NOAEL in many, if not most situations, although notable differences could occur in unique situations.

Operationally, the benchmark lower limit (BMDL) attempts to increase the confidence of the estimate by taking into account the variability of the data, the bars across the dots representing the data points. The BMDL typically uses the lower bound of a 95% confidence interval on the benchmark dose (the left dotted line next to dose–response curve). The BMDU is the upper BMD at the 95% confidence interval on the benchmark dose. The use of the lower bound dose is a subjective judgement to affect a more conservative or lower acceptable exposure estimate. The use of a 1–10% response for the BMD was decided since most biostatistical models do not

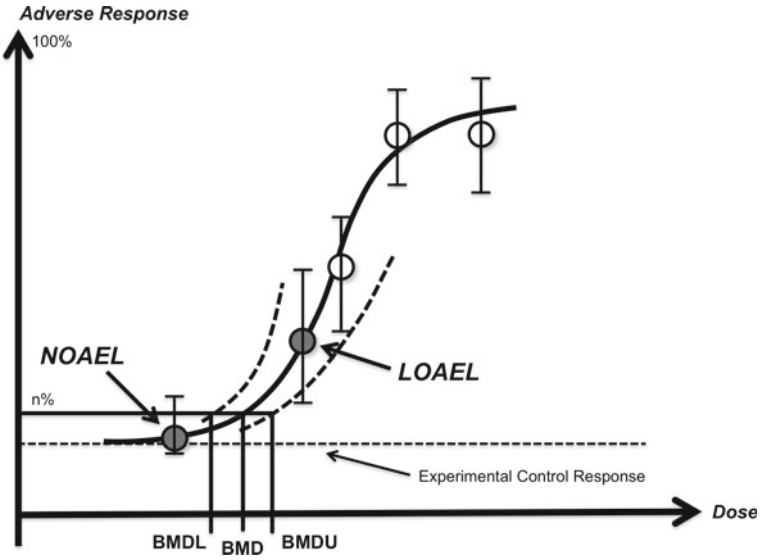


**Fig. 24.2** Benchmark dose, NOAELs and LOAELs

display marked differences with this estimate in this part of the response zone. Thus, model selection to estimate the BMDL is not a controversial decision.

In general, the BMD(L) approach offers an advance over the NOAEL/LOAEL approach by using all the data, but its quantitative significance is usually of a limited nature. Despite the appearance of improved risk assessment procedures, the overwhelming issues in the risk assessment process are the uncertainties in extrapolating from cells (in vitro), animals (in vivo) to humans and how the concept of inter-individual variability is addressed. The higher the AF, the lower the TDIs, ostensibly expressing a more cautious approach to the studied chemical. This we already touched on above.

The TDI is the daily intake of a chemical that, during the entire lifetime, appears to be without appreciable risk on the basis of all known facts at the time. Lower TDIs articulate the axiom that more people are protected. But, as Aldy and Kip Viscusi (2014) remark:

> Because government regulators often assumed that regulation could make lives risk-free, a frequent starting point for risk assessments is to determine risk at the no-observed-effect levels (NOELs) and the no-observed-adverse-effect levels (NOAELs) of exposure to chemicals, where these levels are based on short-term, acute animal studies. To extrapolate these NOEL and NOAEL results to humans and to ensure a reasonable certainty of no harm, analysts then assumed that the safe exposure level for humans required that the threshold animal risk exposure levels had to be divided by 100. This factor is based on the unsupported assumption that people are 10 times as sensitive to risks as animals and that the heterogeneity in susceptibility to risk across the population may differ by a factor of 10. Conservative assumptions such as these will tend to systematically bias risk estimates upwards.

For those chemicals that are defined as genotoxically carcinogenic—compounds that interact with the hereditary material such as DNA—no safe limits are thought to exist. These chemicals are thought to be detrimentally operative on organisms at any dose level, except zero. So, even one molecule of such chemicals is thought to be able to cause disease over a certain period of time. As a result, no safety thresholds can be determined for such chemicals. Here, the LNT model functions (see above).

The fact that such safety thresholds cannot be determined is not a result of the intrinsic hazards of the genotoxic carcinogens per se but a result of the chosen toxicological model. What is clear is that the effects of chemical substances on humans is affected by many factors, including genetics, age, gender, diet, health status, circadian rhythms, gut microflora, stress, exercise, and various types of adaptive and reparative functions. This range of complexity affecting responses to toxic substances is quite daunting.

Given such biological complexities, it suggests that precise estimates of likely population-based responses, are not realistically possible, and should be viewed with considerable skepticism; a perspective that is consistent with the known limits of epidemiology. Thus, organisms (including us) emphatically are not passive recipients of chemicals from multiple sources. As we remarked earlier, *ability to adapt* is the key element of health. Indeed, the unequivocal corollary of the linear approach in toxicology is that any chemical/drug/food-endogenous compound seems to be able to exert *only one* effect that increases with the dose. *Linearity thus imposes its order*

*on the understanding of chemical compounds as either 'good' or 'bad'* a priori. Moreover, from linearity it is deduced that the one must exclude the other. And both can only be described as 'graded' depending on dose. *And that of course is illogical.* Micronutrients are a case in point here: *both* deficiency and toxicity are known for these chemicals depending on the dose given and the individual's physiology (Hanekamp and Bast 2008).

## 24.5 The Social-Economic Impacts of Regulation

Any policy in the field of chemicals should be considered in the bigger picture of benefits and costs, risks and benefits, and risks versus risks. That of course makes for intricate subject matter we cannot address here in full, but is nevertheless essential as chemicals bring forth a wealth of possibilities that any society could not do without. Indeed, since antiquity, and even before that time, chemicals have played a crucial role in societies, which shows a human drive towards harnessing the "molecular world" to our needs and desires.

Any potential risk and cost involved in the introduction of chemicals and its processes in society are, in a way, derivative of its benefits. It is not implied that these risks and costs mostly are trivial or otherwise diminutive; far from it. Yet, in order to understand the value of chemicals and chemical technology, the benefits thereof shape the context of the costs and risks. Without the benefits held in view, chemical production seems, or rather is, asinine.

Costs of chemicals come in many forms. Costs of development, production, and distribution could be regarded as internal. Market demands and development, production capacity and capabilities drive the chemicals market as any other market. The costs of importance here are external costs: environmental and public health.

That being said, as Keeney (1995) astutely observes: "Everyone must eventually die. Hence, if one type of risk is reduced, other risks increase though the timing and cause of one's eventual death are likely to change. For instance, seat belts have reduced the risk of dying in an automobile accident. As a result, for those who wear seat belts, individual risks of dying from cancer or heart disease have increased. *This fact in no way suggests that an individual or society should not manage life-threatening risks.* Most of us would probably rather die of "natural causes" when we are ninety years old than of an automobile accident a year from now. The point is that our life is not saved, it is prolonged. Thus, *when we speak of reducing risk, we mean reducing risks from particular causes, which in turn increases risks from other causes further in the future.*" Obviously, the risks discussed here are of a chemical nature, yet, as Keeney shows, once we try to tackle those risks through regulation, *the nature of risk changes beyond its initial (chemical) boundaries.* With those changes, the socio-economics of the invention/discovery, production, dissemination and societal uses of chemicals change as well.

One way to gauge the overall effectiveness of regulation is through cost calculations of life-saving interventions. This is especially interesting for chemical regulation, as chemicals can impact the health and safety of individuals either through direct exposure (during production and/or use) or indirectly through the environment. The latter route can be diverse as chemicals disrupting ecological services (e.g. food-production) but also as a transporter and modifier of chemicals to which individuals can be exposed. Tengs et al. (1995) proposed their life-saving interventions cost calculations that give some expression of social-economic consequences of regulation. Life-saving interventions were defined by Tengs et al. as reducing the probability of premature death among a specified target population by any behavioural and/or technological strategy. The reported findings of available cost-effectiveness data revealed that there is huge variation in the cost of saving one year of life. The authors added that where "there are investment inequalities, more lives could be saved by shifting resources."

There is a concomitant aspect that is related to regulatory expenditures: cost-induced fatalities. The first empirical estimate that explicitly attempted to calculate income loss that would lead to one statistical death was that of Keeney (1990). He used existing empirical data on the relationship of mortality rates to income and found that the income loss per statistical death was 12.5 million US dollars (in 1992). His study led to legal analyses of government regulations that includes the principle that expenditures could be counterproductive in terms of public health (see e.g. Williams 1993). Empirical estimates of the so-called value of statistical life (VSL) have produced a substantial literature base.

Early on, criticism on this approach was voiced. Much of the criticism of the initial policy suggestions regarding the adoption of the risk–risk approach arose from the uncertainties pertaining to empirical estimates of the mortality risk-income relationship. These uncertainties in valuation are not unique to risk–risk analysis. Other components of the benefits and costs that comprise the typical regulatory analyses are often not known with precision.

Equally, dose–response relationships in toxicology that form the basis of most risk assessments are typically not well understood, but few critics have suggested risk assessments be disregarded altogether until all scientific uncertainties are resolved. By their very nature, policies to reduce risk involve inherent uncertainties, and the task for policymakers is to adopt those policies that will yield the greatest *expected* net benefits to society (Viscusi 1994). Nowadays, value of risks to life as assessed by the risk-money trade-off plays, or should play, an important role in economic analyses of health and safety risks. The value of statistical life emphasizes the probabilistic aspect of the valuation, making it distinct from the amount we are willing to pay to save identified lives (see further Machina and Kip Viscusi 2014).

Also, on an individual level, "richer is safer" (see Wildavsky 1980, 1988); economic costs of risk-reduction policies can induce significant risks on the personal level. Public funds to implement risk-reduction policies, including policies 'paid for' by governments, must come from individuals. This leaves individuals with less money to spend on other daily needs, including personal behaviours and actions to reduce risk (see e.g. Graham et al. 1992; Gerdtham and Johannesson 2002).

For instance, that an occupation and the attendant income creates the greatest health benefit is the fundamental reality chemical regulation, or any other regulation for that matter, could impinge on. In the Dutch statistics database of the Central Agency for Statistics (CBS), for example, it is shown for the years 2011–2014 that the healthy lifespan difference between the lowest and highest income classes for men is some 14 years. For women this is some 15 years. Regulation at some level usually modifies the social-economic circumstances of people. Chemical regulation that focusses on human and environmental health should, firstly, take social stratification and its impact on healthy lifespan into account. That entails that any chemical regulation should clearly define the social-economic consequences of the industries affected. Keeney gave the impetus to a new kind of approach that takes into account regulation and its effects on public health. In this context, regulations (regulatory or secondary laws) are a form of novel (procedural) technology.[2] And this new technology has the potential to create its own health benefits and risks.

Now, cost calculations of life-saving interventions and cost-induced fatalities analyses seem perhaps easier said than done. The complexity and costs involved are far from trivial, and their results are far from certain. Furthermore, the decision-value of the gathered data is not straightforwardly clear. Within REACH, for instance, a huge volume of information through the registration dossiers is collected, but the database is so massive that much of it may never be fully assessed. A first-hand experience of one of the authors in actually composing dossiers for some 60 chemicals to be registered with the European Chemicals Agency (ECHA) gives a sense of the sheer size of the required data compiling. It very well might reduce the REACH registration procedure as nothing other than a system of "data collection and warehousing" rather than a "procedure for protecting the public and the environment from exposures to hazardous substances" (Abelkop et al. 2012).

Also, data-warehousing as done within REACH does not alleviate the problems of false-positive (Type I) and false-negative (Type II) errors. False-positive errors are of concern because both government and industry will waste resources evaluating a chemical that does not pose a health or ecological risk at the relevant production- and exposure-levels. A false-negative error occurs when a chemical is classified as low priority when it should be classified as high priority, or determined to not pose a risk when it should be classified otherwise at the relevant production- and exposure-levels. Usually, false-negatives are regarded as far more serious, as Page (1978) remarked:

> When a regulator makes a decision under uncertainty, there are two possible types of error. The regulator can overregulate a risk [false positive, authors] that turns out to be insignificant or the regulator can underregulate a risk [false negative, authors] that turns out to be significant. If the regulator erroneously underregulates, the burden of this mistake falls on those

[2]It was named social or legal engineering by Roscoe Pound early in the twentieth century. Nathan Roscoe Pound (1870–1964) was a distinguished American legal scholar and educator. He developed the idea of 'sociological jurisprudence' and is considered one of the founders of American 'legal realism'. In his well-known *Interpretations of Legal History* (Cambridge: Cambridge University Press 1923) he remarks that jurisprudence might be considered as a science of social engineering, the ordering of human relations through the action of politically organized society.

> individuals who are injured or killed, and their families. If a regulator erroneously overregulates, the burden of this mistake falls on the regulated industry, which will pay for regulation that is not needed. This result, however, is fairer than setting the burden of uncertainty about a risk on potential victims.

Whether Page, and others with him, are correct is far from clear, as the work of Keeney, Viscusi and others show. Page sees the Type 1–Type 2 dichotomy through a too narrow viewscreen, disregarding societal losses through regulation. Vogel (2012) suggests that since 1990 US risk policy has become increasingly concerned with false positive errors while the EU faced a number of much publicized purported health threats and became more concerned with the false negative error. Of course, the correct policy posture would be to account for both errors and to minimize social costs, *provided* that cause-effect models (basically the Type III error) is properly considered. These points must simultaneously be taken into consideration: type I and II errors are sampling (data) related, whereas type III is about fundamental causation. This simple fact seems to escape the regulatory debates and is not taken into consideration by those who advocate—as opposed to scientifically justify—the choice of a linear, no threshold model for cancer and chemicals exposure, or even a threshold model, as discussed previously, when the evidence is that the effects are either J-shaped (for cancer) of inverse J-shaped for toxic responses (see e.g. Ricci et al. 2012).

## 24.6 Risks, and Risks Versus Risks

Socio-economics are the overarching tradeoffs between chemical regulation and societal costs and benefits. Two aspects were touched on: cost calculations of life-saving interventions and cost-induced fatalities analyses. Here, we will look into more detail what chemical regulation spawns in the chemical field itself. Graham and Wiener, in their 1995-book *Risk versus Risk Tradeoffs in Protecting Health and the Environment*, define a 'risk tradeoff' as the change in the portfolio of risks that occurs when a countervailing risk is generated (knowingly or inadvertently) by an intervention to reduce the target risk (p. vii):

> Whatever we do, we are likely to encounter risks. A short drive to the grocery store brings dangers, however small. So too with a decision to ride a bicycle or to walk instead. So too with a decision to stay at home. If you play tennis to improve your health, you may endanger your health instead. Whenever you reduce or eliminate one risk, you may simultaneously increase or create another. If this is not so troubling, it is because most of the time the risks we face are, or seem, blessedly low. But sometimes each of us must make judgments about how to avoid significant risks, or how to minimize overall risk, when a genuine danger is unavoidable.

As a simple hypothetical example of a tradeoff in the chemical field, banning cancer-causing chemicals subsequently boosts the use of chemicals that are less carcinogenic but which pose greater neurotoxic and reproductive effects. Obviously, such a risk tradeoff would not be welcomed by regulators, politicians and civilians

alike. Nevertheless, it is not always clear how such a tradeoff can be avoided. Indeed, accumulated knowledge of 'old' chemicals stands in contrast to a lack of such knowledge of new chemicals, which ostensibly should be safer. But the latter cannot be simply assumed without the toxicological knowledge gained. Indeed, the intention of REACH, as described in preamble (71) is to "support the aim of eventual replacement of substances of very high concern by suitable alternative substances or technologies, all applicants for authorisation should provide an analysis of alternatives considering their risks and the technical and economic feasibility of substitution, including information on any research and development the applicant is undertaking or intends to undertake. …".

So, chemical risks cannot be regarded in isolation, unless of course chemicals of (very high) concern (SVHC), here understood within the context of the REACH regulation, need to be banned regardless of available replacement chemicals. Note that SVHCs may be subjected to the REACH authorization regime based solely on hazard; within this REACH-framework knowledge on actual exposure and risks is not required. REACH only provides some prioritization criteria to guide the decision in Article 57, such as PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) properties, wide dispersive use and high volumes. Since the authorization programme is unselective with respect to chemical uses in the SVHC-listing procedure, is not risk-based and imposes high administrative cost, it is not necessarily the most appropriate measure for regulating any particular SVHC (Bergkamp and Herbatschek 2014). For instance, if no suitable substitutes are likely to exist in the near future, authorization is unlikely to result in actual substitution. Such a move would create its own (tradeoff) risks, albeit of a different nature. Even worse, where the available substitutes are more harmful than the substance subject to authorization, or that knowledge on risks of the substitutes is very limited, the environment and human health may well be positively harmed. Thus, there is no real substitute for (toxicological) knowledge.

As an example of tradeoffs of the chemical kind we are confronted with every day, let's consider natural and man-made pesticides. Ames et al. remarked already some decades ago (Ames et al. 1990b) that the pesticides in our diet are 99.99% natural. Plants produce an enormous variety of toxins to protect themselves against fungi, insects, and animal predation. These natural pesticides in plants are present in very much greater variety and at levels thousands of times higher than synthetic pesticides. It is estimated that we eat roughly 1500 mg of natural pesticides per person per day, which is about 10,000 times more than we eat of synthetic pesticide residues. Synthetic pesticide consumption is estimated at 0.09 mg per person per day (Ames et al. 1990b).

Over centuries we have been able to improve plants in such a way that the toxins present in plants were reduced, thus making them more suitable for human consumption. Examples of natural pesticides in foods are, however, still easily given. The most discussed agricultural crop family is the *Solanaceae*, or nightshades, which includes the potato, tomato, and eggplant (aubergine). These crop plants synthesize several so-called alkaloids such as chaconine and solanine found in the potato and giving it a bitter taste especially when green. These and other alkaloids possess powerful

insecticidal and fungicidal properties, although some insect species have adapted. And, these potato-chemicals are certainly not harmless to us. In potato breeding, for instance, one should always be wary of the ability of new cultivars to produce toxic levels of alkaloids. The classic case demonstrating this is the Lenape cultivar produced in the 1960s. This then-new potato had good insect resistance and a high solids-content, both desirable characteristics especially for the production of potato chips. However, illness after ingestion of this potato was reported on a number of occasions, such as nausea and vomiting. It was later determined that Lenape had very high levels of alkaloids, and the variety was never released for widespread commercial use as it was too toxic.

Many spices valued for their taste are known to have many different chemicals that act as repellents against many different organisms. Safrole, an successful pesticide, is found in for instance nutmeg and black pepper. Safrole is known to be noxious to the liver and might even induce cancer. Or take mustard and wasabi. Their burning taste is prized by many. Allyl isothiocyanate, also known as mustard oil, is the culprit here. The isothiocyanate is a plant-defense chemical against herbivores (such as horses, deer, cows, elk). In the Japanese cuisine, traditionally wasabi is eaten with sushi. One reason for this custom, apart from the acquired taste, is that the isothiocyanate is bacteriostatic. Thereby, wasabi makes the consumption of raw fish somewhat safer. Certainly, wasabi should not be consumed in large quantities (see further Hanekamp 2019).

To protect crops from pests, there is a tradeoff between nature's pesticides and synthetic chemicals having the same purpose. One consequence of crop plant domestication is the deliberate or involuntary selection for reduced levels of secondary compounds that are distasteful and toxic. Insofar as these chemicals are involved in the defense of plants against their natural predators—viruses, bacteria, fungi, insects, herbivores—the reduction due to artificial selection in these defenses may account, to some extent, for the increased susceptibility of crop plants to pests. This is partly compensated with the use of synthetic pesticides. Considering the above, this a quite fortuitous tradeoff (see further Beier 1990). As Janzen (1977) points out: "Plants are not just food for animals, and animals are not just decorations on the vegetation. The world is not green. It is colored lectin, tannin, cyanide, caffeine, aflatoxin, and canavanine. And there is a lot of cellulose thrown in to make the mix even more inedible."

## 24.7 'Healthy' Toxicology and Regulation: Some Final (Precautionary) Thoughts

Coming back to our opening statements on the two basic routes towards protecting and improving human health, the scientific and regulatory routes have their influencing potential. How can we understand the influencing potential of both routes? Let's start with the regulatory side of the equation.

We already pointed at the VSL (value of statistical life) as a means to cap regulatory expenditure. This is important as we are emphatically not dealing here with a reductive perspective on the value of an individual's life, which would be absurd, but on the limits of regulatory expenditure. When proposing new laws or directives, it should be made explicit by regulatory agencies what are the estimates of the societal costs of this or that chemicals regulation.

Now, with respect to the toxicological models undergirding regulatory efforts as found in most countries, they all tend towards an a priori proportional relation between exposure and risk. That is, the lower the exposure, the lower the risk and vice versa, as expressed both in the LT and LNT models. Apart from the fact that that might require disproportionate regulatory expenditures as discussed earlier, it seems wrong-headed with respect to the biphasic insights that have substantially grown in the last decade or so. Also, the monolithic understanding of chemicals as being either good or bad instead of both, depending on various aspects such as dose, length of exposure, adaptive responses and the like, needs to give way to a more empirically-based understanding.

This leaves us with some uncertainty that is inevitably blurring our expanding, yet incomplete, empirical understanding of both health-impacting routes. One way of dealing with these fundamental and practical uncertainties is the precautionary principle. Roughly two main arguments apply for proposing precautionary policies. First, actions can lead to unforeseen consequences; second, ecosystems and society are vulnerable and may possibly not rebound from exposures to certain chemicals.

The use of chemicals and their diverse environmental and human health consequences, in precautionary vernacular, can be classified as 'wicked' (Rittel and Webber 1973). Complexity of the framework in which chemicals use can be regulated, uncertainty of the results of action taken to counter adverse consequences, and divergence in the interpretation of chemical challenges by different stakeholders, render these issues difficult to solve. Kreuther et al. (2004) see the precautionary principle as a wicked problem-solving "device", in that it calls for "all stakeholders to seek solutions that protect population health against a back-drop of scientific uncertainty." Overall, precaution is thought to tackle uncertainty, complexity and ambiguity in the use and regulation of chemicals.

However, inadvertently precaution itself contributes to uncertainty, complexity and ambiguity, the very problems it should help to avert. First, there is the conflation of fear with the general erosion of trust in scientific knowledge. This turns 'proof beyond reasonable doubt' into 'doubt beyond reasonable proof'. As 'absence of evidence' is not 'evidence of absence' proponents of precautionary actions stress that adverse effects—in spite of all the available evidence to the contrary—may arise in the future. Precautionary politics, therefore, cannot be satisfied with research showing that no adverse effects have been reported, within the binary understanding of the effects of chemicals.

Second and closely related, there is the focus on potential threats for future generations. Here, the focus of risk management on probability has changed into precautionary regulation of the possibility of hazard (see Furedi 2009). Third, there is the focus on the interconnectedness of our actions with regard to different policy

domains. Where precaution is connected to sustainability, its objective is not only to protect future generations but also to recognise the interconnections between actions concerning different policies. Clean air standards, for example, are connected to traffic pollution, automobile production and emission controls, urban and regional planning, and the energy aspects of policy. Sometimes the need to take the interconnectedness of problems into account is put forward with utopian zeal. This is clearly exemplified in the closing sentences of Whiteside's *Precautionary politics* (2006):

> Most important, the PP reflects the realization that the whole community now embraces not only fellow citizens in one's own nation-state but also people across the globe and their successor generations. Precautionary politics means that we must take responsibility for maintaining the robustness of the intricately interconnected ecological systems that sustain life on this planet – even when we are far from understanding all the conditions that make them thrive. Never before has so much wisdom been required of humanity's slowly advancing capacity for political association.

Instead of limiting the problems of uncertainty, complexity and ambiguity, it seems clear that such utopianism is conducive to increasing them (see Hanekamp et al. 2015a, b). The self-promoting logic of the precautionary principle is therefore that as it breeds uncertainty it generates or intensifies the political demand for precautionary regulation. Overall, the precautionary principle is self-defeating. With precaution we enter a vicious circle of (scientific) uncertainty and possibilistic reasoning. Douglas and Wildavsky have pointed out the consequences thereof already in 1982 in their *Risk and Culture*: "To the innocent-sounding question, 'How much safety is enough?' [the] answer is that there can never be enough. Risk, like worldliness, is an ideal target for criticism. It is immeasurable and its unacceptability is unlimited. … There can never be sufficient holiness or safety."

Nevertheless, in the chemical world that surrounds us from the dawn of civilisation, it is reassuring to know that the age-old adagio of healthy food-consumption—eat a varied diet and limit your consumption—is in fact sound and deep-seated toxicological advice, which is in many ways the spice of life. It limits unremitting and recurring chemicals-exposure, which burden our physiology to our detriment, and it increases the probability that we in fact consume those chemicals that keep us healthy and alive. And that includes those chemicals we generally regard as toxic. So, the "promotion of a non-toxic environment" as stated in the 'Strategy for a future Chemicals Policy' whitepaper of the European Commission in 2001 is not only unascertainable; it is bad for our health.

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# Part III
# Health and Healthy Aging in Practice

# Chapter 25
# Lifespan Versus Healthspan


**Eric Le Bourg**

**Abstract** Lifespan is a measure of duration, not of content, and it does not provide the same information as biological markers of ageing. Therefore, one cannot rely on lifespan to infer conclusions about ageing. For example, two centenarians can die in very contrasted physiological states: as bed-ridden for years or during jogging. Healthspan can be measured in animal models by relying on behaviour, resistance to stress, and so on. Biogerontologists working with animal models tend to privilege the measurement of lifespan rather than that of healthspan when the animal lives for a short time (e.g. *Caenorhabditis elegans*, *Drosophila melanogaster*) because measuring lifespan is easy and studying, say, behaviour, is more difficult. Conversely, biogerontologists privilege healthspan when the animal model lives for years (e.g. rodents, non-human primates), because measuring lifespan can be out of reach. In any case, biogerontologists should try to observe both lifespan and indicators of health, whenever it is possible, and not conclude that ageing is delayed when they have simply observed longer lifespans.

**Keywords** Lifespan · Healthspan · Animal models · Non-human primates · Human beings

## 25.1 Introduction

This book is an attempt to precisely define what is health and how various sciences can help to define this concept. This is not an easy task and it has given rise to debates for decades, particularly since the major article by the philosopher Christopher Boorse (1977). The present chapter is concerned with health at old age and with the differences, or absence of differences, between lifespan and ageing. It is necessary to define, at least operationally, what is health in the context of ageing.

Pathology can be broadly defined as too long a distance from a mean functioning, and health as the variation, allowing the normal functioning of the organism, around

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the mean of a given trait (Boorse 1977). This statement implies that health is defined at the population level and not at the individual one: "Individual health is conformity to functional normality" (Giroux 2009). For instance, in human beings, a body mass index (BMI) in the 20–25 kg/m$^2$ range is a "healthy" variation, neither too lean nor overweight. Being in the overweight 25–30 kg/m$^2$ range can be less healthy, but 15 or 40 kg/m$^2$ BMI are clearly pathological because the sign of a disease (e.g. anorexia nervosa vs morbid obesity). However, being far from the mean is not always pathology. For instance, the Jeanne Calment's 122 years lifespan (Jeune et al. 2010) is not a sign of pathology, even if very far from the 85.4 years mean lifespan of French women in 2018 (Pison 2019). Boorse (1977) emphasised that "superior functioning is consistent with health. The unusual cardiovascular ability of a long-distance runner is not a disease". However, the observed mean in a country can be unhealthy, such as for instance the mean BMI in the USA, with nearly 40% of the adult population being obese with a BMI $\geq$ 30 kg/m$^2$ (Hales et al. 2018).

One could argue that the optimal value at old age of any trait should be that observed in young adults. However, this would imply that, for instance, because the growth hormone (GH) levels decrease with age (Roelfsema & Veldhuis 2016), it would be necessary to supplement older adults with GH even if they have no GH deficiency. It is not the case, because supplementation with GH as an attempt to delay ageing is associated with many risks, and thus does not improve health but just the contrary (Harman & Blackman 2004). Hence, it would be an error to consider any age-related change as a sign of lower health. For instance, the age-linked weight increase between 18 and 50 years of age does not increase mortality if weight remains in the 20–27 kg/m$^2$ range (Song et al. 2016). Therefore, the healthy range at old age is not necessarily the healthy range observed at young age.

It is needed to record not only lifespan, but also traits linked to health at old age, because lifespan does not provide the same information as biological markers of ageing. Lifespan is a measure of duration, not of content, and one cannot rely only on lifespan to infer conclusions about the ageing process. For instance, two centenarians could be either bedridden for years or jogging as every morning the day before their death and, thus, knowing the lifespan of individuals is not sufficient to know their physiological status or quality of life. Obviously, a human dying at 40 years of age from a non-accidental cause was probably not healthy.

Nevertheless, many biogerontologists who try to discover means to improve health at old age rely on lifespan as the gold standard to know whether their attempts were successful or not, even if some authors have warned against such a rationale (e.g. Le Bourg et al. 1993; Bansal et al. 2015; Briga et al. 2019). As emphasised by Briga et al. (2019), "the (implicit) assumption is often made that factors changing lifespan will consistently alter healthspan and senescence" and thus that an increased lifespan is similar to a delayed ageing process, and thus to a better health at old age. Conversely, a study reported that the oxygen-sensitive *mev-1* mutant of the nematode *Caenorhabditis elegans* has a high sensitivity to oxygen poisoning and a decreased lifespan in a 60% $O_2$ atmosphere (Ishii et al. 1998). This decreased lifespan was called "premature ageing" by the authors. Therefore, according to them, a decreased lifespan is similar to an accelerated ageing process.

If a long lifespan does not imply being healthy when old, one can wonder why many biogerontologists working with some animal models only measure lifespan. By contrast, clinicians mostly rely on measures of health at old age rather than on lifespan. The various constraints these scientists face when working with animal models can explain these different strategies to study ageing. What are the features of the different animal models when studying ageing and how these models can be of help in such studies? Let us consider the most widely used models: *Drosophila melanogaster* flies, the nematode *Caenorhabditis elegans*, the rodents *Mus musculus* and *Rattus norvegicus*, and the non-human primates *Microcebus murinus* and *Macaca malatta.*

## 25.2 Lifespan and Healthspan in Animal Models

### *25.2.1 Lifespan and Healthspan in Drosophila Melanogaster Flies*

When biologists began to study ageing in *D. melanogaster* flies, more than one century ago, the study of behaviour or of life-history traits was in its infancy (but see below for rodents), precluding to observe the effects of ageing in individuals. In such conditions, the obvious best second choice was to focus on an easy, cheap, and straightforward measure—lifespan—and to assume that it was a *bona fide* surrogate of ageing. Lifespan is easy to measure, amenable to statistical analysis, and conceptually easy to understand. Indeed, if an animal dies at a young age, its death is more probably due to an accident or a disease than to the ageing process. By contrast, last survivors have a higher chance to die because of the natural failure of the organism, i.e. from ageing. Thus, many articles on the effects on lifespan of various treatments such as temperature, food, density of population, and so on, were published before World War 2 (e.g. Loeb & Northrop 1917; Pearl et al. 1927, Kopeć 1928). These early experiments were maybe more of help to know the best ways to rear flies than to really understand the ageing process, as sadly emphasised by Pearl (1928): "In the aggregate many months have been spent in studying matters of fly husbandry, for the sole purpose of learning how to set up definitive experiments". However, what was acceptable before World War 2 is not in the 21st century. Considering that a single number—lifespan—can summarise the whole process of ageing is an outdated view of biology and it is needed to observe not only lifespan, but also ageing, which can require observing animal behaviour.

The first study really observing the effects of ageing on the behaviour of *D. melanogaster* was probably that of Wigglesworth (1949) who showed that the mean "duration of flight to the point of complete exhaustion" of flies tethered by the thorax to the tip of a needle was 133 min ($n = 13$) in one day-old flies, 278 min ($n = 14$) in one-week-old flies, and 100 min ($n = 21$) in 4-week-old ones, no matter the sex. The absence of statistical analysis, the low sample sizes, the rounding of the last

digit to 0 or 5 of values of 1 and 4-week-old flies, but not of those of 1-day-old ones, show that it was really an early, pioneering, study of behavioural ageing in flies. While some studies of behaviour were done in the 1950s and 1960s, most of them only studied young flies and Elens and Wattiaux (1971) were maybe the first authors to study phototaxis in 5- and 30-day old flies. The number of studies greatly increased during the 1980s and Le Bourg (1988) published the first review article on age-related behavioural changes.

It could thus be expected that, nowadays, most biogerontologists record the behaviour of flies at various ages, but it is not the case. As emphasised by Grotewiel et al. (2005), "functional senescence, defined here as the intrinsic age-related decline in functional status, has received much less experimental attention in model organisms than life span" because "assessing death in survival studies is typically more straightforward than measuring a function across age". Furthermore, when authors make use of a behavioural trait, many of them rely on a single one, the climbing ability. In this test, a number of flies is put into a vertical vial that is manually tapped to the bottom: the number of flies reaching a given height in a given time is recorded. For instance, Miquel et al. (1972) put 50 flies into a 250 ml vial, that was tapped 10 times on the bottom, and counted the number of flies reaching the 250 ml mark in 20 s. This test can be repeated with the same flies and the mean number of flies reaching the mark is the climbing ability measure (e.g. Seugé et al. 1985). However, this test has flaws. First, as the vial is manually tapped on the bottom the strength of the shock varies among experimenters or successive trials by the same experimenter. Second, many flies are in the same vial and, as the test can be repeated to get a mean score, it is impossible to know whether the same flies were reaching the mark or not, and if "interindividual interactions" could alter the climbing scores, as emphasised by Garcia and Teets (2019). To overcome these issues Le Bourg and Lints (1992) used individual flies with a test tube shaker providing always the same mechanical stimulation. However, the age-linked decline of climbing ability is so paramount and can be modified by so many factors that even the worst procedure will show age-related changes. As a result, climbing ability has become the most used behavioural test in research on ageing (review in Grotewiel et al. 2005), even if it is difficult to compare the results of studies using different procedures.

Beyond the climbing ability test, other traits linked to behaviour have been used in old flies, such as spontaneous locomotor activity, patterns of movement, habituation and learning of various tasks, memory, phototaxis, threshold to sucrose (reviews in e.g. Le Bourg 1988; Grotewiel et al. 2005; Iliadi & Boulianne 2010; see also Le Bourg 1996, 2004). Can it be possible to link individual measures of behaviour and lifespan of the very same flies, flies showing a "better" behaviour living longer? This is not the case when spontaneous locomotor activity is observed, at young age only of repeatedly throughout life: more active flies are not more or less longevous than less active flies (Le Bourg 1987, Le Bourg & Lints 1984; Le Bourg et al. 1984; Lints et al. 1984). Similar results are observed when the patterns of movement in a circular arena are observed: the paths are more sinuous at old age, but there is no correlation between the shape of paths at young or old age and lifespan (Le Bourg 1985). Therefore, these behavioural traits are not predictive of lifespan.

Other indices of health can also be measured, as for instance resistance to severe stress as a function of age. This resistance can decrease in old flies and a delay in this decline or a better resistance could be considered as showing a slower ageing (e.g. Service et al. 1985). In addition, one could expect that a lower or delayed age-linked decline of these traits is linked with a longer lifespan. In some cases, this is observed. For instance, a mild cold stress at young age can increase lifespan, but it also delays the age-linked decline of climbing ability in males and increases survival time at 37 °C at old age (Le Bourg 2007). By contrast, overexpression of the gene of the antioxidant catalase enzyme increases resistance to oxidative stress, has no effect on climbing ability throughout life or on lifespan at 25 °C, but decreases lifespan if flies are transferred at 29 °C (Mockett et al. 2003). Other examples are reported by Iliadi and Boulianne (2010). All these results show that, even if many authors measure lifespan as a surrogate of ageing, other ones make use of various indices of ageing in addition to lifespan. This is possible because flies are amenable to studies of behaviour, resistance to stress, fecundity, learning, and so on, in addition to the classical biochemical measures, such as enzymatic activity, that can be performed in animal models.

These studies show that lifespan cannot be considered as a shorthand of ageing: to apprehend the ageing state of flies it is necessary to observe various traits at various ages and not only lifespan. Could we at least conclude that an increased lifespan, if not always indicative of better health, is not the sign of worse health? Unfortunately, it is not always the case. For instance, the effect of various compounds has been tested by the same laboratory in the same short-lived strain (mean lifespan being less than 30 days), by relying on the same procedures. There is thus a good chance that these studies will be able to provide results that can be compared. Lee et al. (2010) supplemented flies with curcumin, an extract from the plant *Curcuma longa*, and observed that it increased the lifespan of males (+16%) but not of females. Spontaneous locomotor activity was increased in supplemented 1- and 2-week old males but not in older ones, while a slight increase was observed only in the very last surviving 5-week old females. Finally, climbing ability was improved in males (tested at 1 and 5 weeks of age) and only in old females. On the whole, it seems that a lifespan increase is linked with a better healthspan in males, while lifespan and healthspan of females are barely modified: lifespan and healthspan results are in accordance. The same laboratory studied the effect of lamotrigine, an anti-convulsant drug, on lifespan and spontaneous locomotor activity (Avanesian et al. 2010). The drug increased lifespan by 3 days in both sexes (+15%) and decreased spontaneous locomotor activity at 1 and 4 weeks of age: lifespan results cannot be used to infer that healthspan is improved. These two studies clearly show that lifespan and healthspan are not different expressions of the same phenotype. It is thus necessary to measure phenotypes linked to health in addition to lifespan to infer conclusions about ageing.

### 25.2.2 *Lifespan and Healthspan in the Nematode Caenorhabditis Elegans*

Some decades after *D. melanogaster*, the nematode became a model organism in ageing research when Klass (1983) and Friedman and Johnson (1988) discovered up to twice longer-lived mutants, which are linked to the dauer larval stage (duration in German). In low food conditions, worms can enter this non-feeding stage for up to 2 months before resuming the normal life cycle. This increases the usual 2–3 weeks lifespan at 20 °C in the laboratory (Klass & Hirsh 1976) or the 2 days one in the soil (Van Voorhies et al. 2005).

Observing lifespan of nematodes is straightforward. Worms live in Petri dishes, for only a very few weeks, are easy to feed, and thus most studies of ageing in *C. elegans* report survival curves. However, only a few articles report ageing data and this may be understood because the behaviour of worms is rather poor. It is possible to observe, as a function of age, feeding (e.g. Huang et al. 2004), defecation (Bolanowski et al. 1981), movement (e.g. Duhon & Johnson 1995), habituation of a reflex (Beck & Rankin 1993), or resistance to stress (Cypser & Johnson 2002). Because it is easy to separate movement into 3 classes (Newell Stamper et al. 2018), spontaneous movement (class A), movement only when the worm is touched (B), absence of any movement, close to death (C), "it is generally agreed that assessment of movement is informative" (Ewald et al. 2018) and this is the main behavioural phenotype observed in nematodes. Newell Stamper et al. (2018) showed that long-lived mutants have a longer class B than control worms, the duration of A and C classes being rather similar. It remains that a recent review (Son et al. 2019) reports only a very few results on the relationships between behavioural ageing and lifespan, more active worms being often longer-lived (but see Bolanowski et al. 1981).

Because the available traits to observe ageing in nematodes are not numerous, most authors rely on lifespan but the issue is that wild nematodes live in the soil, and that they cannot escape. This may explain the existence of the dauer larval stage increasing lifespan: because they cannot flee in the event of any threatening stress, such as famine, the best strategy could be to increase lifespan, waiting for better times after entering the dauer larval stage (Le Bourg 2016). Similarly, being unable to flee could explain why nematodes live longer even when subjected to toxic chemicals (juglone + 6–29%: Heidler et al. 2010; plumbagin + 12%: Hunt et al. 2011; 50 ppm hydrogen sulfide + 74%: Miller and Roth 2007). Because escaping is not an option, an appropriate response could be to increase lifespan, waiting for dilution of the chemical or its destruction in the soil. These effects are probably hormetic, i.e. beneficial effects of a low dose of a toxic product, but one can even hypothesise, because nematodes cannot flee, that doses that are toxic in, say, mammals, are not toxic in worms. Nevertheless, these lifespan increases could also be a real positive effect because worms are given essential molecules (e.g. vitamin E: + 22%: Harrington & Harley 1988). Molecules often considered to be beneficial, such as antioxidants (trolox: + 31%: Benedetti et al. 2008), could also have a hormetic effect.

Therefore, it could be that an increased lifespan has been selected in nematodes as an appropriate strategy to survive various threats and that toxic and non-toxic compounds could both increase lifespan. If many chemicals could increase lifespan, one could wonder whether observing lifespan in nematodes can be used to infer about results in other species. For example, the 50-ppm hydrogen sulfide dose increasing lifespan in *C. elegans* (Miller & Roth 2007) is the US Occupational Safety and Health Administration peak permissible exposure limit that should never be exceeded, 20 ppm being the limit for a 15 min exposure (Guidotti 2015). Indeed, it could be hypothesised that a longer lifespan in *C. elegans* is not always indicative of better health but, in some cases, of bad living conditions. Observing only lifespan in nematodes can thus be misleading and relying on other phenotypes linked to health is needed.

### *25.2.3 Lifespan and Healthspan in Rodents*

Rodents are long-lived, expensive to buy and to rear, which implies that recording the lifespan can be an issue and that the sample sizes of lifespan studies are expected to be low when compared to studies with flies or worms. Indeed, if we except a study testing the effect of gamma irradiation with three groups of 300 female mice each, and not a single male (Caratero et al. 1998), other studies do not use so high a number of mice in each group.

Rodents have a large behavioural repertoire, are easy to observe and handle because of their size, and they are mammals. Thus, it is not surprising that experiments on ageing have been done before the two World Wars, for instance, on learning of mice (Yerkes 1909), on exercised and control rats observed throughout life (Slonaker 1912), or on dietary restriction in rats (McCay et al. 1935). Therefore, research on ageing in rodents is very different from that on *C. elegans* and *D. melanogaster*: while studies on these models privilege lifespan rather than ageing, those on rodents focus more on ageing than on lifespan. During the 1970s, Elias and Elias (1976) lamented in a review of the effects of age on learning in rodents that "updated mortality tables for the many inbred strains of rats and mice used in aging research have not been readily available". It is obviously not to say that biogerontologists were not concerned with the lifespan of rodents, but simply that observing lifespan in rodents is a challenge because of technical and financial constraints. However, it can be very informative to observe lifespan and ageing of rodents in the same study. For instance, Winter (1998) reported that *Ginkgo biloba* could improve learning and increase lifespan in rats, but only 10 and 20 rats, respectively in the supplemented and control groups, were used for the lifespan experiment. Similarly, Yu et al. (1985) studied the effect of dietary restriction on metabolic and physical traits of rats, on spontaneous locomotor activity throughout life, and on lifespan (40 rats in each lifespan group).

Is it possible to conclude that studies on rodents of both lifespan and ageing are the best choice to infer about human ageing? Unfortunately, the answer is not clearly positive. For instance, while it is known that, like in rodents, being more

active is linked with a longer lifespan in humans (review in e.g. Le Bourg 2009), dietary restriction, unlike with many studies in rodents, does not seem to increase lifespan of Rhesus monkeys or mouse lemurs (Le Bourg 2018) and reports that life expectancy was longer in Okinawa than on mainland Japan because of dietary restriction are slightly too enthusiastic (Le Bourg 2012). The contrasting effects of dietary restriction in rodents and monkeys can probably be explained by relying on the life-history strategies of rodents. When confronted with famine, rodents can hardly emigrate, contrarily to migratory birds, elephants, and other large mammals, because of predation and of the limited distance they can cover (Bowman et al. 2002). Thus, it can be understood why a longer lifespan in the event of famine has been selected in rodents: the best strategy is maybe to wait at the same place until food is again available, which can require living longer (Le Bourg 2016). As emphasised by Demetrius (2005), "when it comes to studying ageing and the means to slow it down, mice are not just small humans".

Because rodents appear not to be the best animal model to study ageing, the obvious conclusion could be that non-human primates offer the best choice.

### *25.2.4 Lifespan and Healthspan in Non-Human Primates*

Non-human primates are surely the best animal models to infer conclusions about ageing in human beings. Unfortunately, they can live for several years, as the tiny 70 g mouse lemur *Microcebus murinus,* or decades, as the monkey *Macaca mulatta.* Primates are costly, need large facilities, veterinarians, and also succeeding generations of biogerontologists. Studies of non-human primates are therefore scarce, with low sample sizes, and cannot routinely sacrifice subjects as can be done with flies. It is a pity because, for instance, the brains of 20% of aged lemurs show lesions similar to those observed in elderly people suffering from Alzheimer's disease, and lemurs appear to be an appropriate model to study normal and pathological brain ageing (Bons et al. 2006). However, intervention studies could probably not afford to sacrifice many subjects to verify whether the treatment under study is decreasing, for instance, amyloid plaques. It is useless to say that this conclusion also applies to rhesus monkeys that live much longer.

However, as in the case of mice, one cannot assert that mouse lemurs are like small humans. They give birth to two offspring thrice a year after a 60 days gestation and their lifespan can fit to the length of the photoperiod. Their lifespan is indeed plastic: mean lifespan is 3.8 years under a short "year" (3 months with 8 h light/day and 5 months with 14 h light/day) and 5.3 years under a "normal" year (natural light at the 48.7 N latitude, near Paris, France; Perret 1997). In addition, lemurs are not homeotherms: during the winter, their temperature, highly correlated to the ambient temperature, can fall to 10 °C, they enter a daily torpor (Schmid 2000), and they increase their weight by ca 50% at the beginning of the cold season (Génin & Perret 2000). To sum up, mouse lemurs are very different from humans.

Therefore, for instance, one cannot exclude that, if a "vaccine" against neurodegeneration (neurofibrillary degeneration, amyloid plaques) were discovered in lemurs, this vaccine would not work in humans.

The solution to this dilemma could be to study ageing and lifespan only in rhesus monkeys that are more similar to humans than lemurs, provided the laboratory can pursue experiments during decades. It is thus not surprising that only a very few studies are done, beginning many years before publication: studies of dietary restriction in macaques begun in the 1980s reported the first lifespan results in the 2000s (e.g. Colman et al. 2009). Clearly speaking, despite being very informative, studies of ageing and lifespan in macaques will remain a tiny part of the studies of ageing in animal models.

## 25.3 Lifespan and Healthspan in Human Beings

Taking into account the previous parts of this chapter, one could be led to conclude that the best animal model to study human ageing is *Homo sapiens*. However, many technical and ethical reasons make that studies on human beings, while highly useful for obvious reasons, are not easy to perform.

In addition, like for animal models, lifespan cannot be considered as sufficient to infer conclusions about ageing. For instance, it is now well known that life expectancy and disability-free life expectancy can diverge: life expectancy can increase while disability-free life expectancy stagnates (e.g. Cambois et al. 2013). Among the European Union, France has one of the highest life expectancies but its disability-free life expectancy is close to the average (Jagger et al. 2008). It is not to say that life expectancy is not an indicator of health, particularly when one compares different countries or the changes in a given country. For instance, by contrast with other developed nations, there is a severe health issue in the USA: mortality is increasing and life expectancy is stalling (Case & Deaton 2015; Ho & Hendi 2018; Woolf et al. 2018). Today, the USA have the lowest life expectancy of high income countries (Ho & Hendi 2018) and the irony is that Cuba, a small country that cannot be an economic competitor of the USA, has now a life expectancy similar to that of the USA (https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=CU).

Disability-free life expectancy can be a better measure of health than life expectancy, particularly for clinicians because, when they know the lifespans of their patients, that simply means that their work is over. In any case, it is useless to convince geriatricians and biogerontologists working with human beings to focus on healthspan and health indicators rather than on lifespan, because this is their daily practice. It is not to say that knowing lifespan is useless, but studying lifespan obviously implies that subjects are already dead and the results could apply only to extinct cohorts and not to living elderly people. For instance, there is an effect of the season of birth on lifespan: people born in Autumn had a higher birthweight and lived longer than those born in Spring. This effect is less important in more recent birth cohorts (1889–1918 versus 1863–1888), probably because mothers of the ancient

cohorts "who gave birth in spring and early summer experienced longer periods of inadequate nutrition" (Doblhammer & Vaupel 2001). One may bet that this seasonal effect will no longer be observed in cohorts born, say, in the 1960s in high income countries. These results show, however, that early events, even when they happen in utero, can be of the highest importance for life at old age. For instance, a low birthweight can be predictive of cardio-vascular diseases at old age (e.g. Fall 2009; Salam et al. 2014).

## 25.4 Conclusions

Lifespan and healthspan are not synonyms and knowing the lifespan of animals is not always a cue for estimating their physiological state at old age. They can live long with bad or good health and, conversely, a short lifespan can indicate bad health or simply an accidental death. Biogerontologists should thus try to observe both lifespan and indicators of health, whenever it is possible, and not conclude that ageing is delayed when they have simply observed a longer lifespan.

Many animal models have been used in biogerontology but some of them such as rotifers (e.g. Enesco & Verdone-Smith 1980) or *Musca domestica* (e.g. Sohal & Buchan 1981) are no longer used, while new models have appeared such as the short-lived fish *Notobranchius furzeri* (e.g. Cellerino 2009) or the longevous naked mole rat *Heterocephalus glaber* (Lewis and Buffenstein 2016). As emphasised by Cellerino (2009) about *N. furzeri*, "the full potential of this model system for analysis of aging-related phenotypes has yet to be realized". By contrast, biogerontologists working with *H. glaber* have accumulated many results on the ageing of this animal model, probably because its very peculiar biology (it is an eusocial mammal, like ants are eusocial insects) is intriguing and its 30-year lifespan, practically, prohibits studying its lifespan, but is an encouragement to study its ageing process. One may hope that future studies, no matter the animal model, will try to study both ageing and lifespan, and will not privilege lifespan only, thereby suggesting that lifespan is a good surrogate of ageing. It is not.

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# Chapter 26
# Health and Immortality


**Ilia Stambler**

**Abstract** Is maintaining good health potentially compatible with a significant or radical life extension? Historically, these phenomena have often been seen as conflicting. Their potential principal incompatibility has often been derived from either health (functional capacity) or lifespan being understood as finite or limited values. The various concepts of limitations to the lifespan or health quantity are surveyed in this work in their historical development, with reference to several dominant theories of aging and mortality. The incompleteness and ambiguities of the limitation theories are demonstrated. Thus, even when proposing limits to the lifespan or healthspan, these limits have often been seen, even by the same authors, as flexible and modifiable. The exact conditions under which lifespan and healthspan "limitations" end and the "possibilities" of their enhancement begin have remained uncertain in the absence of a reliable quantitative formal theory of aging and mortality. An alternative "life-extensionist" view assumes the potential replenishment of any vital resources expended, and thus presumes no inherent natural limitations to either the lifespan or health quantity (functional capacity). The validity of either of those views may be tested in the future with the development of new medical technologies and a better theoretical understanding of health, aging and mortality.

**Keywords** Health · Lifespan · Healthspan · Functional capacity · Aging · Theory of mortality · Compression of morbidity · Longevity dividend · Rejuvenation · Life-extensionists

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## 26.1 Is Significant Life Extension Compatible with Good Health?

This essay will consider the principal question of the compatibility of health and immortality. Can good health coexist with immortality? Here "immortality" is understood as a trope implying a significant or radical lifespan extension, or unlimited life extension, insofar as literal "immortality" or the certainty of having lived an infinite amount of time is logically unattainable. In contrast, there is no law of logic or nature that precludes the possibility of a significant, radical or even indefinite life extension, even though it is at present technically unattainable. It is in this latter sense of a theoretical possibility of radical life extension that the term "immortality" is used here. Would this radical life extension be commensurable with good health or functional capacity?

A long philosophical and literary tradition has assumed they would not be compatible (Stambler 2014). Such assumptions were likely based on the common observation that long-lived people are usually unhealthy at the end of their lives and the commonsensical, though somewhat a priori, conclusion has been that if the end-of-life period is extended, the illnesses of that period will also be extended, and thus good health cannot be concomitant with radical life extension.

The archetype for this line of thought has been the ancient Greek story of Tithonus, the lover of Eos the Goddess of the Dawn, who obtained from her the gift of immortality. Yet, in his flawed human nature, he forgot to ask for eternal youth, thus the gift of immortality became a curse of eternal suffering. This story has been persistent and highly influential in the history of ideas about life extension. It first appeared in the *Homeric Hymn to Aphrodite* (c. 7th or 8th century BC), was reintroduced in Ovid's *Metamorphoses* (8 AD) (Ovid 1994) and to the present it has been invoked in almost every philosophical discussion of the consequences of extreme longevity. Another resounding instance of this archetype occurs in Jonathan Swift's *Gulliver's Travels* (1726) that features the immortal Struldbrugs eternally suffering from mental and physical debility (Swift 1892). There are other instances, but the general presumption remains that, insofar as the end-of-life period is commonly associated with disease and suffering, the extension of life will also be associated with disease and suffering, and thus extreme longevity would be incompatible with good health. This view has entailed a principal opposition to the pursuit of extreme longevity.

The incompatibility of health and extreme longevity has been commonly assumed by opponents of life extension. Yet, intriguingly, the idea that health may be at odds with longevity also appears in the works of staunch life extension advocates, though with a more positive perspective for longevity. This can be seen in the writings of the German prolongevity hygienist Christoph Wilhelm Hufeland (1762–1836), the author of the term "macrobiotics" that has survived to the present. In *Macrobiotics or the Art of Prolonging Human Life* (1796), Hufeland thus distinguished the art of life extension from the general medical art, and suggested that longevity and absence of diseases are not necessarily equivalent (Wilson 1867, pp. IX–X):

> This art [of prolonging life], however, must not be confounded with the common art of medicine or medical regimen; its object, means, and boundaries, are different. The object of medical art is health; that of the macrobiotic, long life. The means employed in the medical art are regulated according to the present state of the body and its variations; those of the macrobiotic, by general principles. In the first it is sufficient if one is able to restore that health which has been lost; but no person thinks of inquiring whether, by the means used for that purpose, life, upon the whole, will be lengthened or shortened; and the latter is often the case in many methods employed in medicine. The medical art must consider every disease as an evil, which cannot be too soon expelled; the macrobiotic, on the other hand, shows that many diseases may be the means of prolonging life. The medical art endeavors, by corroborative and other remedies, to elevate mankind to the highest degree of strength and physical perfection; while the macrobiotic proves that here even there is a maximum, and that strengthening, carried too far, may tend to accelerate life, and consequently, to shorten its duration. The practical part of medicine, therefore, in regard to the macrobiotic art, is to be considered only as an auxiliary science which teaches us how to know diseases, the enemies of life, and how to prevent and expel them; but which, however, must itself be subordinate to the highest laws of the latter.

Indeed, the emphasis on the treatment of particular diseases may distinguish general medical practice from the pursuit of life extension. The cure of a disease might be more readily and immediately perceived, while the ascertainment of human life extension may be a more lengthy and confounded process. Moreover, the possibility of "radical life extension" can hardly become subject to empirical confirmation any time soon. These might be some of the reasons that, until quite recently, the terms "life extension" or "lifespan increase" or "longevity extension" have not been regularly considered in biological or medical discourse. And critically for the present discussion, life extension may not be seen as necessarily tantamount to good health.

## 26.2 The Limits to Life and the Limits to Health

Another well-established intellectual tradition dealing with the relation of health and life extension has presumed a strict limit to the maximum lifespan and/or maximum inherent health quantity necessary to sustain life. In a sense, this is an even more pessimistic position than just presuming the incompatibility of life extension with good health as adversely influencing each other, seen in the former examples (when life extension is perceived to come at the expense of health, and vice versa). When presupposing limits to life or health, health may be conducive to longevity. However, insofar as health is a limited quantity, also longevity cannot be significantly extended, and vice versa. This view essentially presupposes the incompatibility of life extension with the continuation of life itself, due to fundamental health- and life-limiting mechanisms inherent in living beings, as paradoxical as this statement may sound. In this view, insofar as some degree of health (understood here as functional capacity) would be needed to continue life, this capacity simply could not be maintained for an indefinitely prolonged time, due to an inherent limit to life prolongation and/or an inherent limit to the functional capacity.

The latter line of thought arguably has the same conceptual basis as the former one that posited the incompatibility of life extension with maintaining good health, namely both presume health (functional capacity) to be a limited quantity. What differs is the emphasis and the presumed temporal mode of distribution of that limited quantity. In the former view, there would not be enough 'health quantity' to last, hence life could only be extended with a diminished health. In the latter view, health would only suffice for a limited time beyond which life prolongation would be impossible. But in both ramifications, the presumption of inherent limits to health and life is fundamental.

Yet crucially, at the same time, it has also been realized in the history of ideas about health and life extension, even by the very same thinkers who proposed "limits" to the lifespan and/or the life-sustaining health quantity, that these "limits" are rather flexible and the duration of life and quantifies of health are quite modifiable. The exact extent where the health and lifespan's "inherent limitations" would end and healthy life extension "possibilities" begin, has remained uncertain.

Thus, the founder of Gerontology Elie Metchnikoff posited in 1903 the inherent disharmony of human nature that eventually leads to human demise (Metchnikoff 1961). Yet, he also maintained that under proper "orthobiotic" conditions, human life can be extended to 150 years and beyond. Similarly, the American pioneer of aging research Raymond Pearl argued that the dissonance of differentiated body parts is inexorably engraved in human nature, and that the lifespan is an inherited quantity that can only be manipulated to a very limited degree (Pearl 1922). And yet, in Pearl's experiments, the lifespan of Drosophila flies was extended significantly by genetic selection, decreasing the population density, chemical stimulants, or else by lowering the temperature of their environment and reducing their food supply, generally decreasing their "rate of living." The German physiologist Max Rubner famously posited a limited amount of metabolic activity for any species during their lifespan (Rubner 1908). He found that most mammals, during their life course, consume about the same amount of energy per kilogram body weight (approximately 200,000 kcal) and die when the "life-energy" quota is spent. According to Rubner, for man the value is outstandingly high (~725,000 kcal), but is a preordained quantity nonetheless. Intense metabolic activity was, in this view, fatal. Nonetheless, he also believed in the possibility of life prolongation, according to his famous dictum that "the art of prolonging life consists in learning not to shorten it" (Lautenbach 2010, p. 25).

The uncertainties regarding the "limits" to the human lifespan and health have persisted for quite some time, with their discussion intensifying in the late 1970s—early 1980s. Thus, Nathan Keyfitz (1913–2010) of Harvard upheld the so-called "Taeuber Paradox" (named after Conrad Taeuber, 1906–1999, Chief of the Population Division of the US Census Bureau who observed the phenomenon), which suggested that aging organisms become generally frail, and therefore, if an aging person will not die of one age-related disease, he will die of another. Consequently, even the entire elimination of a major age-related disease, such as cancer, will not significantly increase the general life-expectancy, as some new disease will come in its place. As Keyfitz wrote: "A cure for cancer would only have the effect of giving people the opportunity to die of heart disease." This was a major motivation damper for

attempting to find cures against specific age-related diseases, and clearly posited the incompatibility of life extension with absence of diseases (Keyfitz 1977). However, in the same article, Keyfitz stated: "If cancer, heart disease, etc., are merely alternative ways in which the aging of body cells makes itself manifest, then eradicating any one of them may make little difference. The proper entity to attack is the process of aging itself." Elsewhere, Keyfitz further advocated for increasing research into cellular senescence, as an underlying general cause of many age-related diseases, rather than into any specific single disease. Such research would allow us "to break through the barrier that now seems to be set at about 80 years" (Keyfitz 1978).

Further, the Stanford gerontologists James F. Fries and Lawrence M. Crapo, in *Vitality and Aging. Implications of the Rectangular Curve,* posited that "the maximum life span is fixed at about 100 years, and the median life span is fixed at about 85 years" (Fries and Crapo 1981, p. 140). This "natural" lifespan is determined by "a steady decline in homeostasis and organ reserve in many vital systems" (Fries and Crapo 1981, p. 136). This decline in organ reserves results in an exponential increase in the mortality rate with age (Fries and Crapo 1981, p. 37). The authors predicted that a society will increasingly progress toward a "rectangular survival curve" when health care measures will produce a "compression of morbidity." This basically implied that people will remain sufficiently healthy until the age of about 85 and then collapse and die rapidly, saving on national health care expenditures. This scenario has been elaborated and disseminated (Fries 1980, 1983) and has become highly influential for the later concepts of "healthy aging." The authors called such a scenario "optimistic" and "a celebration of life." Still, the authors believed that "if we could understand the aging process at the cellular level and its underlying molecular mechanisms, then we might be able to alter the information units in the cells and thereby alter the life span" (Fries and Crapo 1981, p. 135, 139).

In contrast to Fries and Crapo's ideal of the "compression of morbidity," an "expansion of morbidity" was often observed in conjunction with life extension, as for example in the seminal work by the American psychiatrist and epidemiologist Ernest M. Gruenberg, "The failures of success" (Gruenberg 1977). Despite the differences of emphases, the main conclusions are similar in that limitations are assumed for the extension of life and of health. Moreover, the extension of life by medical technology is observed often to limit the sum total of population health. As Gruenberg noted, "The goal of medical research work is to 'diminish disease and enrich life', but it produced tools which prolong diseased, diminished lives and so increase the proportion of people who have a disabling or chronic disease." The recommendations from the "expansion of morbidity" perception are also similar to those from the "compression of morbidity" vision, namely the ensuing appeal to increase the portion of health research and health care dedicated to prevention of chronic diseases. In this way, it would be possible to achieve the extension of life concomitant with the extension of health.

Further limits on the human lifespan—biological, technological, ethical and economic—were proposed by J. Michael McGinnis, of the US Department of Health and Human Services, in 1985. Yet, McGinnis concluded with "an essentially optimistic perspective." For example, regarding the limits imposed on life extension by

the deficiencies of available technology, the pace of technological change was said to be rapid and "the limits of today will become the opportunities of tomorrow" (McGinnis 1985).

The question of the "limits" to the human life span and life expectancy has remained open to the present. Thus, at the turn of the twenty-first century, the gerontologists Stuart Jay Olshansky of the University of Illinois at Chicago and Bruce Alfred Carnes of the University of Oklahoma, in *The Quest for Immortality. Science at the Frontiers of Aging* (2001) suggested that "given the current state of medical technology, life expectancy at birth will not rise above 85 years." But the qualification regarding "the current state of medical technology" seems to be crucial. "The legitimate science of aging," the authors maintained, "has already led to remarkable extensions of life for many people. We can expect the hard work of researchers and medical practitioners to add to that success in the future." Thus, once again, a limit to the lifespan is posited, but it was understood that it can be quite flexible and modifiable. As the author admit, "The ongoing debate over limits to life expectancy is not likely to be resolved any time soon" (Olshansky and Carnes 2001, p. 142, 149, 211, 219).

Later on, Olshansky and collaborators have developed those ideas and disseminated the notion of the "Longevity Dividend" based on the concept of "healthspan" (healthy lifespan) extension, namely the aspiration to use medical technology to increase the healthy life expectancy in the population, while keeping constant or changing little the general life expectancy. Simply put, in this view, people are hoped, so to paraphrase, 'to die healthy' or 'live healthy until their death' (or almost until their death). The achievement of this visionary scenario is supposed to produce massive savings ("dividends") for the healthcare and welfare systems (Olshansky et al. 2006; Olshansky 2019). The same vision is presupposed by the "Geroscience" school of gerontology who perceive aging as the main "risk factor" for multiple age-related diseases and hope that by intervening into the aging process it may be possible to postpone the emergence of those diseases and increase the population's healthy life expectancy or healthy lifespan, but not necessarily the general life expectancy or lifespan. Or, at the very least, the gains in healthy life expectancy are hoped to exceed the gains in general life expectancy (Sierra and Kohanski 2017). In fact, this view posits a limit to the human lifespan, but not to the healthspan (until it reaches the value of the lifespan). It assumes the ability of biomedical technology to intervene into human biology, but only to modify the "healthspan" up to that lifespan limit. Thus, the uncertainties and ambiguities concerning the limits of life and health extension have remained.

## 26.3 Theories of Mortality

Despite the ambiguity regarding the actual value of the "limits" of lifespan vs. "possibilities" of life and health extension, the existence of some limits to life extension and/or health extension, and their potential incompatibility, were posited by the

majority of researchers of aging so far. But what is the precise law of this compatibility or incompatibility? Why is it, exactly, that life cannot be extended indefinitely and health improved indefinitely, as assumed by the proponents of the lifespan or health limitations? Or else, why should people "die healthy" as professed by the advocates of the "compression of morbidity" scenario? Why would the "one-hoss shay" metaphor often used in the "compression of morbidity" discussions (Holmes 1858; Fries and Crapo 1981), where the "shay" (carriage) stands intact until it suddenly falls apart in its entirety, be relevant for the human organism? Or why, in principle, can't people continue to live on healthily while their life is being extended, as maintained by the observers of "expansion of morbidity"? These are fundamental theoretical questions that could be answered by formal, mechanistic and mathematical theory-based models of aging and mortality. Such quantitative theoretical models might be able, in principle, also to account for or predict, in a formal and quantitative manner, the actual values for the "limits" or "possibilities" for life and health extension. Yet, there has been a traditional scarcity of such models. Indeed, any theory of aging may be perceived as an explanation of the limit of life or health, or of the incompatibility of life extension with health extension. Yet, formal, mathematical and mechanistic explanations have been few. This may have been partly due to the paucity of relevant data and partly due to the specifics of common training of biologists of aging and gerontologists that placed less emphasis on formal mathematical modeling. Yet some formal theories started to be developed, about 60 years ago, in the 1950s–1960s. Since then, the formal mathematical theories of aging and mortality appear not to have developed very strongly, but mainly reiterated the original premises.

The theories of mortality developed in the 1950s built on much earlier concepts, such as Benjamin Gompertz's law of an exponential increase in mortality rate with age, posited in 1825, or Karl Pearson's population mortality statistics of 1900. Yet, they were more elaborate, quantitatively relating the rate of (molecular and cellular) damage and loss to the rate of mortality. Several theories of mortality were formulated between 1952 and 1960. Thus, according to the theory of Elaine Brody and Gioacchino Failla, the "mortality rate is inversely proportional to the vitality." In the theory proposed by Henry Simms and Hardin Jones, death was attributed to "autocatalytic accumulation of damage and disease," where "the lessening of vitality [is regarded] as the accumulation of damage" and "the rate at which damage is incurred is proportional to the damage that has already been acquired in the past." George Sacher's theory stated that "death occurs when a displacement of the physiologic state extends below a certain limiting value" (Mildvan and Strehler 1960).

Yet, perhaps the most developed and publicized theory of mortality was the theory proposed by Bernard Strehler and Albert Mildvan or "the Strehler-Mildvan theory" (Strehler and Mildvan 1960). It claimed that "the rate of death is assumed to be proportional to the frequency of stresses which surpass the ability of a subsystem to restore initial conditions" (Mildvan and Strehler 1960). The theory was based on the Maxwell–Boltzmann distribution (originally formulated for the kinetic theory of gases in the 1860s), where the linear decline of function of particular organs in time was supposed to eventually lead to an exponential increase of risk for systemic failure of homeostasis of multiple organ systems and hence an exponential increase

of mortality rate. The loss of organ function or "organ functional reserve" was potentially attributable to progressive loss of functioning organ and tissue units, such as cells, or gradual impairment in the functional capacities of individual cells (Mildvan and Strehler 1960; Strehler 1960a; Shock 1960a, b). This model formed the theoretical basis for the "compression of morbidity" concept (Fries and Crapo 1981; Shock 1977). Recently, the Strehler-Mildvan theory was criticized for its presumably uncertain statistical basis, and accordingly its positing of a limit to lifespan extension was questioned (Tarkhov et al. 2017). Yet, to the best of my knowledge, no equally comprehensive formal theory of mortality has yet been proposed.

Though these theories did not appear to refer to any specific goals of life extension, they were designed for a thorough quantitative elucidation of the aging process, deemed a necessary precondition for any actual intervention. Indeed, despite positing a formal theory of lifespan limitation, Strehler was among the most active seekers of life-prolonging means, mainly focusing on enzymatic mechanisms of DNA repair, as he believed that an improved DNA repair system can protect the stability of the human genes against mutations and thus radically increase the human lifespan (Strehler 1960b; Kahn 1985).

In yet another line of theory-building, since the 1950s to the present, there have been ongoing efforts to create theoretical constructs that relate the aging process and mortality with an increase of physical entropy (disorderliness or chaos) of living systems (Hirsch 1955; Quastler 1958; Hershey and Lee 1994; Krut'ko et al. 2018). Considering the second law of thermodynamics that posits the inevitable increase of entropy and the ultimate thermodynamic death of any closed system, an ostensible analogy with the aging process and dying of living organisms intuitively appealed to biologists (Hayflick 2007). Such an analogy suggested the sense of fatality, of inevitable destructibility of living beings, or a limit to their existence. Notably, such entropy-related descriptions of aging and dying have often been qualitative, without concrete quantitative predictions, providing no tangible estimates as to the actual terms of mortality or values of morbidity, and hence the immediate application of such constructs for any practical medical, clinical or demographic purposes has been minimal. Moreover, it has been generally established since the seminal work of Erwin Schrödinger *What is Life?* (first published in 1944) that the notion of a closed system, and accordingly the inevitable increase of physical entropy and thermodynamic equilibrium (death), is not strictly applicable to living systems. Schrödinger explained biological equilibrium in terms of order and organization, as a low entropy (high order) system maintaining its orderliness by increasing the disorder of the environment (Schrödinger 1996). Implicitly, such "entropy parasitism" (in Schrödinger's words, "feeding on negative entropy") seemed to present no inherent physical constraints to its maintenance, and thus, theoretically could be sustained indefinitely. Thus, this class of theoretical constructs, relating entropy with aging and mortality, also presents a strong ambiguity regarding the inevitability of limits vs. possibilities of life and health extension.

Furthermore, a series of limiting models emerged from the "reliability theories" of aging, longevity and mortality (Koltover 2018). For example, one of such theories proposed that "even those systems that are entirely composed of non-aging elements

(with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are redundant in irreplaceable elements" (Gavrilov and Gavrilova 2001). Despite this premise of inevitability of aging and demise, the theory still had explicit positive propositions for the possibility of practical life extension: "It also follows from this model that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements (j) can potentially result in a remarkable fall in mortality and a significant improvement in lifespan" (Gavrilov and Gavrilova 2001).

Another version of biological reliability theory suggested that in a given system there exist tradeoffs between robustness (duration) and performance (function), which might provide another way of conceptualizing and justifying the incompatibility of life extension and healthy function and a proposition of a limit for either (Kitano 2007; Cohen 2016). The tradeoff between robustness and performance has a strong relation to yet another set of explanations for the potential incompatibility of life extension and health extension, namely the incompatibility of constancy and change.

## 26.4 Life Extension Implies Constancy, Health Implies Change: Are They Compatible?

Another persistent line of arguments against the compatibility of prolongation of life with prolonged maintenance of health has been predicated on the notion of the inherent mutability of healthy life. Health has been associated with the ability to change, to adapt and respond to changing circumstances. In contrast, life extension has entailed the maintenance of certain core components of life unchangeable or with minimal change (Stambler 2017a). Thus, there appears to be an opposition of functions.

On a continuum between the desire for absolute change and the desire for absolute constancy, the proponents of life extension would seem to stand closer to the pole of constancy. Indeed, without some notion of constancy, the concept of life extension, even of survival, would be meaningless. Consider such cases as the atoms of a decomposing human body merging with the Universe, or human life being transformed into the life of grave worms, as for example discussed by Jean Finot in *The Philosophy of Long Life* (Finot 1909). Many boundaries are "transcended" in such "transformations," but one can hardly speak of "life extension." If extinction is determined by "a critical rate of long-term environmental change beyond which extinction is certain" (Burger and Lynch 1995)—notice, *any* change—then proponents of life extension would wish to be as far from this rate of change as possible. Or else, they would wish to design the technological armor that would make us impervious to such changes. Without work invested in maintaining constancy, spontaneous deteriorative change may be expected. Thus, the proponents of life extension might engage the rhetoric of progressive change, but not just any change for change's sake, but only

such change that would serve to perpetuate some existing structure. In the words of the protagonist of Giuseppe Tomasi di Lampedusa's *The Leopard,* "If we want things to stay as they are, things will have to change" (Tomasi di Lampedusa 1960). And in the words of Lewis Carroll, "it takes all the running you can do, to keep in the same place" (Carroll 1871). In this sense, the pursuit of life extension may be a fundamentally "conservative" or "conservationist" enterprise (Stambler 2010).

In contrast, the proponents of maximum health might be more likely to advocate substantial change, as would be required for growth and adaptation. This opposition may have not only psychological or semantic underpinnings, but may have biological or evolutionary roots. In several recent theories of aging, a deficit of species variability has been linked with the possibility of non-aging and/or radical life extension. In these theories, an absence of aging would impair variation and thus reduce the species evolvability and adaptability. For example, an ideal DNA repair mechanism would make mutability impossible (all mutations would be immediately corrected). And without mutability, there would be no diversity and no evolution. Any new threat (e.g. a new infection) could then wipe out the entire stagnant population. (Still, improved immunity and DNA repair may be assumed to provide improved defense against a greater range of pathogens and environmental threats, such as radiation, temperature changes and toxins, including bio-toxins, hence the ambiguity regarding "limits" vs. "possibilities" remain.) A recent evolutionary model argued almost precisely to the effect of incompatibility of change with radical life extension: "when the system is completely stable, no mutation going on and no changing conditions for worse, … it is to be expected that a population that shows senescence will be driven to extinction." However, "When conditions change, a senescent species can drive immortal competitors to extinction." The author concludes: "We age because the world changes" (Martins 2011). Several other contemporary researchers have pondered a return to August Weismann's theory of evolutionary programmed aging, proposing a direct evolutionary selection for senescence. A major suggested reason for such a selection is that an absence of senescence would diminish the species' variability and diversity, hence impair its adaptability and evolvability (Goldsmith 2004; Mitteldorf 2004; Skulachev 1997).

In cognate terms, it was further suggested that complexity and variability (a proxy for adaptation) might be associated with youth and good health, whereas simplicity and homogeneity (a proxy for stability) may be seen as a sign of aging and disease (Lipsitz and Goldberger 1992; Blokh and Stambler 2017b).

Notably, virtually all the researchers of aging under consideration, even those proposing limitations to lifespan or healthspan, seem to be in favor of finding at least some modest aging-ameliorating and life and health-extending means for humans, suggesting that through a better understanding of the mechanisms of aging, including evolutionary mechanisms, tradeoffs and thresholds, factors affecting health and longevity can be identified and manipulated for people's benefit.

## 26.5 Killing for Health

As seen in the previous examples, the propositions of limits to lifespan and healthspan have been commonly accompanied by various ambiguities and caveats, where the "limitations" would seem not really limiting, and the possibilities of life and health extension emerged quite tangible. This appears to be the prevalent position of many researchers of aging. Yet, in some authors, the supposition of a limit to lifespan and/or healthspan was relentless. In their view, the limits are "written in stone" and any attempts to modify them to any noticeable degree are futile and even in some sense immoral. This view of the truly insurmountable limit to human life and/or health, and of the incompatibility of health maintenance with life extension, has often yielded some rather appalling practical implications and recommendations. A common practical consequence has been the implicit or even explicit suggestion of the desirability of death and abandoning health care for older people, when their "life quality" (health) is below some acceptable limits.

There are quite a few famous examples of this attitude. In 1905, the renowned Canadian physician William Osler (1849–1919) spoke of the "uselessness of men above sixty years of age" (Osler 1905). The essays of the "humanistic" British philosopher and mathematician Bertrand Russell (1872–1970) from the 1930s–1940s provide another stark example. Thus, in his essay "On Euthanasia" (1934), Russell suggested killing people in extremely ill health, such as in cases of "hydrophobia," "pneumonic plague," "congenital idiocy" and other cases which "cannot be useful to society." Also "criminals condemned to long terms ought to have the option of euthanasia" (Russell 1975a). Russell was consistent and logical, hence, according to him, the prolongation of life was undesirable both for the very sick and the very old. Thus, in "The Menace of Old Age" (1931) he was greatly worried by the prospect that "every increase in medical skill is bound to make the world more and more conservative." Hence, he proposed "to prevent all researches calculated to prolong the life of the very old" (Russell 1975b). And in "How to grow old" (1944), he maintained that "in an old man … the fear of death is somewhat abject and ignoble" (Russell 1956). In a less blatant form, the Australian immunologist, the Nobel Laureate in medicine of 1960 and the author of the "intrinsic mutagenesis" theory of aging, Frank Macfarlane Burnet (1899–1985) "doubt[ed] very much whether anything worthwhile would be gained by extending the human life span beyond its present bracket of 70–100 years—and that if we wanted this extension of life, I am deeply sceptical about our chance of ever achieving it." And furthermore, "death in the old should be accepted as something always inevitable and sometimes as positively desirable" (Burnet 1974, p. 63, 66).

These are not just theoretical attitudes. Under certain circumstances, they may well translate into practice, specifically denying care for extremely ill elderly patients, as "useless" and "hopeless." Thus, as early as 1666, the British physician Dr. John Smith urged (Freeman 1938):

> Let none give over their patients when they come overburdened with the infirmities of Age, as though they were altogether incapable of having any good done unto them. Those that

> are negligent toward their Ancient Friends, are very near of kin to those inhuman Barbarians and Americans, who both kill and devour them.

This basic neglect of care may have come true in some of the severe cases of "ageism" or discrimination based on age in healthcare (Ehni 2014; Wyman et al. 2018).

Alternatively, the valorization of "health" (understood as the maximization and optimization of function) over "life extension" (or the "mere" continuation of life) may well take the form of devising medical treatments that may invigorate ("rejuvenate") the person for the short term, with a semblance of "good health," yet in fact shortening the older persons' life, essentially killing them "for health." This possibility was vividly envisioned by Aldous Huxley, in *Brave New World* (1932). In *Brave New World*, biotechnology is used by the society first and foremost for pleasure, and not for the prolongation of life or intellectual growth. The residents of the "New World" undergo "death conditioning" to inculcate the idea that death is a natural, good and pleasant event: "Death conditioning begins at eighteen months. Every tot spends two mornings a week in a Hospital for the Dying. All the best toys are kept there, and they get chocolate cream on death days. They learn to take dying as a matter of course" (Huxley 1965, p. 125). Those who prolong their days and become old are the savages who live at the Reservation. The "civilized" ones are simply not allowed to age and to live long, but die young and healthy at the age of sixty (Huxley 1965, p. 84):

> That's because we don't allow them to be like that [growing old]. We preserve them from diseases. We keep their internal secretions artificially balanced at a youthful equilibrium. We don't permit their magnesium-calcium ratio to fall below what it was at thirty. We give them transfusion of young blood. We keep their metabolism permanently stimulated. So, of course, they don't look like that. Partly, he added, because most of them die long before they reach this old creature's age. Youth almost unimpaired till sixty, and then, crack! the end.

It is unclear from the text why the balancing of the metabolism would lead to a pre-determined early demise, but the passage seems to imply that this is due to an excessive and permanent stimulation. Thus, *Brave New World* appears to reduce to absurdity the common assumption of the incompatibility of life extension and good health and shows its possible "logical" and "practical" conclusion: killing by keeping good health.

Will our "Developed World" follow this "Brave New World" scenario via designing "anti-aging," "rejuvenating" and "bio-hacking" treatments that may momentarily improve function ("health") but disregard possible long-term adverse effects and earlier death?

This is a possibility a founder of prolongevity hygiene, Christoph Wilhelm Hufeland warned against. According to Hufeland's views (to express them in somewhat more modern terms), any treatment of old age should consider the aging organism and the aging process as a whole. Any attempt to artificially strengthen some faculty, at the disregard of the general sensitivity and available resources of the entire aging system, can further advance the disarray and bring about death sooner. The ultimate goal is not "rejuvenation" for the sake of "rejuvenation," but "macrobiotics"—the

prolongation of life. And paradoxically, "rejuvenation" or an immediate improvement of function or health, can become an enemy of life prolongation. In Hufeland's own words, as stated in his *Macrobiotics or the Art of Prolonging Human Life*, Part 3 "Means which prolong life," Chap. 18 "Old Age. Proper Treatment of It" (translated in Wilson 1867, p. 292):

> Old age, though the natural consequence of living, and the commencement of death, can itself, on the other hand, be a means for prolonging our existence. It does not, however, increase the power to live, but it retards its being exhausted; and one may thus affirm, that a man in the last period of life, at the time when his powers are lessened, would, were he not old, finish his career sooner.
>
> This position, which appears to be somewhat paradoxical, is confirmed by the following explanation.
>
> Man, during the period of old age, has a much smaller provision of vital power, and a much less capacity for restoration. If he lived with the same activity and vigor as before, this provision would be much sooner exhausted, and death would soon be the consequence. Now the character of age lessens the natural irritability and sensibility of the body, by which the effects of internal as well as external irritation, and consequently the exertion and wasting of the powers, are also lessened; and, on this account, as consumption is less, he can with such a stock of powers hold out much longer. The decrease in the intensity of the vital processes, as age increases, prolongs therefore vital duration.

This is a lesson by Hufeland that may be well heeded by some contemporary reductionist "anti-aging" attempts who seek immediate health improvement in the elderly without consideration of long-term effects and actual effects on the person's life duration (Le Couteur and Simpson 2011). It should also be well heard by radical advocates of "healthspan" improvement and "healthy longevity dividend" who, in extreme cases, may despise "mere" life extension per se as useless, if it is not accompanied by high functional performance. If taken to extreme, in a "Brave New World" scenario, this attitude may result in some forms of "killing for good health."

## 26.6 "And Yet It Moves". The Denial of Lifespan and Healthspan Limitations and the Possibility of Radical Life Extension (or Biological Immortality)

Beside the schools of thought that posited relentless and inexorable limitations to the human lifespan and/or healthspan, or limitations that are rather flexible, but still finite, there has existed a school of thought that denied the necessary existence of such limitations altogether. In this school of thought, theoretically no material limits are inherent in the duration of life of organisms, as well as in the possibility of the development of their functional capacities (health).

According to the proponents of this vision, it is theoretically possible to produce changes in the organisms' inner biological structure and/or environmental conditions, thanks to improvements in biomedical technology, which may dramatically modify any existing limitations on life and health imposed by the present conditions. Of

course, it has been realized, even by the most optimistic advocates of human life extension (often termed "life-extensionists"), that there are currently clear practical limits and constraints in our ability to increase the human lifespan with the current medical technological means (Stambler 2014). The life-extensionists simply do not reconcile with those limits; they desire and strive to overcome them by improving biomedical technology.

The assertion of limits on life and health presupposes the existence of some limited life-sustaining material resource or reserve, a sort of nourishing substrate for the "vital force" of a restricted amount that is being exhausted during the life course and cannot be replenished, thus creating the limit. This putative irreplaceable material resource could be the telomere length, the extant stem cell populations, maximum DNA repair capacity, or some mysterious limited "adaptation energy" hypothesized by the founder of stress physiology Hans Selye. Yet, the fundamental characteristic of the life-extensionist worldview is that it strongly asserts the possibility to replenish any material resources necessary for life, and thus modify any restrictive limits. This view is quite ancient. It was, for example, expressed by the renowned Jewish philosopher and physician Maimonides (1135–1204, Rabbi Mosheh ben Maimon) who stated: "For us Jews, there is no predetermined end point of life. The living being exists as long as replenishment is provided [for that amount of] its substantive moisture [i.e. bodily humors] that dissolves" (Rosner 1998). This proactive view has persisted and intensified to our time (Stambler 2014). Hans Selye, even though he believed that "as far as we know, our reserve of adaptation energy is an inherited finite amount," nonetheless admitted the possibility of its replenishment, and thus life and health extension. As he wrote: "If [the adaptation energy] amount is unchangeable, we may learn more about how to conserve it. If it can be transmitted, we may explore means of extracting the carrier of this vital energy—for instance, from the tissues of young animals—and trying to transmit it to the old and aging" (Selye 1956, pp. 276, 303–304). The same proactive principle could be applied for any type of limiting material resources.

Despite the well-recognized current practical limitations, the life-extensionists have strongly asserted that, on the basic theoretical level, there is no law in nature that sets a strict insurmountable limit to the lifespan or functional capacity of the human organism. Regarding the presumed incompatibility of significant life extension with optimal health, or the frequent fear of increasing "life quantity" at the expense of "life quality," the life extensionists denied any natural limitations to those values and asserted the human ability to intervene and enhance them. This position was well stated at the Galileo Symposium in 1964 by the Nobel Prize winning physicist Richard Phillips Feynman (Feynman 1999, p. 100):

> There is nothing in biology yet found that indicates the inevitability of death. This suggests to me that it is not at all inevitable, and that it is only a matter of time before the biologists discover what it is that is causing us the trouble and that that terrible universal disease or temporariness of the human's body will be cured.

Among the sources of hope, the life-extensionists have often cited the existence of non-aging, slowly aging, and even "potentially immortal" life-forms and the constant

evolutionary adaptations of the lifespan even for the humans, according to particular changing environmental and genetic conditions. There may be contingent limitations due to the inner biological structure and external environment, but these are not "limits" in the principal physical sense (like "nothing can travel faster than the speed of light"). The existing practical limits to the human lifespan and functional capacity, due to internal disorder, adverse environment and imperfect medical capabilities, are "rules that can be broken."

Some authors opposed the premises of limitation theories on specific points. An intense debate over the limits to life and health expectancy took place in the 1980s. Thus, the view proposed by Nathan Keyfitz about the intrinsic limit to aging health and life-expectancy was disputed by Arthur Schatzkin of the US National Institute of Cancer. Schatzkin suggested that a single health care measure can improve the outcome for several age-related diseases and the elimination of several risk factors can have a cumulative effect, leading to a significant life extension (Schatzkin 1980). Several authors disputed Fries and Crapo's conclusions about the compression of morbidity and argued that an approximation of a perfect "rectangular survival curve" will not be possible, and health care measures can produce an extension of life expectancy far beyond the 85-year "limit" (Schneider and Brody 1983). Later on, additional evidence was presented about the existence of the "compression of morbidity" and "rectangularization of survival" (temporal concentration of deaths) trends, agreeing with the limitation theories (Faria 2015; Stallard 2016). Yet, these trends were also debated (Crimmins and Beltrán-Sánchez 2011). Moreover, recently a strong critique of the Strehler-Mildvan theory of mortality (lifespan limit) emerged (Tarkhov et al. 2017) explicitly aiming to encourage the search for anti-aging and life-extending therapies.

Yet, many life-extensionists resist the imposition of a limit on life and health not on any specific technical grounds, but on the sheer postulate of the human ability to employ natural processes to achieve benefits for humanity. Their greatest source of hope is the rapid development of therapeutic means for health improvement and life extension. The primary proofs of feasibility are based on the successful cases of health improvement and life extension experimentally achieved in animal models and emerging human studies, and the development of new intervention techniques, based on the ever-better elucidation of the mechanisms of aging (Stambler 2017b). There are now clear proofs of practical technological feasibility of interventions into aging processes and healthspan and lifespan modification. These feasibility proofs for aging modification and health and lifespan intervention are a part of the more general and very encouraging trend of the rapid development of biomedical technologies. The fact of progress in scientific, technological and medical capabilities is difficult to deny. Though, of course, this progress is not a given, and may be brought to naught in the absence of persistent human effort, ingenuity and investment. Yet, the present progress gives encouragement and hope for overcoming the present practical limitations of both the lifespan and healthspan, for extending life concomitantly with the extension of good health, for keeping intellectual, physical and spiritual capabilities without expecting a rigidly set end point. This is the profoundly optimistic vision of health and life promoted by the life-extensionist school of thought.

The truth or error of each school of thought will be shown in time, with fateful impacts on the lives of every one of us, within our yet limited lifespan and healthspan.

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# Chapter 27
# Health and Pro-Longevity Interventions


**Alexander Vaiserman and Oleh Lushchak**

**Abstract** A century-long rise in life expectancy in all developed countries across the globe is, unfortunately, not accompanied by the same extension of human healthspan. This is because the aging process per se is the main risk factor for most chronic diseases affecting the elderly. Therefore, slowing down the aging rate is believed to be more effective in delaying aging-associated chronic disorders than combating them one by one, which is the conventional approach in a current disease-based paradigm. Now, different drugs designed to treat specific pathological conditions and shown to have pro-longevity properties in experimental models are being increasingly developed and investigated in pre-clinical and clinical trials to determine whether they have potential for human healthspan extension as well. The aim of this chapter is to discuss whether the conventionally used drugs can be repurposed to target the aging process per se. The advances and challenges in this emerging research field are summarized and future research directions are discussed.

**Keywords** Healthspan · FDA-approved drugs · Longevity · Life extension · Anti-aging intervention

## 27.1 Introduction

Over the past several decades, human life expectancy was significantly raised across all developed countries. This demographic trend is, however, not accompanied by the same extension of healthspan (Crimmins 2015). This is because the aging process per se is the main risk factor for most chronic diseases affecting the elderly, including immunosenecence, atherosclerosis, cardiovascular disorders, type 2 diabetes, hypertension, osteoporosis, sarcopenia, frailty, arthritis,

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cataracts, Alzheimer's and Parkinson's diseases and most cancers (Jaul and Barron 2017). Therefore, slowing down the aging rate is believed to be more effective in delaying aging-associated chronic conditions than treating them one by one, which is the conventional approach in a current disease-based paradigm. Thus, the development of efficient means for age-related disease prevention, healthspan extension and compression of morbidity to the very last years of a person's lifespan only becomes a priority task for policy makers and research organizations (Yabluchanskiy et al. 2018). In a translational perspective, a key component of research activities aimed at healthspan extension is the achievement of so-called "optimal longevity". The condition of optimal longevity is referred to as "living long, but with good health and quality of life" (Seals et al. 2016) and includes improved functioning and independence during the later stages of life.

Currently, the research activity aimed at improving the healthspan is primarily focused on slowing down the molecular and cellular mechanisms underlying aging. These studies are focused on investigating the processes commonly mediating aging such as impaired proteostasis, stem cell maintenance and cell energy sensing, mitochondrial dysfunctions, deregulated growth and stress resistance pathways, cellular senescence, and also oxidative stress and inflammatory responses (Kumar and Lombard 2016; see also Fig. 27.1 for illustration).

Since diet and physical activity are essential modifiable risk factors for most age-related chronic disorders, including type 2 diabetes, cardiovascular disease and cancer, the promotion of healthy diet and exercise regimes is an important goal for a public health policy oriented toward healthy aging (Sowa et al. 2016). In addition to modifiable life-style factors, great expectations in this regard are related to the use of various pharmacological interventions shown to be pro-longevity in different experimental models, from worms to rodents. Therapeutic modalities, which are based on these interventions, are being increasingly developed and investigated now in pre-clinical and clinical trials to determine whether they have potential for human healthspan extension (Vaiserman and Marotta 2016; Vaiserman and Lushchak 2017). These pharmacological interventions have been shown to reduce chronic inflammation, prevent cardiovascular disease, and also slow down certain functional declines. Moreover, they were found to be able to inhibit carcinogenesis by interfering with various aspects of cell metabolism, apoptosis, proliferation, and also angioneogenesis (Figueira et al. 2016). Most promising anti-aging pharmaceuticals include, among others, synthetic drugs such as rapamycin, metformin, aspirin and statins (Vaiserman et al. 2016). High hopes are also placed now on compounds derived from natural sources, e.g. polyphenols such as resveratrol, quercetin, curcumin, catechin and epigallocatechin gallate (Martel et al. 2019) and bioactive compounds from seaweeds such as fucoxanthin (Muradian et al. 2015). In addition, present-day anti-aging treatment modalities include removal of senescent cells, change in gut microbiota, transfer of blood components from young donors, and also gene- and cell-based therapies (Partridge et al. 2018). These therapeutic modalities have, however, reached the stage of preclinical testing only, so their effectiveness and safety has not been confirmed in clinical trials so far.

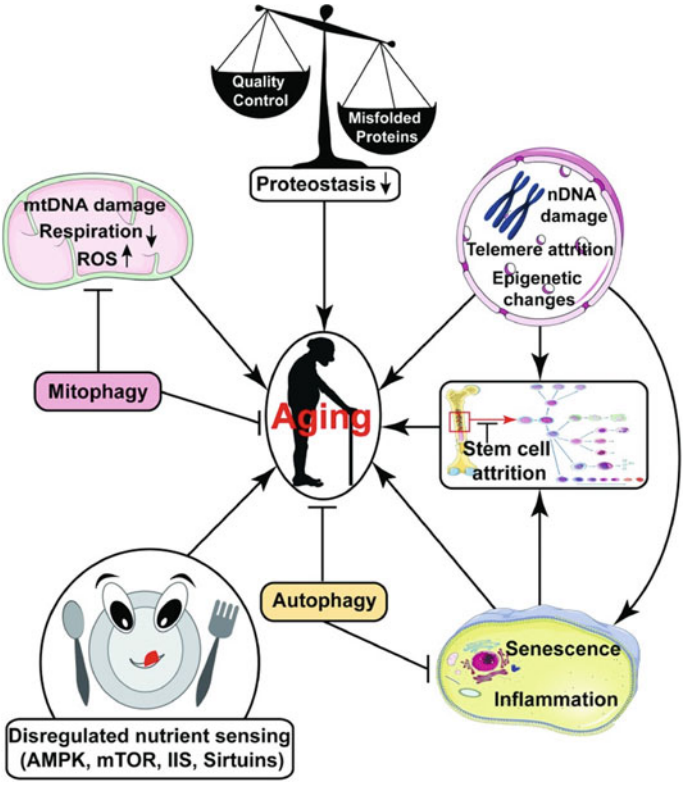


**Fig. 27.1** Summary of various factors that may contribute to aging. Dysregulation of nutrient-sensing pathways, mitochondrial dysfunction, loss of proteostasis, stem cell attrition, accumulated DNA damage, reduced autophagy, accumulation of senescent cells, and increased sterile inflammation are some important pathways thought to drive aging. This figure is reproduced from an Open access article by Kumar and Lombard (2016), which is published under a Creative Commons Attribution License

In considering healthspan-promoting effects of pharmacological agents, some theoretical considerations have to be taken into account. In particular, within the reductionist paradigm which is still accepted by many experts in the field, the organism is regarded as a totality of relatively independent mechanical components and processes. From this point of view, interventions aimed at expanding the human healthspan are considered as those which do not differ significantly from those used in car repairing. Within this paradigm, it is assumed that the aging rate may be slowed by affecting separate cellular and molecular pathways involved in specific aspects of the aging process. However, accumulated research evidence indicates that such a view is too simplistic. Since aging is a very complex trait influenced by multiple genetic pathways and environmental factors, it seems quite difficult, if not impossible, to develop pharmacological interventions able to effectively slow aging and extend healthspan by targeting only single molecular pathways (Vaiserman 2014).

One potential solution to this problem is using more complex ("holistic") therapeutic modalities (e.g. drug cocktails) to simultaneously target multiple molecular cascades related to aging.

The main aim of this chapter is to discuss whether pharmacological interventions approved by the U.S. Food and Drug Administration (FDA) and other regulatory agencies for treatment of particular diseases and shown to demonstrate pro-longevity activities in experimental models may have potential for human healthspan extension as well. Several products currently regulated by FDA as dietary supplements (e.g. vitamins and melatonin) but thoroughly investigated in clinical trials and widely discussed in the context of anti-aging medicine will be also reviewed.

## 27.2 Could Aging Be Targeted by Drugs?

At present, regulatory agencies across the world, such as the FDA, do not recognize aging as a feasible target for the pharmacological intervention (Prattichizzo et al. 2019). Nevertheless, the development of drugs specifically targeted at age-related pathologies is one of the most actively developing biomedical fields. In the search for druggable molecular targets, experimental approaches based on applying gain- or loss-of-function phenotypes are widely used to identify genetic pathways which are potentially suitable for anti-aging intervention (López-Otín et al. 2013; Moskalev et al. 2014). Even though identification of processes underlying aging is obviously a challenging task because these processes are extremely complex, significant progress has been achieved in this field over the last years.

The substantial potential for anti-aging therapy was *observed* in many natural (Cătană et al. 2018) and chemically synthesized (Vaiserman et al. 2016) substances. Compounds able to mimic the effects of calorie restriction (e.g., rapamycin, metformin, etc.) are thought to be the most promising among them (Madeo et al. 2019). High hope in treating aging-associated chronic disorders also are placed on antioxidants such as quercetin, coenzyme Q10, vitamins A, C and E and melatonin (Wojcik et al. 2010). Other potentially promising anti-aging therapeutics include inductors of autophagy (Nakamura and Yoshimori 2018; Madeo et al. 2018) and senolytics (drugs that selectively target senescent cells) (Li et al. 2019; Sikora et al. 2019). Pharmacological agents targeted to enzymes involved in processes of epigenetic regulation, in particular, inhibitors of histone deacetylases such as suberoylanilide hydroxamic acid (SAHA), valproic acid, sodium butyrate and trichostatin A are one more promising drug class for pro-healthspan and anti-aging intervention (Vaiserman and Pasyukova 2012; Pasyukova and Vaiserman 2017; McIntyre et al. 2019). All compounds mentioned above were found to have the potential to extend life expectancy up to 25–30% in various animal models and some of them have already reached clinical trials for treating age-associated conditions (Vaiserman et al. 2016). Additionally, profound capabilities to combat aging-related disabling conditions and chronic illnesses were shown for many phytobioactive compounds including catechins, curcumin, epigallocatechin gallate (EGCG) and genistein (Martel et al. 2019).

Substantial anti-hypertensive and anti-obesity capacities have been also found for certain secondary metabolites derived from seaweeds (Muradian et al. 2015; Seca and Pinto 2018). The safety and efficiency of these compounds were, however, not approved by the FDA by now, so they are not discussed in this chapter.

An important consideration in this context is, however, that most agents having anti-aging potential are obviously multifunctional and targeted at different molecular and cellular pathways underlying aging processes. Furthermore, overall health benefits of these substances have only recently begun to be examined and only limited evidence was found for their capacity to substantially promote human healthspan to date. Research findings from observational and clinical studies aimed at evaluating the efficacy and long-term safety of these drugs are often inconsistent and vary among different investigations. Furthermore, data from some studies indicate that long-time uncontrollable intake of such medications can be unnecessary or even dangerous. In the subsequent sections, research findings in this field will be summarized and discussed.

## 27.3 Antioxidants

Long-term consumption of dietary antioxidants is traditionally considered by most healthcare professionals and patients/consumers as a reasonable option to promote human health and wellbeing (Huang 2018). They are also suggested to combat various aging-associated diseases such as atherosclerosis, inflammatory conditions, cardiovascular disease and cancers (Tan et al. 2018). This therapeutic strategy is based on the assumption that excessive production of reactive oxygen species (ROS) and subsequent decrease in vascular bioavailability of nitric oxide (NO) is the common pathogenetic mechanism of the endothelial dysfunction and atherosclerotic process, resulting from diverse cardiovascular risk factors such as hypercholesterolemia, hypertension, metabolic syndrome, type 2 diabetes, and smoking (Münzel et al. 2010). It is commonly believed that dietary antioxidant supplementation may be especially useful in therapy for aging-associated diseases. This is because elderly people are quite susceptible to high oxidative stress levels due to the decreased performance of their endogenous antioxidant systems (Conti et al. 2016).

Life-extending effects of antioxidants were reported in many animal models. These effects were generally accompanied by reduced levels of oxidative stress, elevated activity of antioxidant enzymes, enhanced stress resistance and reproductive activity, and also by changed expression of aging-related genes (Vaiserman et al. 2016). Findings from pre-clinical and clinical studies examining the effects of dietary supplementation with antioxidants such as vitamin C, vitamin E, and also folic acid in combination with vitamin E in human populations have been, however, disappointing. Overall health outcomes of such interventions are often ambiguous or uncertain (Goszcz et al. 2015). Indeed, meta-analyses of observational studies and clinical trials on the topic have indicated that long-term consumption of dietary antioxidants, e.g., β-carotene and vitamins A and E, may even result in adverse health outcomes

and in elevated cancer and all-cause mortality rates; these unfavorable outcomes were shown to be more pronounced in well-nourished populations (Bjelakovic et al. 2013, 2014). Such discrepancy between data from animal and clinical studies is now commonly referred to as an "antioxidant paradox" (Biswas 2016). This paradox, consisting in little or no preventive/therapeutic effects of dietary antioxidant supplements despite obvious involvement of oxidative stress in most chronic diseases, can likely be explained by the dual roles of antioxidants in ROS production. Indeed, exogenous antioxidants may act not only as ROS scavengers, but they can also be easily oxidized and act as pro-oxidants thereby promoting damage of biomolecules when present in large concentrations (Milisav et al. 2018). Moreover, since oxidative stress and inflammation coexist in most diseases, the failure of clinical trials with dietary antioxidants can be explained by their incapability to simultaneously target both oxidative stress and inflammation. Indeed, they can block certain pro-oxidative and/or proinflammatory pathways but at the same time reinforce others (Biswas 2016). In addition, increasing evidence indicates that ROS play essential roles as important secondary messengers implicated in various vital processes such as cell survival, apoptosis, proliferation, differentiation and intracellular signaling, and also stress and immune responses (Bardaweel et al. 2018; Milkovic et al. 2019). The considerations above imply that oxidative stress may cause both harms and benefits for human health, depending on particular conditions and circumstances (see Fig. 27.2 for illustration), and targeting ROS-induced diseases by dietary antioxidants is an extraordinarily complex and difficult task (Toledo-Ibelles and Mas-Oliva 2018).

In conclusion, dietary supplementation with synthetic antioxidants can likely prevent ROS-induced damage under oxidative stress caused by environmental oxidant exposures or at impaired endogenous oxidative stress responses of an aged individual. The existing evidence however suggests that supplements with synthetic antioxidants often cannot provide appropriate protection against oxidative damage in normal situations and that using antioxidants to prevent aging-related chronic disorders is controversial in the situation of the normal oxidative stress levels. Thus, dietary antioxidant supplementation may be admissible in case of chronic diseases, including aging-associated ones, caused by strongly disturbed balance between oxidative and antioxidative processes and related sustained inflammation such as inflammatory bowel disease, chronic obstructive pulmonary diseases, and also neurodegenerative and cardiovascular disorders (Liu et al. 2018). Therefore, there is a need for accurate determination of the levels of individual's oxidative stress before prescribing the antioxidant supplements. In addition, development of innovative biotechnological strategies (e.g. nanotechnology-based platforms for targeted antioxidant delivery to specific organs or tissues differing in redox state within the body) may open new horizons for further healthspan-promoting antioxidant therapies (Lushchak et al. 2019).

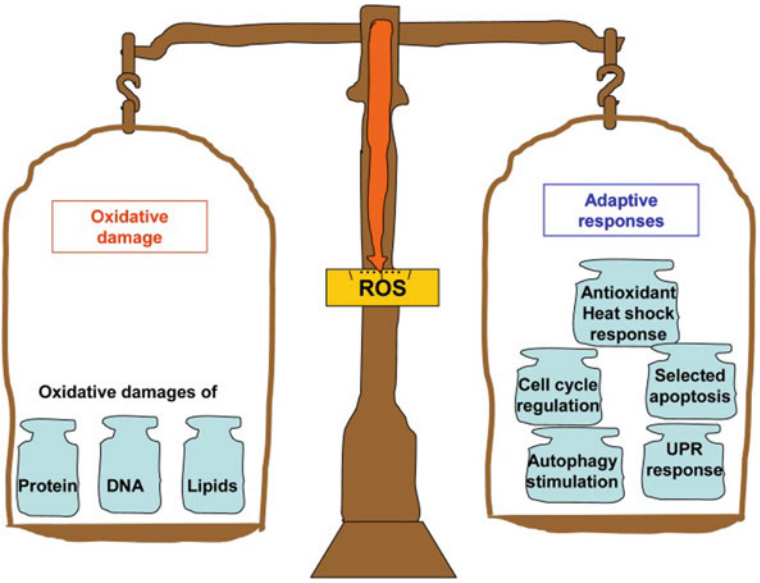


**Fig. 27.2** Summary of the bifurcated effects that can be induced by ROS. On the one hand, ROS induces the oxidative damage to proteins, DNA and lipids. On the other hand, they also trigger the organism's adaptive responses including antioxidant and heat shock responses, fatty acid deacylation-reacylation, cell cycle regulation, DNA repair and apoptosis, unfolded protein responses, and autophagy stimulation. On the other hand, they also trigger the organism's adaptive responses including antioxidant and heat shock responses, cell cycle regulation and apoptosis, unfolded protein responses, and autophagy stimulation. This figure is reproduced from an Open access article by Mao and Franke (2013), which is published under a Creative Commons Attribution License

## 27.4 Melatonin

Melatonin is a natural hormone secreted from the pineal gland at night. Aside from the key role in regulating sleep–wake cycle, it demonstrates many vital abilities, including antioxidant, anti-inflammatory, neuroprotective, blood pressure-reducing, pain-modulating, retinal, vascular and anti-tumor activities (Claustrat and Leston 2015; Emet et al. 2016). The role of melatonin in aging-associated processes is clearly evident from observations that various aging-related pathological conditions are related to the loss of melatonin secretion and declining the amplitude of the circadian melatonin rhythm (Hardeland 2012, 2013).

Despite high hopes associated with the use of melatonin, there are yet some concerns about its supplementation. An important point is that it is differently regulated across countries. Indeed, it is regulated in Canada as a natural health product, in the USA as a dietary supplement, and in Australia as a prescription medicine (Dwyer et al. 2018). Therefore, it is available in varied doses and formulations, representing a very heterogeneous group of products whose efficacy and safety are supported

by limited data only. Moreover, although melatonin is relatively non-toxic, several moderate side effects have been reported, especially under long-term supplementation at doses much higher than those which are normally produced in the body. These potential side effects include drowsiness, headaches and nausea (Posadzki et al. 2018). Thus, the issues related to the overall safety and potential side effects of melatonin still need to be addressed. This is especially true for older people. Evidence was obtained that melatonin can stay active in elderly people longer than in young subjects and leads to daytime drowsiness. In particular, the 2015 guidelines by the American Academy of Sleep Medicine recommend against the use of melatonin for patients with dementia (Auger et al. 2015).

## 27.5 Caloric Restriction Mimetics

Caloric restriction (CR) is regarded now as the most effective and reproducible strategy to slow down aging and increase the healthspan. CR commonly refers to a reduced calorie intake without essential nutrient deficiency (Most et al. 2017). Generally, CR represents feeding a diet containing all essential nutrients, minerals and vitamins but having reduced (by 20–60% compared to ad libitum levels) amounts of calories (Ingram and Roth 2015; López-Lluch and Navas 2016). In experimental studies, CR was shown to be the most effective pro-longevity intervention to date (Liang et al. 2018).

The ability of CR to slow down aging and promote longevity has attracted great scientific attention since the pioneering works of McCay and colleagues conducted as early as the 1930s. In these experiments, it has been demonstrated that rats maintained on a 40% CR had up to 50% longer median and maximal lifespans than rodents fed a standard diet. Afterwards, it has been repeateadly confirmed that CR may slow down aging processes and extend longevity in various species including yeast, worms, insects and rodents (Ingram and Roth 2015; Ingram and de Cabo 2017). Recently, evidence has also been provided that CR may delay the onset of aging-associated pathologies in nonhuman primates such as rhesus monkeys. More specifically, CR slowed down the rate of age-associated muscle loss, reduced body fat levels, improved glucose tolerance and insulin sensitivity, and also lowered incidence of cardiovascular disease, type 2 diabetes and cancer (Colman et al. 2014; Balasubramanian et al. 2017). Furthermore, CR led to a reduced rate of age-related mortality in primates (Colman et al. 2014). Accumulating data also indicate that moderate CR can reduce cancer risk, and cause protective effects against hypertension, type 2 diabetes, obesity, inflammation, and cardiovascular disease in humans. Observational studies and randomized clinical trials have demonstrated that CR in humans caused metabolic and molecular adaptations similar to those found to improve health status and retard the accumulation of age-related molecular damage in various animal models (Most et al. 2017). Generally, the beneficial outcomes of CR have been shown to be mediated by activating pathways that are known to contribute to the regulation of repair, immunity and metabolism, as well as thermoregulation and appetite (Le Couteur et al.

2012). Such advantageous effects of CR likely result from highly regulated processes arising through activation of specific effectors (Mouchiroud et al. 2010). Among the nutrient-sensing pathways implicated in the control of longevity by CR, there are the insulin/insulin-like growth factor signaling, adenosine monophosphate (AMP)-activated protein kinase (AMPK) and mTOR pathways, and also sirtuins, particularly SIRT1. These pathways are well known to be key regulators of cell growth, mitochondrial function, autophagy and proliferation, and they are also known to be regulated by interaction with one another.

Despite the fact that CR may clearly postpone the development of most aging-associated disorders, it is a subject of debate so far whether it could extend the human health- and lifespan. In experimental studies, CR did not always lead to uniquely positive effects with respect to longevity (Sohal and Forster 2014). Several authors assume that control animals that fed on basal ad libitum diet are often overweight and are at risk for associated health problems. Thereby, they would seem not to be suitable for investigating longevity (Sohal and Forster 2014). Nonetheless, even despite these obvious challenges and limitations, the concept of CR continues to be one of the major paradigms in modern biogerontology (Ingram et al. 2006; Ingram and Roth 2015).

From a translational perspective, an important point is that long-term (usually more than 3 months) CR is necessary to induce pro-healthspan effects in human beings (Ingram and Roth 2015; López-Lluch and Navas 2016). It seems obviously problematic, making such interventions difficult to apply for most modern people. Doubts about the applicability of the CR-based treatments have driven a rising interest in elaboration of alternative treatment strategies that might provide pro-healthspan CR benefits without severe restriction in food intake. Currently, several compounds are developed for use in these therapies. Such substances are commonly referred to as CR mimetics (Lushchak and Gospodaryov 2016). Basic characteristic properties of CR-mimicking agents are as follows: (1) inducing the physiological, hormonal and metabolic effects which are similar to those induced by CR; (2) activating the stress response pathways like CR; (3) extending the lifespan and delaying the onset and/or reducing the incidence of age-related disorders (Ingram et al. 2006). The most promising pharmacological agents modulating these pathways by mimicking CR effects and also challenges related to their application are reviewed and discussed in the subsections below.

## 27.6 Metformin

Currently, metformin (dimethyl-biguanide) is considered to be a first-line drug in treating type 2 diabetes (Sanchez-Rangel and Inzucchi 2017). It is the derivative of galegine, a hypoglycemic substance from the plant French lilac, *Galega officinalis,* which was widely used in herbal medicine in medieval Europe (Bailey 2017). After the long-term cardiovascular benefits of this glucose-lowering medicine were identified in 1998 by the UK Prospective Diabetes Study (Turner 1998), metformin was

implemented as an initial therapy to manage hyperglycemia in type 2 diabetes. Physiologically, the effects of this antidiabetic biguanide may be explained by suppressing hepatic gluconeogenesis without inducing weight gain, enhancing insulin secretion, and posing a hypoglycemia risk (Madiraju et al. 2014). The precise molecular mechanisms underlying these effects remain largely unknown, but modulating the AMPK pathway which maintains the cellular energy balance by changing ATP production appears to play a major role in metformin action (Rena et al. 2017). These effects are also likely related to (AMPK)-independent mechanisms, such as inhibition of mitochondrial respiration and lysosome-related mechanisms. Due to these mechanisms, metformin inhibits the liver mitochondrial respiratory chain, resulting in activation of AMPK, improving insulin sensitivity (due to effects on fat metabolism) and reducing the mRNA levels of gluconeogenic enzymes (Rena et al. 2017).

Since metformin decreases hepatic glucose production, it may also act as a CR mimetic (Viollet et al. 2012). Treatment with metformin was shown to cause life extension in various animal models including worms, flies and rodents (Piskovatska et al. 2019a, b). Evidence for pro-health effects of metformin, including reduced incidence of neurodegenerative disease and cancer, has also been provided in several human studies (Soukas et al. 2019). Significant improvement in body mass index, total cholesterol, low-density lipoprotein cholesterol, and non-high density lipoprotein cholesterol was, in particular, found in the metformin-treated children with metabolic syndrome (Luong et al. 2015). Anti-cancer effects of metformin have also been observed in both diabetic and non-diabetic persons (Coperchini et al. 2015).

It is, however, unclear to what extent these pro-healthspan effects of metformin may be mediated by activating AMPK. Over the past decade, a simple view that metformin may improve glycemic status by acting on the liver through the activation of AMPK, has been moved to a much more complex view reflecting the multiple modes of action of this drug (Rena et al. 2017). Indeed, evidence is obtained that AMPK-independent pathways may also be implicated in its effects, either beneficial or harmful (Zheng et al. 2015). These pathways include inhibition of mitochondrial shuttles, suppression of glucagon signaling, induction of mitochondrial stress and autophagy, attenuation of inflammasome activation and reduction of terminal endoplasmic reticulum stress (Hur and Lee 2015). Remarkably, substantial similarity between alterations in gene expression profiles induced by both metformin and CR was shown by microarray analysis (Dhahbi et al. 2005). Moreover, importantly, some observations suggest that beneficial effects of metformin might be indirectly mediated by the effects on intestinal microbiota (MacNeil et al. 2019). Recent evidence indicates that metformin may modulate the gut microbiome via promoting the expansion of beneficial bacteria and counteracting the growth of harmful bacterial species (Prattichizzo et al. 2018). It is hypothesized that such an action may positively shift the balance between pro- and anti-inflammatory mediators, thereby improving glycemic control and promoting healthspan.

A recent meta-analysis indicated that therapy with metformin may exert beneficial effects on all-cause mortality and incidence of aging-related diseases, such as cardiovascular disease and cancer, in type 2 diabetes patients compared to diabetics receiving other therapies, and also to non-diabetic populations (Campbell et al. 2017).

These findings, collectively, suggest that metformin can act as a geroprotective agent. To verify this assumption, a placebo controlled, multi-center study named TAME (Targeting Aging with MEtformin) in ~3000 elderly aged 65–79 has been recently designed (Barzilai et al. 2016). The aim of this study was to investigate whether metformin can be repurposed to target aging per se and whether it is able to reduce the risk for various geriatric syndromes and aging-related diseases as well as the functional health status. An important point is that this research has been developed in consultation with the FDA to obtain a novel FDA indication to specifically target aging. It is believed that such an indication would allow regulatory authorities to approve designs aimed at the development of next-generation drugs to target aging and extend human healthspan.

In implementing a therapy with metformin in aged healthy persons, however, certain potential side effects related to such a treatment modality should obviously be taken into account. Indeed, reasonable concerns exist among many medical professionals regarding the adverse effects of metformin such as gastrointestinal disorders and lactic acidosis (Pryor and Cabreiro 2015). It has also been found to induce hyperhomocysteinemia, deficiency of vitamin B12 and vascular complications in type 2 diabetes patients (Glossmann and Lutz 2019), and also cognitive dysfunction (Porter et al. 2019). These side effects of metformin should be, of course, thoroughly evaluated before such a therapy will be put into practice.

## 27.7 Rapamycin

Rapamycin (sirolimus) is a natural macrocyclic lactone fermentation compound produced by the bacteria *Streptomyces hygroscopicus*. Initially, rapamycin was developed as an antifungal agent but subsequently it has been shown to have strong regulatory effects on basic biological processes such as cellular growth and proliferation and also on inflammatory pathways due to its inhibitory action on the mTOR pathway (Lamming et al. 2013; Lushchak et al. 2017). Since rapamycin has been found to inhibit immune responses, it was subsequently applied in immunosuppressive therapy in order to prevent graft rejection and treat autoimmune diseases (Ingle et al. 2000). Presently, rapamycin and its analogs (rapalogs), such as everolimus and temsirolimus, are assumed to be among the most promising anti-aging ingredients (Blagosklonny 2007). In different rodent models, rapamycin administration was repeatedly found to be able to delay aging-associated pathological conditions, including accumulation of the sub-cellular myocardium changes, endometrial hyperplasia, tendon stiffening, liver degeneration, and decline in physical activity (Wilkinson et al. 2012). It is also proved to be efficient in combating various aging-related pathologies including retinopathy, atherosclerosis, cardiac hypertrophy, cognitive decline, neurodegenerative disorders, and loss of stem cell functioning (Blagosklonny 2017).

However, even although rapamycin was approved by the FDA and is now being widely used worldwide, many clinicians believe that its application may result in

serious metabolic impairments, including type 2 diabetes and, therefore, this medication cannot be safely used as an anti-aging drug. This concern is primarily due to the fact that long-time intake of rapamycin can be associated with enhanced risk of developing insulin resistance (Blagosklonny 2012). Such an effect of rapamycin, however, may be more complicated and ambiguous than it seems to be at first sight. Indeed, rapamycin may induce, in certain circumstances, a complex conglomerate of conditions related to (dys)regulation of insulin signalling, including insulin sensitivity, insulin resistance and also glucose intolerance without insulin resistance (Blagosklonny 2019a, b). Remarkably, these effects are similar to those seen in very low caloric diets or fasting. An important point is that both these dietary regimes are shown to improve insulin sensitivity and reverse type 2 diabetes, but they also may lead to a specific kind of glucose intolerance currently referred to as starvation-induced pseudo-diabetes. The concept of starvation-induced pseudo-diabetes is related to the idea that insulin resistance is an adaptive mechanism which can become maladaptive under particular conditions. From these assumptions, it is suggested that starvation/fasting may result in decreased insulin levels and cause insulin resistance originating as a compensatory response designed to saving glucose for the brain (Watve and Yajnik 2007; Tsatsoulis et al. 2013). Moreover, glucose utilization by the brain is decreased during prolonged starvation since the brain begins to utilize ketone bodies as the major fuel. Remarkably, there is evidence that the insulin-resistant state can be associated with life extension in animal models. For instance, insulin receptor substrate 1 null mice (Selman et al. 2008) and Klotho overexpressing mice (Kurosu et al. 2005) were shown to live longer than controls even though they exhibit insulin resistance. Recently, Blagosklonny (2019a,b) introduced the term benevolent pseudo-diabetes, or benevolent glucose intolerance to refer to this phenomenon. Indeed, there is no indication until now that starvation-induced pseudo-diabetes is detrimental. Although pseudo-diabetes shares several hallmarks with "typical" diabetes, it is really not true diabetes and does not lead to the most common diabetic complications. By contrast, it was associated with improved health and life extension in several studies. To overcome concerns related to inducing hyperglycemia through rapamycin treatment, Blagosklonny (2019a) proposed to use a combination of rapamycin and an anti-diabetic drug such as metformin. Indeed, some experimental evidence indicates that rapamycin-induced hyperglycemia can be attenuated by simultaneous treatment with metformin (Weiss et al. 2018), and such treatment may be well tolerated by patients (Sehdev et al. 2018). So, such a therapeutic strategy may likely be useful in further healthspan-promoting interventions.

## 27.8 Aspirin

Aspirin, also known as acetylsalicylic acid, is a most commonly used nonsteroidal anti-inflammatory drug. Historically, this synthetic drug was developed based on an extract from the bark of the white willow tree, *Salix alba* (Montinari et al. 2019). Its active ingredient, salicin, is converted to salicylic acid in the body, thus resulting in

many therapeutic benefits. Due to these benefits, the bark of the willow tree has been used medicinally since ancient times. Currently, aspirin is one of the most widely used non-prescription drugs. Its mechanism of action is based on inhibiting the activity of a specific enzyme, cyclooxygenase (COX) and preventing the formation and release of prostaglandins and precluding inflammation (Botting 2010). However, by inhibiting this enzyme involved in the prostaglandin synthesis, aspirin and aspirin-like drugs also prevent the production of physiologically important prostaglandins protecting the stomach mucosa from damage by hydrochloric acid and maintaining kidney function and aggregate platelets when required (Vane and Botting 2003). Moreover, it has been discovered that there exist two different isoforms of the COX enzyme. The constitutive isoform, COX-1, was shown to support vital homeostatic functions, while inflammatory mediators activate the inducible isoform, COX-2, and its products cause symptoms of inflammatory states such as osteoarthritis and rheumatoid arthritis (Vane and Botting 2003). Presently, aside from inflammatory conditions, aspirin is widely applied to treat pain, fever, and platelet aggregation, as well as to prevent cardiovascular diseases and cancer (Thun et al. 2012). Since aspirin may affect ROS production, cytokine responses and block glycooxidation reactions, which are all regarded as common hallmarks of aging, it was proposed to be a promising anti-aging agent (Phillips and Leeuwenburgh 2004).

Evidence was obtained that aspirin is able to reduce age-associated functional declines and extend longevity in different animal models (Danilov et al. 2015). In humans, aspirin is widely used due to its established antithrombotic action. It can inhibit the platelet function by irreversibly inhibiting the COX activity; therefore, it has been mainly used until recently for primary and secondary prevention of arterial antithrombotic events (Mekaj et al. 2015). Furthermore, this medication is commonly indicated for primary and secondary prevention as well as for the treatment of various diseases. Among them, there are cardiovascular diseases such as acute coronary syndrome, peripheral artery disease, myocardial infarction, acute ischemic stroke, and also transient ischemic attack. In epidemiological and clinical studies, evidence was also obtained that aspirin may reduce cancer incidence and mortality by influencing both COX and non-COX pathways (Ma et al. 2017). Several studies also indicated that aspirin, among other non-steroidal anti-inflammatory drugs, may reduce the risk for age-related neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, although findings from these studies are rather inconclusive (Auriel et al. 2014).

Although aspirin is currently among the medications most widely used by middle-aged and older adults to prevent heart attacks and stroke, its regular use is largely limited by serious adverse effects (Huang et al. 2011). When tested in clinical trials for primary prevention of predominantly low risk individuals, aspirin was demonstrated to decrease the rate of cardiovascular events but with an almost equivalent increase in the risk of gastrointestinal bleeding (Nansseu and Noubiap 2015; Gelbenegger et al. 2019). Consequently, expert recommendations for aspirin use in primary prevention of cardiovascular events differ substantially, reflecting uncertainty of the benefit/risk ratio in the choice of treatment strategies for at-risk patients.

## 27.9 Statins

Statins are a drug class able to significantly reduce levels of cholesterol and triglycerides in the bloodstream. Their lipid-lowering effect is attributed to inhibiting the critical step of cholesterol synthesis in the liver via the mevalonate pathway. An important point is that, as the mevalonate pathway also affects the inflammatory responses, as well as endothelial function and coagulation, the effects of statins can reach well beyond their cholesterol-lowering capabilities (Pinal-Fernandez et al. 2018). Owing to these pleiotropic effects known to play an important role in aging-related processes, statins have attracted a lot of interest in anti-aging medicine recently. In the U.S., a highly significant negative association with death was demonstrated for statin users, and the mean age at death was two years higher among statin users than among nonstatin users, even despite the statin users being at a higher risk of death (Mehta et al. 2006). Treatment with statins caused significantly increased survival rate among the very old subjects (aged 85–90 years). Remarkably, the extension of life in these individuals was independent of the cholesterol level (Jacobs et al. 2013). More recently, preserved resilience and survival were found among the statin users in the community-dwelling male octogenarians (Luotola et al. 2019), and also in debilitated nursing home residents (Schlesinger et al. 2019). In a retrospective cohort study, statin use was not associated with a reduction in atherosclerotic cardiovascular disease or in all-cause mortality in participants older than 74 years without type 2 diabetes (Ramos et al. 2018). In the presence of type 2 diabetes, however, treatment with statins was associated with substantial reduction in the incidence of atherosclerotic cardiovascular disease and in all-cause mortality. This effect was diminished after the age of 85 years and disappeared in nonagenarians.

The potential adverse effects of statin therapy are also described. Along with unfavorable effects on liver and muscle recognized soon after introducing statins in the 1980s, these effects include risks of new-onset diabetes, cognitive impairments and hemorrhagic stroke associated with achieving very low levels of low-density lipoprotein cholesterol (Adhyaru and Jacobson 2018; Newman et al. 2019). Recognition of these side effects of statins and the increased media attention to potential adverse events associated with their use cause concerns about initiating such a therapy or its discontinuation by many patients. However, recent large-scale studies on this issue indicated that the frequency of these adverse effects is extremely low, so benefits of statin therapy in patients for whom statin treatment is recommended by current guidelines, far outweigh any perceived or real risks (Adhyaru and Jacobson 2018; Pinal-Fernandez et al. 2018).

One of the most debatable issues in this context is whether statins can be used in the elderly. Indeed, while for most patients, the benefits of statin therapy outweigh its possible adverse effects, the impact of statins on musculoskeletal ability, cognitive function, and independence need to be heavily weighed before prescribing such therapy in individuals over 75 years of age (Leya and Stone 2017). It seems especially important considering that levels of serum cholesterol tend to increase in adult age, but subsequently decrease in the very elderly. Therefore, the use of cholesterol-lowering

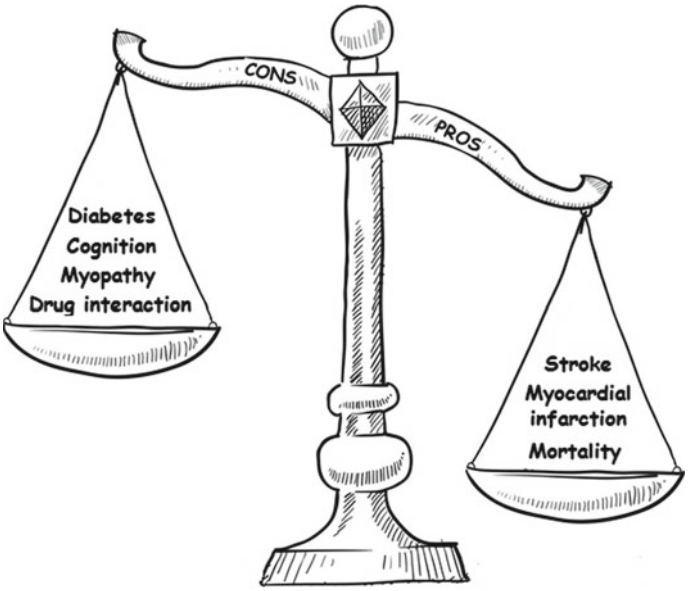


**Fig. 27.3** Pros and cons for the statin use

agents like statins in old age seems extremely controversial and the benefit/risk ratio have to be weighed carefully before prescribing statins, especially to patients over 75 (Leya and Stone 2017; see also Fig. 27.3 for schematic illustration).

## 27.10 Conclusions

The aging process is commonly believed to be an inevitable part of the human life cycle. According to many experts, however, this opinion appears rather questionable (Mitteldorf and Fahy 2018). A large body of research evidence indicates that aging is neither inevitable nor universal; indeed, germ lines and several organisms (e.g. *Hydra*) do not exhibit any noticeable senescent decline (Flatt and Partridge 2018). Therefore, aging is assumed to be "druggable" like other pathological conditions (Flatt and Partridge 2018). One widely-discussed issue among the general public, physicians and governmental regulators regarding intervention in the aging process is the concern that the rise in human life expectancy might lead to a rise in the proportion of older people in general populations across countries and, consequently, to a higher prevalence of aging-associated chronic conditions. It could become an overwhelming economic and social burden for the future generations. These concerns, however, seem largely unfounded. Indeed, in various animal models, pharmacological lifespan extension was shown to be accompanied by decreased or delayed morbidity, including a reduced incidence of neurodegenerative and cardiovascular

diseases, as well as cancer (Fontana et al. 2010). Moreover, observational findings obtained from human populations are mostly consistent with these findings from animal models. For example, centenarians living in so-called Blue Zones (regions where people live much longer than average) were found to remain free from disabilities and chronic diseases until a very old age (Willcox et al. 2008). Based on this, we can assume that properly matched pharmacological interventions in the aging process would rather lead to healthspan extension due to delaying the onset of aging-associated chronic pathologies and to compressing aging-related morbidity to only the very last years of the life course. Another potential issue is that certain anti-aging drugs may exert beneficial effects on some aging-related pathways but simultaneously adversely impact others. In order to overcome this obstacle, the application of drug cocktails to contemporaneously affect multiple pathways was proposed (Ingram and Roth 2015). One example of such a treatment approach is the use of metformin to overcome the rapamycin-induced glucose dysmetabolism (Mendelsohn and Larrick 2012). Another example is the combined therapy of rapamycin with statins, proposed to mitigate the rapamycin-induced dyslipidemia (Blagosklonny 2017). Such a combined approach can likely provide a more balanced and secure treatment mode than if one drug alone is used, especially in healthy individuals. Evidence for efficiency of such a cocktail-based approach was recently obtained in a small-size Thymus Regeneration, Immunorestoration and Insulin Mitigation (TRIIM) trial conducted by Fahy et al. (2019). In this trial, the cocktail consisting of the growth hormone and two anti-diabetic drugs, dehydroepiandrosterone and metformin, was applied. Anti-diabetic medications were used in this study since it is known that treatment with growth hormone may promote diabetes. In this trial, improved risk indices for various age-related diseases and a mean epigenetic age approximately 1.5 years less than baseline have been observed after one year of treatment. The immune systems of the study participants also demonstrated signs of rejuvenation.

Conducting clinical trials aimed at investigating the healthspan-promoting potential of conventionally used drugs certainly represents a very difficult task. This difficulty is, in particular, related to the fact that elderly patients are typically multimorbid and get multiple drugs. According to current estimates, more than one third of elderly patients simultaneously use five or more prescription drugs, often along with the intake of one or more over-the-counter drugs or dietary supplements (Maher et al. 2014). Therefore, the results of clinical trials conducted with geriatric patients can be significantly confounded by certain drug-drug interactions (Shenoy and Harugeri 2015). One more important limitation of randomized controlled trials in geriatric patients is considering defined age and/or concomitant disease as exclusion criteria. It makes it difficult to precisely estimate the entire spectrum of anti-aging and healthspan-promoting effects of the investigated medications (Zulman et al. 2011). Furthermore, since many drugs have a “therapeutic window” of effect, which means that either too little or too much (and also too early or too late) intervention may prevent the optimal response, the proper dosing and life-course timing of healthspan-promoting drugs have to be thoroughly determined prior to their application (Burd et al. 2016; Piskovatska et al. 2019a, b). An important question is also whether health

status could depend differently on the mode of intervention, e.g., cholesterol-reducing effects of statins, glucose-lowering effects of metformin, anti-inflammatory effects of aspirin, autophagy-inducing effects of spermidine, etc.

The important consideration in designing clinical trials for healthspan-promoting interventions is also the choice of outcome measure (Fleming and Powers 2012). Indeed, clinical evidence for effectiveness of such interventions is typically based on the data regarding the prevention or treatment of particular aging-related disorders, but not on the early markers of age-related functional declines and aging rate per se. This is an important obstacle in terms of a translational perspective. Indeed, as stated in the WHO World Report on Ageing and Health (2015), "healthy ageing is more than just the absence of disease; the maintenance of functional ability has the highest importance." Thus, the conclusion about the efficiency of healthspan-promoting interventions cannot be done only based on disease prevention/treatment. In addition, the success of such therapy obviously depends on the health status of the intervention group. Indeed, the success of such therapy in a group of sick people will not necessarily mean that it will be just as successful when used in healthy subjects. The lack of reliably measurable biomarkers to evaluate the rate of human aging and effectiveness of anti-aging interventions remains an important challenge in this field (Moskalev et al. 2016). Therefore, the development of innovative algorithms to accurately determine the biological age of people in order to evaluate their health status and to access the efficiency of healthspan-promoting interventions is of paramount importance in biogerontological research.

In conclusion, since processes implicated in aging are extraordinarily complex and intertwined, the healthspan-promoting effects of anti-aging pharmacological interventions are often unsatisfactory and greatly limited by their side effects. So, implementation of such treatment modalities in routine clinical practice is apparently a long-term process that will require numerous translational steps to address ongoing and future challenges in the field. After overcoming these obstacles, however, implementing such therapeutic approaches can undoubtedly provide innovative strategies for human healthspan extension.

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# Chapter 28
# Hormesis, Resilience and Mental Health: Enhancing Public Health and Therapeutic Options


**Vittorio Calabrese, Maria Scuto, and Edward J. Calabrese**

**Abstract** The concept of acquired resilience and its role in medicine and public health has emerged as a central topic for the new decade. Stress is a response to any environmental adversity (i.e., biological, emotional and cognitive) but dysregulation of adaptive stress responses which lowers resilience and health, can increase vulnerability to pathological conditions such as brain disorders, particularly, neuropsychiatric (i.e., schizophrenia, depression, anxiety, autism spectrum disorders), and neurodegenerative diseases (i.e., Alzheimer's diseases and Parkinson's disease). Mild stress can be beneficial by upregulating adaptive responses which enhance biological performance and protect against subsequent toxic challenges. In contrast, toxic stress reflecting an inability to cope, results in a dysregulation of adaptive stress response mechanisms and low resilience which can increase vulnerability to illness. In this context, resilience is the process of adapting and successfully coping with adverse life events, including chronic stress, socio-environmental factors, trauma, some type of catastrophe, physical or sexual abuse, negligence or parental mental illness. Detailed evaluations of biological systems showing acquired resilience reveal an hormetic biphasic dose response relationship, being reported as the result of either a direct low dose stimulation or within the context of a preconditioning experimental protocol. The hormetic dose response defines the expression, amplitude, duration and limitations of the acquired resilience in all biological systems. These acquired resilience-hormetic dose responses are reported in the pharmacology and nutritional literature with considerable information now clarifying underlying mechanisms at the level of receptor and cell signaling pathways. The study of human resilience is still a mostly phenomenological literature which has only begun to characterize

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biological factors in resilient individuals that are associated with more successful coping responses. Integration, optimization and tailoring of such developments to the treatment of patients offers a profound challenge and opportunities to the progress of biomedical sciences and therapeutic medicine.

**Keywords** Resilience · Healthy brain · Hormesis · Vitagenes · Plant polyphenols

## 28.1 Introduction

Resilience, as the ability to adequately adapt and respond to homeostatic perturbations, is a recent emerging concept. Although resilience has been associated with positive health effects, the neurobiological basis of resilience is still a matter of investigation and remains an open question.

It is generally recognized now that multiple factors, such as severity and number of traumatic events during prenatal neurodevelopment and adolescence, timing of exposure to adversity, developmental history, cognitive flexibility and environmental changes such as toxicant exposure compromise health and wellbeing over the lifespan. Consistent with this notion, in the attempt to operationalize at cellular level the neurobiology of stress resistance, cellular resilience describes the ability of a cell to cope with detrimental metabolic and signaling conditions where cellular metabolism does not collapse immediately after the hit or enter into cell death. Rather, this cellular ability puts in motion a programmed cell life program through stress responsive signaling which promotes a new homeostasis under stress. The processes of reverting "back to normal" have not been studied so extensively at the cellular level. The defense and resilience programs include a number of cellular stress responses, such as rearrangements in energy metabolism, oxidative stress responses, including hypoxia signaling via HIF-1, the heat shock response via HSF-1, the antioxidant response via Nrf-2, stress kinase signaling via JNK and AP-1, DNA damage responses via p21 or BCL2, and the unfolded protein response/amino acid starvation response via ATF-4/ATF-6 activation of anti-apoptotic pathways and DNA repair mechanisms. The actual contribution of these adaptive responses to reestablishing homeostasis represents an emerging area of interest in need of clarification. Efficient functioning of resilience processes, by enhancing endogenous cellular redox homeostatic mechanisms, integrate adaptive stress responses via the heat shock and Nrf2 related pathways (Fig. 28.1), as well as sirtuins via AKT/mTOR signaling, thus representing a complex operational network under control of genes, termed vitagenes (Calabrese et al. 2010) (Fig. 28.2), as well as epigenetic changes that leave a molecular "memory/scar"—mirroring alterations that are the consequence of the stress experienced by the cell.

These memories might have long-term consequences, both positive (resistance) and negative (vulnerability), that contribute to chronic and delayed manifestations of hazard and, ultimately, disease. Compromised adaptive responses to adversity, such as brain trauma or psychological stresses, i.e., low resilience, can increase vulnerability to pathological conditions such as anxiety, depression, post-traumatic stress

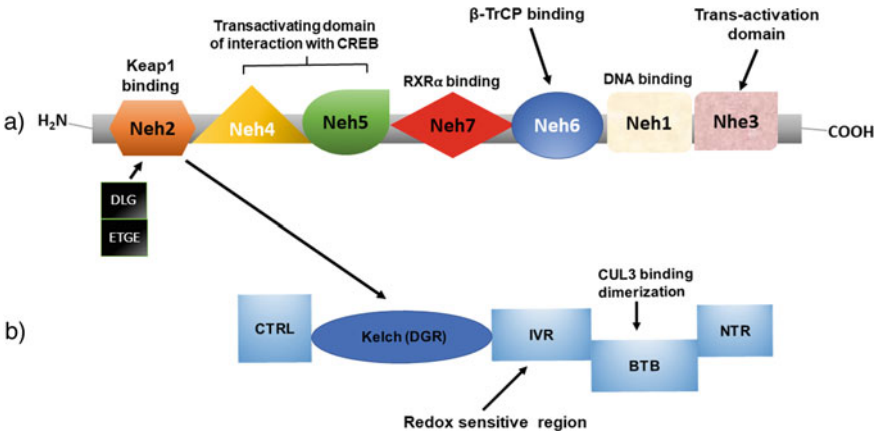


**Fig. 28.1** Schematic representation illustrating domains structure of Nrf2-keap1. **a** Nrf2 contains seven highly conserved homologous domains (Neh 1–7). Neh1 is a DNA binding protein associated to sMaf in form of heterodimers which mediates binding to ARE in the promoter region of Nrf2. Neh2 is keap1 binding protein domain, containing the low affinity DLG motif and high affinity ETGE motif responsible of ubiquitination and proteosomal degradation of Nrf2. Neh3 is the transactivation domain recruiting CHD6. Neh4 and Neh5 are transactivation domains that recruit CREB. The Neh6 and Neh7 domains mediate interaction with β-TrCP and, respectively, RXRα, both negative regulators of Nrf2. Keap1 is divided into five regions: CTR region; BTB region which binds Cul3 ligase responsible of keap1 dimerization; **b** Kelch (DGR) region consisting of six repeated sequences that interact with DLG and ETGE of Nrf2, IVR redox sensitive region containing cysteine residues associated to Nrf2 ubiquitination. NTR region. Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), Kelch-like ECH-associated protein 1 (keap 1), cAMP response element-binding protein (CREB), retinoid X receptor alpha (RXRα), β-transducin repeat-containing protein (β-TrCP), small musculoaponeurotic fibrosarcoma proteins (sMaf), antioxidant response element (ARE), chromo-ATPase/helicase DNA-binding protein 6 (CHD6)

disorders (PTSD) (Sexton et al. 2015), and neurodegenerative pathologies (Gupta et al. 2014), although not everyone exposed to adversity develops these disorders. Higher-resilient individuals, on the other hand, show an enhanced ability to bounce back from adverse events, revealing greater emotional and cognitive control and are more persistent. Linked to the areas of disaster research, the concept of resilience, applied initially to critical infrastructures, has been consolidated in the process of prevention for subsequent possible hits (Taleb 2007). In the brain, the corresponding neurobiological Achilles' heel is represented by mitochondria, where reduced efficiency of the electron transport chain (ETC), enhancing oxidative stress by ROS and reducing energy production occurring in response to many hazards, initiates apoptotic cytochrome C release associated to mitochondrial dysfunction and neurodegeneration. Consistent with this notion, in facing challenges, adaptive responses (hormetic triggers) such as caloric restriction or increased metabolic demand would generate an improved mitochondrial function efficiency, which substantially contributes to the maintenance of homeostasis (Nunn et al. 2016). Hence, the brain is continuously

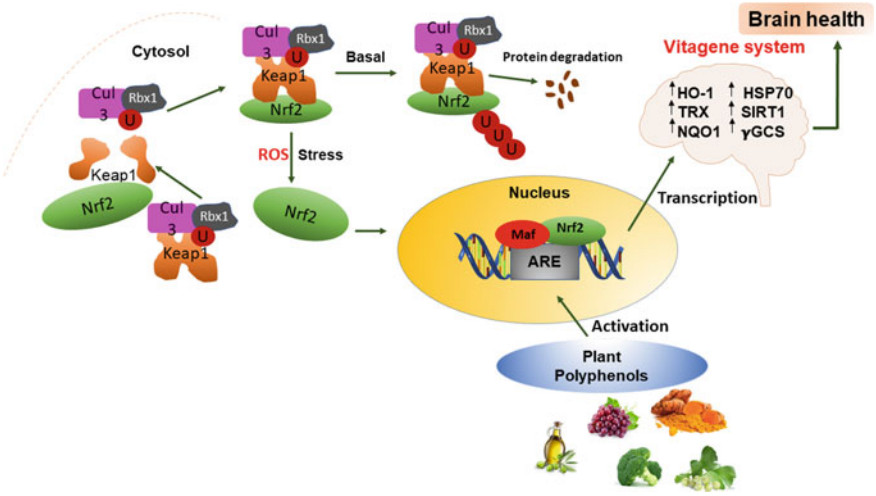


**Fig. 28.2** Modulation of Nrf2-vitagene pathway by plant polyphenols in the brain. In basal conditions Nrf2 is bound to its inibitor Keap1 and is restricted to the cytosol, where it undergoes ubiquitination and proteasomal degradation via association with the Cul3-Rbx1 based E3/ubiquitin ligase complex. Under stress conditions, Nrf2 is released from Keap1 and is translocated into the nucleus where it binds to the phase 2 of ARE in etreorodimeric combination with Maf transcription factor in the DNA promoter region. Plant polyphenols are small molecules that reverse stress and ROS production by activating Nrf2 nuclear translocation and transcription of neuroprotective vitagenes. The upregulation of vitagene pathway such as HO-1, Hsp70, Trx, sirtuin Sirt1, NQO1, γ-GCS improves brain health and protect against neurodegenerative damage. Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), Kelch-like ECH-associated protein 1 (Keap1), antioxidant response element (ARE), heme-oxygenase 1 (HO-1), heat shock protein 70 (Hsp70), thioredoxin (Trx), sirtuin 1 (Sirt1), NAD(P)H: quinone oxidoreductase 1 (NQO1), γ-glutamylcysteine synthetase (γ-GCS)

adapting to perturbations in bodily homeostasis, and a resilient brain integrates adaptive responses that regulate behaviors associated with coping, fear, attention, cognitive flexibility, and emotional regulation (Baratta et al. 2013; Russo et al. 2012). More generally, high resilient individuals display more effective modulation of brain circuits involved in emotion and fear (Southwick et al. 2014).

A recent paradigm shift in operationalizing resilience has moved away from the focus on the non-emergence of pathology or symptoms after exposure to adversity, to include "resilient-conductive" factors such as personality traits, confidence, flexibility, optimism, or emotional liability, which can help promote positive subjective appraisal, negotiation, adaptation, or management of adverse situations with increased coping (Kalisch et al. 2015). Yet, information on the neurobiological correlates of these complex psychosocial and spiritual factors is lacking (Pietrzak et al. 2010). Individual traits such as subjective well-being (both hedonic or eudaimonic) could also be protective factors against adversity (Di Fabio et al. 2015). Hedonic well-being refers to cognitive evaluation of life satisfaction and positive affect, whereas eudaimonic well-being is related to the determination of life-meaning and self-actualization. Resilience is related to both types of well-being (Di Fabio et al.

2015). Positive affect is thought to facilitate resilience by broadening one's attention and coping abilities, and by decreasing susceptibility to disease through increased vagal control (Oveis et al. 2009). The overlap between measures of positive affect and resilience has also been observed in various conditions such as chronic pain (Strand et al. 2006) or brain trauma. The identification of neurobiological correlates associated with resilience endophenotype may therefore be a critical first step in the identification of individuals with increased vulnerability to develop diseases. Identifying brain signatures of resilience as biomarkers of vulnerability to stress-related diseases can have implications for the development of training interventions, such as preconditioning or post conditioning effects associated to hormesis, which increase effective coping and management of stress conditions.

In the brain, a resilient neuronal cell does not necessarily correspond to a healthy cell, as in the case of a cancerous phenotype being very resilient towards chemotherapy. In some tumor cells, high resilience mechanisms lead to a resistance to drugs despite being exposed to the same concentrations as their neighboring cells. Such changes can be long-term, or even permanent, constituting cellular biological memories associated with beneficial outcomes, as in the context of cellular hormesis. Such beneficial outcomes, particularly with respect to ischemia–reperfusion, can be seen where an initial stressor makes cells more resilient to subsequent stress to organs. Here, the so called "pre-conditioning", or alternatively after an adverse situation, a subsequent stressor "post-conditioning", are used and developed, both experimentally and clinically (Smirnova et al. 2015). Long-term effects can however also be detrimental and lead to adverse outcomes, especially when exposure is of limited duration, as in the case of mixture toxicities.

The underlying strategy of hormesis in these cases entails the upregulation of adaptive mechanisms that results in the development of biological resilience. New resilient phenotypes will conform to the quantitative and temporal features of the hormetic dose-time response relationship, often within a preconditioning context. While the amplitude of induced resilience is modest, being about 30–60% greater than the control group/background at maximum, and the duration of resilience is limited, it appears possible to significantly extend the duration of the resilience in some models depending on preconditioning stimulation methods (Gidday 2015). Similar insights on increasing the amplitude of the resilient phenotype remain to be explored. Since Parkinson's Disease (PD) onset and progression is highly age dependent, it is important to recognize that preconditioning-induced hormetic resilience decreases profoundly with age in a variety of animal models. However, some success has been achieved in restoring pathway functions via various exercise schemes, dietary modifications and pharmacological approaches (Calabrese et al. 2015, 2016, 2018b).

Ultimately, the concept of resilience is difficult to operationalize, since it encapsulates many divergent behavioral phenotypes. Indeed, the study of human resilience is still a mostly phenomenological literature which has only begun to characterize biological factors in resilient individuals that are associated with more successful coping responses. Thus, integration, optimization and tailoring of such developments to the treatment of patients offers a profound challenge and opportunities to the progress of biomedical sciences and therapeutic medicine. In the subsequent

sections, we aim to provide evidence for possible prevention and early intervention approaches targeting humans and animals, and their correlation with environmental stressors, that can reduce the risk of brain disorders (i.e., neurodegenerative and neuropsychiatric disorders) and foster resilience mechanisms which maintain cellular homeostasis in response to stressors or adverse life experiences.

## 28.2 Resilience and Brain Health in Early Life

A growing field of recent research is focusing on the concept of resilience in the context of early brain health and its role in successful aging in order to elucidate neuroprotective resilient pathways and activation of stress responses against stress-related neuropsychiatric and neurodegenerative disorders. In this context, resilience is an active brain process that involves adaptive synaptic plasticity and cellular coping mechanisms to face the negative effects of stressful early experiences (i.e., physical and sexual abuse, socio-emotional neglect and maltreatments) (Russo et al. 2012; Southwick et al. 2014). In contrast, low resilience and high vulnerability to stressful or traumatic experiences, in particular during the prenatal neurodevelopment period and adolescence, alter brain circuits to affect sensory systems, network architecture and neuronal mediators involved in threat detection, emotional regulation and reward anticipation. These alterations leave a molecular mark on the genome in the form of epigenetic modifications that result in a "biological embedding" of these stressful life events throughout the life course, contributing to the development of mental illness such as psychiatric (i.e., depression, anxiety and post-traumatic stress disorder (PTSD)) and neurodegenerative disorders (i.e., Alzheimer's diseases) both in humans and animal models (Gravitz 2018; Teicher et al. 2016; Lesuis et al. 2018; Cohen et al. 2013). Moreover, preclinical studies reported that early life interventions modulate aversive memory reconsolidation in the dorsal hippocampus and may program the resilience or vulnerability to psychopathologies of traumatic memories later in life in rodents (Couto-Pereira et al. 2019). On the other hand, the identification of pro-resilience predictive pathways that confer neuroprotection by restoring cellular homeostasis following genetic, epigenetic and environmental stressors has been associated with positive mental outcomes such as reduced depression and mortality risk (Gooding et al. 2012) thus promoting lifespan and well-being (Jeste et al. 2013).

Psychological resilience is the ability to bounce back after a stressful or traumatic event (Southwick et al. 2012) and accounts for whether or not an individual develops a mental illness such as psychiatric and post-traumatic stress disorders (Cathomas et al. 2019). The epigenome may drive adaptive response mechanisms to environmental stressors or traumatic events, on the interface between dynamic environmental changes and the inherited genome, possibly allowing an "epigenotoxic effect" (Szyf 2007). Epigenetic modifications such as DNA methylation, DNA hydroxymethylation, histone modification, miRNA expression have been widely described to mediate the effect of these stressful experiences and to be involved in the vulnerability to depression (Januar et al. 2015), as well as for other stress-related brain disorders

(Nestler et al. 2016). Within this context, epigenetic alterations especially during early life sensory period provide a "*molecular memory*" to neuroplastic responses of environmental stressors and are central to the generation of vulnerable or resilient endophenotypes throughout life (Franklin et al. 2012; Silberman et al. 2016). The imprint from earlier exposures to adverse events, which can manifest as an epigenetic scar (rendering cells more sensitive) or resilience (more tolerant), needs to be considered to understand real-life exposures and measure risk. Sometimes the results of stressors are "bad memories," such as mutations, or other functional impairments that may predispose to disease or lead to adverse lifetime, or even transgenerational, outcomes. The fine line between resilience and maladaptation may need to be defined according to the situation. In the context of transgenerational transmission of early stress and mental disorder (i.e., schizophrenia, bipolar disorder and severe depression), a longitudinal cohort study reported early preventive strategies for transmission of risk or resilience from a parent with severe mental illness to their infant: stress-sensitivity, caregiving representation and quality of parent-infant interaction leading to the possibility of decreasing rate of mental illness in offspring (Harder et al. 2015).

Interestingly, a recent study suggested that early maternal care can epigenetically reprogram the behavior of offspring for their entire lifetime through modulation of neuroplasticity, neurogenesis, cell survival, resilience and specific stress response genes later in life (Vogel Ciernia et al. 2018). On the other hand, many studies reported that early maternal deprivation leads to epigenetic changes (i.e., histone acetylation and DNA methylation) in specific imprinted genes causing attention-deficit/hyperactivity disorder (ADHD), such as anxiolytic-behavior, hyperactivity as well as learning and memory deficits in adolescent rats and in maltreated children (Naumova et al. 2019).

Compelling evidence supports the crucial contribution provided by epigenetic memory in the form of changes to the DNA methylation pattern that could protect (offer resilience) or contribute to pathogenesis and cellular vulnerability to long-term subsequent stressors (Tyagi et al. 2015). Moreover, a recent study suggested that short- and long-term neonatal exposure to early life adversity induces epigenetic changes in dopaminergic molecular pathways and thus can alleviate or aggravate depressive-like symptoms in animal models of chronic stress later in life (Köhler et al. 2019).

All this highlights the importance of resilience and epigenetic processes to counteract vulnerable traits in humans and animal models of mental disorders. Hence, the epigenome may contribute to rendering the system more resistant to the development of neurodegenerative and psychiatric diseases occurring at a later stage of life.

### *28.2.1 Neurobiology of Brain Resilience*

Recently, a large amount of evidence sheds light on the neurobiological factors underlying stress resilience, with particular emphasis on the hypothalamic–pituitary–adrenal (HPA) axis, brain-derived neurotrophic factor (BDNF), serotoninergic (5-HT), glutamatergic and γ-aminobutyric acid (GABA) systems (Faye et al. 2018). Modulating these receptors may promote resilience or vulnerability during stressful events.

#### 28.2.1.1 Hypothalamic-Pituitary Axis

A neurobiological factor required for adaptive stress regulation is the hypothalamic-pituitary axis (HPA axis). The HPA axis is the central neuroendocrine pathway involved in response to stress and adaptation in humans and in animal models (Bomholt et al. 2004). The system is subject to diurnal circadian fluctuations and is also sensitive to both acute and chronic stress. Therefore, the HPA axis is important for understanding resilience or vulnerability to stress. Thus, individuals perceive stressful events differently, and when the stress response becomes overactive, the recovery mechanisms fail to work, leading to increased susceptibility to stress. Some individuals are less vulnerable to stress than others and are deemed resilient. When faced with adversity, people with low resilience are at risk of mental illnesses. Conversely, people who are able to integrate well socially, mentally or physically despite exposure to stress or adversity demonstrate resilience. It is important to note that childhood stress and trauma alter the HPA axis and its long-term dysregulation is associated with increased risk of adverse health outcomes. In addition, recent findings indicate that a dysregulation of the HPA axis induced by chronic stress in aged subjects correlates with negative health outcomes, such as a higher risk for mood disorders (i.e., anxiety and depression) and cognitive disorders (i.e., Alzheimer's disease), where individuals are predisposed to the effects of unstable emotional regulation (Kuhlman et al. 2018; Janak et al. 2015; Bao et al. 2018; Gupta et al. 2014).

In response to challenge or threat, the HPA axis produces a cascade of hormones leading to the release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), which are neuropeptides from the hypothalamus and the pituitary, respectively. Lastly, this pathway culminates in the secretion of glucocorticoids and release of cortisol (or corticosterone in rodents) from the adrenal cortex. Diurnal cortisol is a physiological biomarker of HPA axis activity that contributes to stress resilience. Accordingly, altered diurnal or stress-induced secretion of the hormone cortisol (i.e., higher diurnal cortisol levels), combined with lower resilience resources (i.e., emotion dysregulation and poor social support), could predispose older adults to negative health outcomes (Gaffey et al. 2016). Thus, circulating cortisol levels change due to both environmental and endogenous influences. Several lines of evidence reveled that, in older adults, blunted diurnal cortisol secretion has

been associated with frailty (Johar et al. 2014), whereas lower diurnal cortisol is correlated with longevity (Noordam et al. 2010).

#### 28.2.1.2 BDNF Pathway

It is well documented that stress is a common risk factor for a great range of brain disorders by targeting brain-derived neurotrophic factor (BDNF). BDNF is a potent neurotrophic factor implicated in synaptic plasticity, neurogenesis, memory processes and neuronal stress resistance (Marosi et al. 2014). Downregulation of BDNF expression has been associated with neuronal atrophy and death occurring in neurological disorders (Murer et al. 2001), and chronic stress typically decreases BDNF hippocampal expression (Smith et al. 1996). Reduced levels of BDNF have been reported not only under normal aging conditions but also in neuropathological conditions such as Alzheimer's disease (AD). Yet, experimental findings provide evidence on how the BDNF-TrkB pathway involved in neuroplasticity modulates stress vulnerability and resilience. Reduced BDNF-TrkB signaling contributes to vulnerability of β amyloid-related effects on cognition in the pathogenesis of AD (Devi et al. 2015).

#### 28.2.1.3 Serotonin Pathway

Serotonin or 5-hydroxytryptamine (5-HT) is an important monoamine neurotransmitter implicated in stress resilience and vulnerability. 5-HT is synthetized in the body from the essential amino acid tryptophan (TRP) by the enzyme tryptophan hydroxylase (TRH). This neurotransmitter contributes to brain development and to the maintenance of normal brain function (Nordquist et al. 2010). Thus, low TRP leads to low 5-HT levels in the brain or exposure to psychosocial stress, which promotes the etiology of mood disorders in humans and animals (Gutknecht et al. 2015; Caspi et al. 2003). On the other hand, elevated levels of 5-HT are associated to neurotoxicity (Dell'Osso et al. 2016). Moreover, the 5-HT transporter gene is another actor of neurotransmission homeostasis and plays a role in modulating an individual's vulnerability or resilience to stress (Lesch et al. 1996). Stress induce alterations in the serotonin system are associated with structural and functional epigenetic changes in the brain. In this regard, epigenetic modifications such as hypermethylation in *HTR2A, HTR3A* and *5HHT* serotoninergic genes are associated with childhood trauma and psychiatric disorders in adulthood (Schechter et al. 2017; Kang et al. 2013). Serotonin 5-$HT_{1A}$ receptors have been proposed as key mediators of serotonergic signaling in the hippocampus (Savitz et al. 2009). Chronic stress reduced the levels of 5-$HT_{1A}$ receptors in different brain areas and increased the risk of depression in vulnerable patients and animals (Watanabe et al. 1993). On the other hand, high levels of hippocampal 5-$HT_{1A}$ receptors represent a molecular marker that exerts resilience actions on limbic functioning and serotonergic homeostasis in the face of stress (Zurawek et al. 2019).

#### 28.2.1.4 Glutamate Pathway

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS), and under physiological conditions, plays an important role in synaptic plasticity, learning, memory and emotional responses (Lin et al. 2019). Accumulating evidence suggests that less resilience is associated with dysregulation in glutamatergic neurotransmission (i.e., phencyclidine (PCP), ketamine, and N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl- 4-isoxazole propionic acid (AMPA) receptors), which induces microglial activation, neuronal damage or death by excitotoxicity and in the end leads to the pathogenesis of numerous neuropsychiatric disorders such as schizophrenia, depression, autism, and neurodegenerative diseases (Reus et al. 2018). Notably, glutamate neurotransmission, including neurotransmitter synthesis, signaling, and glutamate receptor functions and expression seem to be involved in both stress vulnerability and resilience. Chronic stress decreased resilience and consequently the levels of glutamatergic neurotransmission of AMPA receptors, in animal models of depression (Li et al. 2018).

#### 28.2.1.5 GABAergic Pathway

The γ-Aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, progressively decreases during stress in animals (Zhang et al. 2016) and humans (Schür et al. 2016). Dysfunction of GABAergic neurotransmission is implicated in the development of stress-induced psychiatric disorders in both clinical and preclinical research (Jacobson et al. 2007; Albrecht et al. 2017). Notably, GABAergic neurons in the nucleus accumbens of the limbic system are correlated with the resilience and vulnerability to chronic stress for major depression (Zhu et al. 2017). Interestingly, the $GABA_{B(1)}$ subunit is expressed as different isoforms, and in the brain the predominant isoforms are $GABA_{B(1a)}$ and $GABA_{B(1b)}$. These isoforms, $GABA_{B(1a)}$ and $GABA_{B(1b)}$, exhibit differential cognitive and conditioned fear responses and regulate stress resilience or vulnerability to psychiatric illness in animal models (O'Leary et al. 2014). Several lines of evidence suggest that upregulation of the $GABA_A$ receptor α1 subunit in the ventral hippocampus increases resilience in animal models of juvenile stress and can lead to the development of stress-related psychopathologies (Ardi et al. 2019). The impact of basolateral amygdala activation on synaptic plasticity in the hippocampus, under conditions of heightened stress, induces alterations in the GABAergic system in limbic and prefrontal cortical areas. Thus, reducing GABAergic inhibition of specifically the axon initial segment of principal neurons within the basolateral amygdala represents a protective factor against traumatic stress on hippocampus-dependent cognitive and plasticity functions in rats (Saha et al. 2018).

### *28.2.2 Mitochondrial Resilience*

It is well established that genetic predispositions, epigenetic changes as well as various environmental influences (comprising adverse life events such as childhood maltreatment, migration, or chronic stress) contribute to mental illness vulnerability. Mitochondrial stress occurring in response to many oxidative injuries, impairment of energy metabolism and calcium homeostasis that initiates apoptotic cytochrome C release is associated with mitochondrial dysfunction and neurodegeneration (Mosconi et al. 2011). On the other hand, mitochondria dynamically interact with each other and respond to different stressors to generate signals of resilient adaptation. Within the cell, mitochondria are in close proximity to the cell nucleus and, in response to environmental signals, undergo dynamic, morphological and functional changes leading to the production of biochemical signals to which the cell and its plastic epigenome evolved molecular sensitivity (Picard et al. 2013; Shaughnessy et al. 2014; Houtkooper et al. 2013). Recently, studies have in fact demonstrated the existence of a functional crosstalk between mitochondria and nuclear epigenome as a new aspect of bidirectional mito-nuclear communication: mitochondria are essential mediators of epigenetic processes and, conversely, changes in the epigenome regulate mitochondrial function. Consequently, their functions are fundamental aspects of cellular health (Matilainen et al. 2017). Accordingly, recent studies of gene-stress-interaction demonstrated that downregulation of *cacna1c* gene expression promotes mitochondrial resilience against oxidative stress in neuropsychiatric disorders (Michels et al. 2018). Mitochondria synthesize and metabolize stress hormones (i.e., glucocorticoids and catecholamines). It is interesting to note in the context of stress resilience that stress hormones display a biphasic role in regulating mitochondrial function, i.e., a hormetic mechanism. An integrative view of chronic stress targeting mitochondrial bioenergetics thus opens new opportunities to study mechanisms of resilience adaptation across the lifespan.

Consistent with this concept, mitochondria regulating energy homeostasis and brain resilience adaptation processes represents a major marker of brain health (Picard et al. 2018a). Importantly, chronic stress induces mitochondrial damage and dysfunction in various brain regions, with impairment of neurotransmission underlying development and progression of neurodegenerative and neuropsychiatric pathogenesis. Moreover, prolonged exposure to glucocorticoids causes respiratory chain dysfunction, increased ROS generation, mitochondrial structural abnormalities, apoptosis and cell death in skeletal muscle cells and hippocampal neurons (Picard et al. 2018a). In light of this, glucocorticoids should be regarded as *mitokines*, i.e., mitochondria-derived hormones, mediating mitochondria-to-mitochondria communication among distant sites throughout the organism (Picard et al. 2018b). Notably, moderate mitochondrial stress can enhance mitochondrial antioxidant capacity through upregulation of antioxidant enzymes and, hence, increase resilience to metabolic stress (Lee et al. 2010), with impact on lifespan in mice (Schriner et al. 2005).

### *28.2.3 Regional Specificity of Brain Resilience and Vulnerability to Stress: A Neuroimaging Approach*

In recent years, neuroimaging techniques have become an increasingly important tool to study neural correlates of adaptive and non-adaptive behavior. Neuroimaging studies, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), provided substantial evidence of both brain structure and function in supporting vulnerability or resilience to stress in different neurological disorders.

Resilience is associated with morphological changes of brain regions involved in cognitive and affective processes related to the cortico-limbic system and plays an essential role in preserving mental function and physiological trajectories of brain network. In this context, higher levels of resilience are related to distinct morphological alterations in brain regions involved in executive control and emotional arousal networks, suggesting individuals with low resilience may have compromised cortico-limbic inhibition, making them more vulnerable to stress or trauma (Gupta et al. 2017).

Interestingly, the connectivity of these brain regions modulates resilience and vulnerability processes during stress or brain trauma (i.e., early life trauma, childhood maltreatment) (McEwen et al. 2016a). Accordingly, these brain regions are implicated in the storage of cognitive control, memory consolidation, neurogenesis as well as emotion regulation (McEwen et al. 2016b). The structural changes in the brain induced by chronic stress play a critical role in the pathophysiology of both neurodegenerative and neuropsychiatric disorders in animal and humans (Ebertowska et al. 2020; Kawaike et al. 2019). In addition, alterations observed in the cytoarchitecture of the hippocampus and amygdala have been related to stress resilience and vulnerability in animal models of PTSD (Cohen et al. 2014).

In humans, several studies demonstrated that chronic stress or traumatic experiences in childhood maltreatment (i.e., parental neglect, early deprivation, physical, sexual and emotional abuse) are associated with morphological alterations in specific brain regions. Specifically, there is increased atrophy of neurons in the hippocampus, prefrontal and parietal cortex, involved in memory, selective attention, and executive function (Bremner et al. 2005; Gupta et al. 2017). Similarly, these negative events cause hypertrophy of neurons in the amygdala involved in emotional processing and arousal, fear conditioning, anxiety and aggression as well as diminished striatal response to anticipated reward. This leads to increased vulnerability and development of neuropsychiatric and neurodegenerative illness (Guo et al. 2018). Moreover, animal studies have shown smaller amygdala volumes associated with lower levels of resilience, in keeping with neuroimaging findings demonstrating that amygdala volume is reduced in individuals who have been exposed to early adverse life events or maltreatment. For example, smaller amygdalae have been observed in individuals undergoing conditions of childhood poverty (Luby et al. 2013), as well as in adolescents having experiences of childhood maltreatment (Edmiston et al.

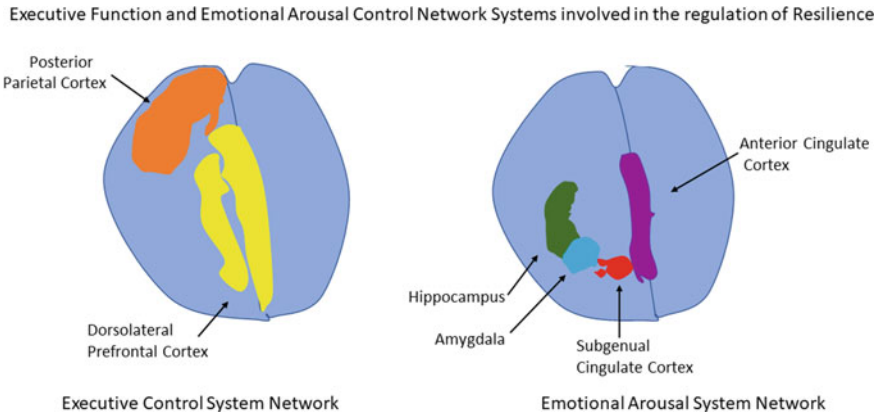


**Fig. 28.3** Regions involved in the executive control and emotional arousal functions. Executive Control Network System: Dorsal-lateral Prefrontal Cortex, Posterior Parietal Cortex. Emotional Arousal System Network: Anterior Cingulate Cortex, Subgenual Anterior Cingulate Cortex, Amygdala and Hippocampus

2011). Smaller amygdala volumes have been also observed in individuals exposed to childhood adversities such as physical abuse, neglect, or being raised in poor households (Hanson et al. 2015) and in PTSD populations compared to healthy controls (Depue et al. 2014). These studies indicate that impaired executive control and emotional arousal networks in critical cortico-limbic structures, such as the dorsal-lateral prefrontal cortex, posterior parietal cortex, and respectively anterior cingulate cortex, anterior mid-cingulate cortex, subgenual anterior cingulate cortex, amygdala and hippocampus, show inhibition in response to trauma, suggesting that they may play a critical role in the mediation of low resilience or vulnerability to disease (Fig. 28.3).

Moreover, a recent study demonstrated that glucocorticoid receptor stimulation by early maternal stress and long-term gene expression changes induced aberrant DNA methylation in prefrontal cortex of rats (Urb et al. 2019). A few neuroimaging studies have investigated the response to adversity as a "proxy" of resilience, reporting quite important resilience-related differences in brain structure (DeYoung et al. 2010). Retrieval of emotionally-valenced words in females with histories of early abuse has been linked to decreased blood flow in the inferior parietal cortex (Bremner et al. 2003). In an emotional Stroop task, there was decreased parietal cortex activity in females with histories of PTSD and abuse (Bremner et al. 2004). The parietal cortex is a key region of the executive control network, and is associated with inhibitory control, attention, working memory, planning, and response (Uddin et al. 2011). Therefore, the findings are consistent with the hypothesis that high resilient individuals may be better able to engage the executive control network, including its role in inhibitory functions in relation to real or perceived challenge to their homeostasis.

The emerging links between neurogenesis and mental health support the idea that improving resilience represents a neurogenic strategy to treat patients suffering

from major depression, schizophrenia, and neurodegeneration (Apple et al. 2017). Neurogenesis plays a critical role in the synaptic plasticity of brain functions, such as olfactory discrimination, memory formation, and fear extinction (Shors et al. 2001; Alonso et al. 2006; Pan et al. 2012). In this context, it has been reported that stressful or traumatic events induce glucocorticoid release and decrease adult hippocampal neurogenesis (Snyder et al. 2011). Animal studies of early maternal and social deprivation reveal stress enhanced neurogenesis in the dentate gyrus of the hippocampus and in the amygdala. In fact, mice exposed to early life stress exhibited a reduction in amygdala/hippocampus-dependent fear memory because they have reinforced stress resilience to cope with future stressors and maintain a normal homeostatic state (Daun et al. 2020). Accordingly, dysfunction of adult neurogenesis enhances vulnerability of the hippocampus, and development of age-related neurodegenerative diseases, as well as neuropsychiatric diseases. On the contrary, enhancing neurogenesis confers resilience to stress by regulating the processing of both cognitive and emotional functions. Animal studies reported that increasing hippocampal neurogenesis promotes resilience to chronic social defeat stress by moderate exercise (Nguemeni et al. 2018) and inhibiting ventral dentate gyrus (Anacker et al. 2018). Brain imaging data of the hippocampus in patients and stress-induced animal models with either depression or anxiety disorders indicated a remarkable reduction in region volume and dendritic spine numbers. By contrast, larger hippocampal volumes could be a biological marker of resilience, whereas, loss of hippocampal neural plasticity (e.g., loss glial cell and smaller neuronal cell nuclei) after chronic stress is a determinant factor to the pathophysiology of depression in vulnerable human and animal models (Park et al. 2019; Carboni et al. 2018).

Additionally, a recent report suggested that hippocampal proteomic changes are associated with protein alterations involved in mitochondrial and metabolic pathways and lead to increased vulnerability or resilience to stress-induced depression and anxiety in stressed rats (Tang et al. 2019). Recently, several studies have correlated increased amygdala reactivity as a protective factor that promotes resilience to depression following early life stress (Yamamoto et al. 2017). In contrast, others studies have revealed that high emotional resilience is associated with lower levels of connectivity in the ventral amygdala network independent of depression status. Instead, lower depression symptoms were associated with higher connectivity between the amygdala and dorsal frontal networks in older adults (Leaver et al. 2018). In addition, repeated stress induces a pro-inflammatory state by increasing the amygdala's neuronal and microglial activation, which triggers anxiety-like behaviors in rodents (Munshi et al. 2020).

Taken together, these data showed brain network connectivity in the main brain regions such as hippocampus, amygdala as well as prefrontal and parietal cortex in response to stress or trauma and how neural factors are involved in increasing resilience or vulnerability after stressful events across the lifespan. A history of stress exposure can have a lasting impact on future stress reactivity in different brain regions. Finally, the elucidation of brain region alterations will undoubtedly lead to more effective and better tolerated treatment approaches to enhance resilience and its use as a potential biomarker of healthier adulthood adaptations to childhood trauma.

## 28.3 Plant Polyphenols Improve Resilience and Brain Health via "Vitagenes"

Emerging research has focused on brain resilience, for neuroprotection, elicited by plant polyphenols through the activation of the Nrf2-vitagene signaling pathway (Figs. 28.1 and 28.2). The latter encodes redox sensitive genes, such as heme oxygenase-1 (HO-1), heat shock proteins (Hsps), thioredoxin and sirtuin system, termed vitagenes which are involved in preserving brain health and cellular homeostasis in response to stress or trauma in major neuropsychiatric and neurodegenerative disorders (Calabrese et al. 2010; Trovato et al. 2014, 2016a). Increasing evidence suggests that plant polyphenols (i.e., resveratrol, hydroxytyrosol, oleuropein, sulforaphane, curcumin, as well as gingko biloba) may exert healthy benefits acting in a hormetic-like manner through the modulation of vitagenes, making the hormesis concept fully applicable to the field of nutrition (Scuto et al. 2019a, b; Amara et al. 2020a; Trovato et al. 2016b, 2018; Calabrese et al. 2014, 2018a).

Interestingly, recent in vitro and in vivo studies suggest that Hydroxytyrosol (HT) and Oleuropein (OLE) inhibit the inflammatory response and induce brain resilience to aging process through different pathways regulated by several members of the sirtuin family (e.g., Sirt1, Sirt2, Sirt3 and Sirt6) (Leri et al. 2020; Zhi et al. 2018; Gallardo-Fernández et al. 2019; Corpas et al. 2019a). The thioredoxin system (Trx/TrxR) is an important thiol/disulphide redox controller ensuring the cellular redox homeostasis and resilience to mental illness (Calabrese et al. 2012; Amara et al. 2020b; Dang et al. 2019). In this context, some studies showed that HT induces neuroprotection and cellular antioxidant defenses via activation of the Keap1-Nrf2-TRXR1 pathway (Peng et al. 2015).

Sulforaphane is an herbal isothiocyanate enriched in cruciferous vegetables obtained in high concentrations from broccoli seeds and sprouts. Recently, it has been reported that sulforaphane induces health benefit by upregulation of Nrf2 pathway against oxidative stress and inflammation in prenatal prevention of autism spectrum disorder, as well as for the early treatment of young children with this disorder (Nadeem et al. 2019). Preclinical studies suggested that intake of 0.1% sulforaphane during juvenile and adolescence protect against inflammation and stress depression-like behaviors via Nrf2 signaling and confers stress resilience in adulthood (Yao et al. 2016). Moreover, a recent paper has suggested that lower levels of BDNF-Nrf2 pathway are strongly associated with oxidative stress and vulnerability to depression in rats. On the other hand, activating Nrf2 translocation restored redox homeostasis and induced resilience to stress (Bouvier et al. 2017).

Several studies have reported the antioxidants, anti-inflammatory and cognitive resilience properties of resveratrol (3,5,4′-trihydroxy-trans-stilbene), a polyphenol found in red wine presently under clinical trial against neuropsychiatric and neurodegenerative disorders. Recent compelling evidence indicated that resveratrol improves brain resilience and proteostasis through the activation of Sirt1 pathway against amyloid and tau pathologies caused by accumulation of aberrant proteins in AD

mouse models, as well as in lymphocytes of AD patients (Corpas et al. 2019b; Cosìn-Tòmas et al. 2019). Curcumin is a polyphenol compound extracted from the rhizome of *Curcuma longa Linn* (family Zingiberaceae) commonly used as a spice to color and flavor food. Increasing evidence demonstrated that curcumin promotes resilience and may prevent the emergence of a range of anxiety-like symptoms in individuals during exposure to chronic social stress (Aubry et al. 2019), as well as depression-like behaviors in rats (Huang et al. 2011). Recently, Ginkgo biloba extracts showed effectively as an alternative medicine for treatment and prevention of neurodegenerative and neuropsychiatric illness and acts in a hormetic-dose response manner (Calabrese et al. 2020). Moreover, several studies reported the beneficial effects of Ginkgo biloba extracts in modulating fear memory retrieval through serotoninergic, GABAergic, and glutamatergic receptors in the dorsal hippocampal formation, by enhancing cognitive function and resilience in psychiatric disorders (Gaiardo et al. 2019). Taken together these data indicate that brain resilience is an active protective process that involves a set of neural and cellular mechanisms leading to avoid some of the negative consequences of excessive stress therefore improves mental health.

Finally, in the field of neuroprotection, moderate and chronic consumption of low doses of plant polyphenols could be considered as a promising "natural preventive medicine" which confers resilience through the activation of stress responsive *vitagenes*. By activating neuroprotective cascades such interventions could be effective to prevent neuroinflammation, promote brain resilience and improve brain health in aging-related cognitive decline as well as in neuropsychiatric disorders in humans.

## 28.4 Conclusions

Aging is one of the most challenging public health issues and it is considered as a "cellular danger response" to environmental stressors or injury leading to the development of neurodegenerative disorders. Emerging research has focused on how biological resilience may be elicited by consumption of phytonutrients, particularly vitamins and plant phenols. These interfere with multiple signaling pathways involved in protein homeostasis, DNA repair, metabolism regulation, and antioxidant defenses in response to environmental stressors. Accordingly, the prevalence of harmful stressful events, or so-called "black swans," may contribute to establishing a particularly resilient or vulnerable endophenotype.

Resilience comprises different physiological parameters, epigenetic modulators and neurobiological markers. In this review, we have provided a brief overview of some biological mechanisms underlying stress resilience and have explored how resilience changes throughout age. The neurobiological network represented by the HPA axis, BDNF, Serotonin, Glutamate and GABAergic pathways operate as the first line of response to stress or challenges by promoting resilience and preserving mental health against the onset of brain disorders such as depression and anxiety, but they also slow neurodegeneration across the lifespan in both human and animal models. Epigenetic mechanisms are a key to understanding the effects of early stress

in childhood, such as poverty, maltreatment, maternal social and nutritional deprivation, familial genetic as well as sexual abuse. In light of this, identifying personalized biomarker signatures of resilience can help us characterize biologically vulnerable individuals (e.g., maltreated children). Relevant to this, psychobiological challenge tasks designed to evoke a resilient behavioral response, neuromodulation strategies visualized by neuroimaging of circuits that mediate resilience, together with antioxidant interventions enhancing resilience, are all fundamental preventive strategies aimed to operationalize resilience as a multifactorial determinant of brain health for translation into a clinical setting. Finally, neural signaling pathways activated by healthy lifestyles, such as moderate physical exercise, caloric restriction, intermittent fasting, heat shock response and antioxidant polyphenols, can also stimulate mitochondrial biogenesis in neurons in the brain, thereby facilitating neuroplasticity and hormetic-resilience pathways that modulate aging and longevity in humans.

Further studies are necessary, however, to evaluate the real importance of the neurobiological mechanisms impacting on target genes, as well as on epigenetic and mitochondrial pathways in specific brain regions. These studies will help to elucidate resilience factors, which promote brain health in response to stress, and to unravel the potential therapeutic interventions able to effectively increase resilience and improve stress management in vulnerable populations.

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# Chapter 29
# Healthy Ageing in the Clinical Setting: Current Concepts and Future Prospects


**Marios Kyriazis**

**Abstract** It is necessary to define 'health' in order to know how to deal with disease. This is particularly important when we deal with real patients in clinical settings, and even more so when the patient is elderly. Here, an attempt is made to define health in a way that reflects the above concerns, and is of practical use to clinicians. The discussion cannot focus only on established narratives of health. Our society is changing, and it is necessary for our health care models to also change in order to reflect the new necessities faced by people. Therefore, in this chapter I discuss some novel approaches to health, based for example on hormesis, adaptations to digital technology, the complex interactions between cognition and physical functioning, as well as some speculative arguments such as new definitions of the terms 'ageing', 'natural', and the need to shift from a physical model of health to a more cognitive one. In order to deal effectively with these issues, it is necessary to use both a theoretical and a practical approach, which nevertheless can provide a clinically useful overview of the problems involved.

**Keywords** Ageing · Hormesis · Enriched environment · Cognitive enhancement · Comprehensive geriatric assessment · Gut-brain microbiome · Adaptation · Unique disease principle

## 29.1 Introduction

Health, from a medical point of view, depends not only on biological or genetic factors, but also on environmental and cultural ones. Challenges originating from a variety of environmental sources stimulate the body to respond and adapt. A loss of the ability to rapidly respond to a new challenge is associated with dysfunction and thus, eventually, with disease. We normally respond to environmental stresses in at least four ways, which may have synergistic effects:

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1. Genetic change (slow, over several generations),
2. Developmental (relatively slow, over a lifetime), for example intentional deformities, or plastic surgery,
3. Acclimatization (reversible adjustments), for instance building muscle mass through exercise, or fat through overeating,
4. Culture and technology, for example digital communication effects, exposure to ionising radiation, migration.

It may be argued that an individual who is able to successfully overcome any challenges originating from the environment, through one or more of the above mechanisms, will continue to function well within that particular environment, and is considered to be healthy.

Matters become more complex when we consider the issue of ageing and how this process is affecting health. The first obstacle here is to properly define 'ageing'. While there have been many definitions of ageing, (for example, da Costa et al. 2016) it could be relevant in a clinical setting to define ageing simply as '**Time-related dysfunction'**. This common-sense definition sees a progressive loss of function which is related to the passing of time, a chronologically-dependent erosion of our functions, which makes it increasingly difficult for us to manage and operate within a given environment. The usefulness of this definition here is that it bypasses complex biological, statistical, biodemographic or other definitions of ageing, and focuses solely on real people in everyday situations. If any appropriate current or future interventions slow down this loss of function, then it means the patient is healthy, even though he/she may have a distinct illness. For instance, consider a person who has a diagnosed cardiac anomaly which is only evident when that person runs marathons. If the person does not run marathons, he is considered healthy because his environment is appropriate for his needs. However, it must be emphasized that health in practical terms, is not always seen in black or white terms ('healthy' or' not healthy'), but there are intermediate shades of gray.

Furthermore, what is important from a practical point of view, is to have suitable function matching a person's own environment **which may constantly change**. This environment (everyday situations or challenges) change all the time and it is necessary to keep adapting to these challenges in order to maintain a suitable, useful performance. It is also important to make clear to the patients that comparing their current function to their previous situations (i.e. they may be less able to do certain things compared to the past) is counterproductive. It is the present day that matters and how one is able to achieve a reasonable level of daily operation. Therefore, even if a person is affected by a certain illness or a health problem, this remains irrelevant if that person can adapt to it, modify his/her daily behaviour and continue life with the new restrictions or impediments without being overwhelmed by these. Ultimately, health is the ability to adapt and to function well despite physical, psychological or social challenges (Huber et al. 2011).

It is imperative to highlight that it is not the environment itself (social, cultural, biological etc.) that is the determinant of health, but the **ability** of the patient to respond and adapt. This ability depends both on genetic and epigenetic factors. In

addition, the intrinsic capacity of an individual is only one determinant of health. Other determinants include the interactions that take place between the person's internal milieu and external environment, as well as the ability of the person to overcome barriers to physical, psychological or social situations (Beard et al. 2016). These authors quote:

> These environments provide various resources or barriers that will ultimately decide whether a person with a particular capacity can engage in activities that matter to them. Thus, although an older person with severe osteoarthritis might have restricted intrinsic capacity, they might still be able to do the shopping if they have access to an assistive device (such as a walking stick, wheelchair, or scooter) and live close to affordable disabled-access transport.

## 29.2 Technology and the Patient's Environment

Consequently, if health depends on responding to challenges from the environment, it is necessary to examine this environment, as it is unfolding, in order to match our (perhaps ever-changing) advice to the fluctuating health needs of the patient. In a modern technological setting, health cannot be seen in terms of biology alone (Alami et al. 2017). Health must also reflect the good function of technological devices, not only of the biological body (Reis 2019). We are increasingly being coupled with devices and networks, including assistive digital devices, both in a medical and a social sense. Examples are insulin pumps, dialysis machines, cardiac monitors, health evaluation devices etc., as well as digital assistants, for instance iPhones, and the social media. For example, if a lonely, isolated person depends on social media for some quality interactions, and that particular social media platform fails, then there is a risk of social isolation which may, at some stage, result in physical problems. Digital health technologies play an increasingly important role in disease management, delivery of care, and reduction of future risk. Patients can be informed on health matters via SMS or wearable devices, and also apps (Khan et al. 2017). If these devices or technologies are compromised, health could be affected.

Perhaps it would be fair to say that currently 20 or 25% of our health does not depend on physical or psychological aspects or abilities but on digital/technological machines. This percentage may well increase in the future. It follows that any monitoring and assessment of health must take into account the monitoring and function of the digital device itself, and not only the person's own biological function. If, for instance a patient is connected to a faulty dialysis machine, there will be adverse health consequences originating from this fault, consequences which are not dependent on the patient's genetic profile or physiology, but could be dependent solely, for example, on a malfunctioning microchip. Therefore, we should take into account all aspects of the patient's environment, in order to form a complete picture on this patient's health.

## 29.3 Clinical Aspects of Health

Apart from a digital environment, there are four other areas, which have immediate relevance when it comes to evaluating the health status of adults and elderly people: polypharmacy, multimorbidity, social environment, and health facilities. These are interdependent and mutually influencing. Each one may lead to loss of function and deterioration of health, therefore each merits a summary discussion.

1. **Polypharmacy**. The issue of polypharmacy has been receiving prominent attention in clinical practice for decades. However, it has not been adequately defined. In general terms, polypharmacy is the concomitant use of many medicines (drugs), but there is no standard definition. One definition is "the administration of more medicines than are clinically indicated, representing unnecessary drug use" (Montamat and Cusack 1992). Others (Rankin et al. 2018) have defined it as the use of four or more medicines in a day, although this number is arbitrary. The concept of polypharmacy is related to inappropriate prescribing, which has been defined as: "medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available" (Beers et al. 1991). Potentially inappropriate medicines and inappropriate omissions may lead to adverse outcomes in disease or in prevention. The literature on polypharmacy in the elderly is huge and it is beyond the scope of this discussion to provide detailed information. However, it is important for physicians or other prescribers to have these issues actively in mind, in order to avoid problems with drug interactions, non-compliance and poor clinical effectiveness.
2. **Multimorbidity**. Polypharmacy may be a logical intervention when there are multiple health problems that affect any given patient. In any case, multimorbidity (defined as two or more chronic conditions) (Yarnall et al. 2017) in later life is a real challenge not only from the pharmacological point of view but also from the social and psychological ones. Multiple ailments that affect an ageing patient may be recognized as distinct diseases such as osteoarthritis, hypertension or cancer, but could also be other poorly-defined chronic situations such as frailty, weakness, dizziness, or loss of sleep, all of which may overlap and result in an adverse additive outcome.
   The problems associated with multimorbidity may be adequately addressed as a first step, by the Comprehensive Geriatric Assessment discussed below. Consequently, strategies should be devised in order to address all the ailments, not in isolation, but considering the patient as a whole.
3. **The influence of the social environment**. Social interactions play a valid role in improving health (Tough et al. 2017) including mental health and general well-being. These interactions may be physical (person to person) or digital/virtual. As mentioned above, a virtual social environment plays an increasing role in improving health in older people (Leist 2013) as it diminishes the negative effects of loneliness, facilitates exchange of information, even gossip, and may improve depression (Hunter et al. 2019). This is also important in the many cases of

home-bound people, such as those with physical disabilities that impede a face-to-face physical interaction. Nevertheless, the social situation of any patient plays a considerable role in defining health.

4. **Availability of health care facilities**. A significant proportion of older people need resources and assets in order to manage age-related chronic degenerative diseases. It is predicted that the numbers of people aged 80 and over will more than double within the next 30 years (World Health Organisation statistics https://www.who.int/news-room/fact-sheets/detail/ageing-and-health, retrieved 10 November 2019). The need for providing affordable and effective care is increasing, and more so is the need to avoid institutionalization, with 'stay-at-home' schemes.
   Older people use a disproportionate amount of health service resources and this need is increasing with time (Nishino 2017). The combination of multimorbidity, frailty, polypharmacy and a failing social environment leads to the need for extended facilities of care, and these may lack in certain countries. There is a general tendency to favour 'Aging in Place' healthcare models, where the older, frail patient is given all necessary facilities in order to remain in their own house, rather than use hospitals or care homes. Emerging digital technology may help in this respect, because it facilitates prevention and early intervention (Knight et al. 2018). New terms are being coined, that reflect this increasing need. For instance:

   - 'Digital Enhanced Living' is the provision of facilities that address emotional, as well as physical needs of the patient at home (Grundy et al. 2018).
   - 'Smart Home solutions', where virtual reality and home sensors are used in order to enhance and improve health care at home (Majumder et al. 2017).
   - 'mHealth Technologies', which rely on wearable sensors and devices, with smartphone apps, for home monitoring and assessment of health variables (Prochaska et al. 2017).

Therefore, we see the complexity of issues and factors when dealing with the health of older people. These factors are becoming an amalgam of biological, physiological, social and technological elements, all of which need to be taken into consideration by health care practitioners in order to provide efficient care and prevention. But in addition to the above factors, novel ways of viewing conventional concepts such as 'health and nature' are now beginning to emerge.

## 29.4 A 'Natural' Environment?

What practical advice can we possibly give to healthy people who want to prevent future health problems? The current widely-established advice about natural life and natural health products is well known. However, we must recognise that living a 'natural' lifestyle was suited to humans who depended on hunting animals, gathering food, working the land, finding their way in the forest and having to be physically

strong in order to cope with the rigours of life. This advice may not be appropriate to people living in modern technological societies. Concepts such as 'natural' need to be re-evaluated. Here, by 'natural' it is meant an environment which is not man-made, although this definition is confusing and contradictory. Instead, a new definition of 'natural' may be 'an environment which is produced by a process of self-organisation, evolution and adaptation to complex and unpredictable situations' (Heylighen 2018 personal communication). This is very relevant with regards to health, because health depends on the environment the person is in, and this environment needs to be defined in order to see if it is healthy or not. Therefore, 'natural' is a term that refers **less** to the established notion of the term (i.e. 'non-man made') and **more** to the environment (including a technological one) AS IT EVOLVES while obeying existing physical and biological laws. The important characteristic of such an environment is the unpredictability and complexity, which is not only encountered in conventionally natural environments such as forests, lakes and mountains, but also in modern technological environments that are man-made. The ability to adapt and evolve remains important in any such environment, and it has a crucial importance in promoting health.

For example, the current established advice is to avoid sugar in the diet if at all possible. The adverse health benefits of excessive sugar intake are well-recognised. However, based on the discussion above, the line between natural and artificial is now becoming blurred. A person living today may have different energetic needs compared to an earlier ancestor. For instance, people (including older people) now use digital technology which requires constant attention span, increased speed of information processing and the need for faster response times. This is particularly true of people who use such technology in a meaningful way, in the sense that they are exposed to information that requires them to act. The cognitive processes associated with such actions need instant energy supply from sugars or other foods or nutrients not normally considered healthy (Kann et al. 2014). Of course, here one must be careful about balancing the potentially positive effects of sugars (for instance, in providing instant energy, as discussed above) and the negative effects (for instance, the well-known risks of obesity, diabetes, heart disease etc.).

In order to be able to strengthen the mechanisms that contribute to health, we need to consider these new needs of individuals, which may not have much to do with how life was lived in previous periods in human history. It is no longer evolutionarily relevant to be able to run for long distances or lead a physically-demanding life. What is relevant, and this is becoming even more so with the pace of technological progression, is to be able to have appropriate and meaningful function of our cognitive processes, to make us better able to cope with the demands of a technological modern life. While it is true that physically-demanding exercise is also very effective in improving cognitive function, here the argument is that, within the framework of an increasingly cognitive environment, any cognitive stimulation may also come from cognitive activities and not only from physical ones.

## 29.5 Physical Versus Cognitive Functions

The information burden associated with our modern—and increasing—technology such as Ambient Intelligence, the Global Brain, (Heylighen and Lenartowicz 2017), or the Internet of Things (da Costa et al. 2018; Fisher et al. 2019) is having unprecedented effects on our stress response processes, which is at odds with commonly-held beliefs about nature and health (Kyriazis 2015). Fast epigenetic changes which help us adapt to an increasingly complex environment are becoming relevant, and are worthy of further study. Little-studied natural processes such as degeneracy (Cropper et al. 2016; Mason 2015; Mason et al. 2017), and exaptation (Andriani 2017; Larson et al. 2013) provide the basis of biological adaptation to a changing environment, and it may be relevant to examine these further in order to provide practical advice to people in everyday situations.

An interesting concept that can be considered here is that cognitive function (and cognitive exercises) may affect physical health. For instance, it is becoming increasingly appropriate to advise people at large to improve cognitive processes, such as information processing, decision making, problem-solving and memory, rather than place emphasis on becoming physically stronger. This may be contradictory to common health prevention advice which places emphasis on physical exercise, leading to physical strength which is less needed in a cognitively-oriented environment. We know that physical exercise positively influences cognitive health (for instance, Cai and Abrahamson 2016). What is less commonly appreciated is that improved cognitive function has benefits on other somatic tissues apart from the brain itself. Therefore, instead of focusing our attention solely on promoting physical exercise for good overall health, we may need to modify this advice and place more emphasis on cognitive exercises alongside physical ones (Table 29.1).

Some studies have even shown that cognitive training not only improves physical functioning but its effects may persist for several years (Rebok et al. 2014). The effects of cognitive enhancement on physical parameters can be studied with some accuracy on chess players (Troubat et al. 2009). For example, modifications in heart rate variability have been seen in both high and low performance chess players (Fuentes-Garcia et al. 2019). Of course, it is necessary to study many more examples in order to make a rigorous recommendation for improving health in everyday prevention. The argument here is that cognitive activities may help improve physical health, as the need for physical exercise diminishes in a digital society.

## 29.6 Cognitive Nutrition

The example of whether sugars perhaps play a more relevant role than conventionally believed, has been mentioned above. There are other examples where foodstuffs or compounds which are considered detrimental to health, may in fact play an important role, if considered within the context of a cognitive environment. It has been

**Table 29.1** Examples where improved cognitive health has a positive repercussion on somatic tissues/organs

| |
|---|
| Mental imagery may improve muscle strength without the need to perform physical exercise (Clark et al. 2014; Slimani et al. 2016). Cortical activation (in this case via mental imagery) resulted in attenuation of muscle weakness |
| While up-regulation of Brain Derived Neurotrophic Factor (BDNF) is possible through physical exercise, up-regulation of BDNF can also be achieved via cognitive stimulation (Walsh and Tschakovsky 2018). Therefore, here we encounter an example where multimodal intervention results in biological amplification of the action of BDNF for achieving a better final result |
| Immunity may improve after exposure to a cognitively-stimulating environment (Gurfein et al. 2014; Takai et al. 2019) |
| Cognitive exercises such as those improving the speed of information processing can also improve physical health and socio-emotional functions in older people, including vitality, physical well-being, and pain (Wolinsky et al. 2006) |
| Exposure to a cognitively-enhanced environment positively regulates heart rate variability (Zebunke et al. 2013; Normann et al. 2018) |
| Mental exercise involving cognitive faculties may improve general health, quality of life, and psychological status (Wolinsky et al. 2010; Goghari and Lawlor-Savage 2018) |

argued that chocolate (containing cocoa flavonols) may play a more relevant role in improving cognitive performance, compared to physical exercise (Brickman et al. 2014).

Returning to the case of sugars, I argue that it may be carrying an unfair label as an unhealthy food. It is known that the presence of glucose aids efficient and fast neuronal responses, and that deprivation of glucose supplies is detrimental to gamma oscillations (Galow et al. 2014; Vodovozov et al. 2018), which are present during a cognitive task such as information processing and formation of memories (Kann et al. 2014). Sugar intake has also been found to be of benefit to tasks requiring sustained attention (Giles et al. 2018). It may be less controversial to suggest that intake of glucose in a background of a sedate, inactive and non-cognitive environment is indeed detrimental to health, whereas glucose intake, even at relatively high levels in a context of physical and cognitive stimulation, becomes beneficial. Nevertheless, it is clear that these issues are complex and, at present, there is not enough evidence to offer firm suggestions which go against currently held beliefs about health nutrients. At this point it is worth considering how 'screen time' (time spent in front of a screen, such as television or computer) affects satiety signals. Screen time and satiety is still a controversial issue. Some researchers did not find a relationship between the two (Totosy de Zepetnek et al. 2017), whereas others did find some relationship, which depends on the type of cognitive engagement (Lyons et al. 2013). Yet others found an association of time spent in front of a screen and obesity, but only in girls and not in boys (Hume et al. 2009). Certainly, the relationship between satiety signals and increased time spent in front of a computer screen is complicated and far from clarified. For instance, it is necessary to clarify if it is the actual screen electromagnetic emissions that cause a disruption of satiety signalling to the brain, or if it is purely

a matter of physical inactivity, or both. The cognitive engagement and its energetic needs also need to be taken into account. At present, it seems that this issue requires further consideration.

## 29.7 Comprehensive Geriatric Assessment (CGA)

Let us return to more conventional ways of dealing with health and disease. I have already remarked that, in order to optimize health management in a clinical setting, assessing the health status of an adult in a holistic manner is imperative. In older people this assessment is even more important because older people may have challenging multimorbidity, functional limitations, or minor health issues. A very useful approach is the CGA, when healthcare practitioners evaluate the state of the patient particularly in frail and vulnerable individuals (Pilotto et al. 2017). The assessment involves a multidisciplinary approach by health care professionals who have an expertise in a specific area of health each (Table 29.2). It has been shown that CGA improves several health outcomes, if used correctly either in an inpatient or an outpatient setting, in a collaborative manner involving physical, mental, social, functional and environmental parameters (Parker et al. 2018; Tatum et al. 2018).

Based on the above discussion, it would soon be necessary to include in the assessment technicians and/or digital technology experts who would assess the function of the digital environment of the patient (Levine et al. 2018).

In any case, the CGA is used on people who are neither too well, nor too ill: in patients therefore who are likely to derive benefit from the assessment. Patients may be selected according to their comorbidities, psychosocial situation, problems related specifically to older age such as dementia, falls or sarcopenia, and previous or predicted use of health care facilities. It is beyond the scope of this chapter to provide detailed information about CGA. Sufficient to mention that, if used correctly, this is a most promising tool for evaluating health in later life, increasing the chances of offering suitable prevention and cure interventions.

**Table 29.2** Multidisciplinary approach by health care professionals who have an expertise in a specific area of health (Åhlund et al. 2017; Birch 2016)

| |
|---|
| Geriatrician: physical general health |
| Pharmacist: medication, prescriptions, compliance |
| Physiotherapist: motion, balance, muscle strength and abilities |
| Nurse: skin, ulcers, continence and general nursing |
| Social worker: social needs, relative availability and help |
| Speech therapist: swallowing, speech, etc |
| Occupational therapist: ADL and environment the patient is in (home or care home, hospital) |
| Dietitian: nutrient intake, malnutrition, advice re cooking meals |

In everyday clinical situations, a health professional needs to consider not just the clinical function of the patient, but also the domain of vitality. The concept of vitality is an important one, because it influences the health and well-being of the individual. Vitality can be affected by positive and meaningful daily activities (physical and cognitive), the inner feeling of strength and personal power/self-esteem, and positive relationships with other members of the community (Söderbacka et al. 2017). Therefore, health professionals should assess vitality, particularly in older people who are at risk of an increasingly restricted lifestyle and a failing physiological state (van de Vijver et al. 2018). There is a number of commercially-available vitality health checks, which a patient may take online, for example: https://www.discovery.co.za/vitality/vitality-assessments-lead-healthier-life (retrieved 20 November 2019).

## 29.8 The Role of Positive Psychology in Health

In addition to technological, physiological and clinical elements of health, there are emotional and spiritual elements that need to be considered, especially in older people (Levine and Cooney 2018). Briefly, it is known that positive psychological constructs, such as optimism, can improve health outcomes (Huffman et al. 2017). In addition, other positively-charged emotional factors such as positive affirmations can help (Ferrer et al. 2017). Emotional affection or love feelings expressed towards a sick person, come under this category. Expression of love towards a sick person may improve motivation, and reduce stress and anxiety (Esch 2005; Kok et al. 2013).

There exist evaluation instruments being developed for assessing these feelings (Barrett et al. 2019). Love and compassion may play a significant role in chronic disease management, such as for instance, Alzheimer's dementia (Monin et al. 2015). This aspect of health needs further study.

## 29.9 Microbiome, an Important Health Determinant

A discussion about clinical health cannot be complete without a reference to gut microbiota and how this affects overall health. The gut microbiota has a capacity to affect health, either in a positive or in a negative way because it modulates immunity, inflammation and cognition, among others (O'Toole and Jeffery 2015). Relevant issues relating to older people such as sarcopenia and ageing mechanisms are also affected (O'Toole and Jeffery 2018).

It has been shown that gut microbiota affect general health, and also, specifically, brain health differently in older people compared to younger ones (Lubomski et al. 2019). This is relevant in older people who may have neurodegenerative conditions such as Alzheimer's disease or Parkinson's disease. A surge in awareness in the role of the gut microbiome in shaping health is now helping to clarify many questions regarding not only bowel health but also brain health.

**Table 29.3** Nutritional recommendations which may help promote healthy gut microbiota

| |
|---|
| Avoid processed foods, which may suppress the function of beneficial bacteria (Kordahi and DePaolo 2019) |
| Consume a wide range of plant-based foods which improve the variability of microbes (Clark et al. 2017) |
| Include fibre, either in the everyday diet (fruit, vegetables, pulses, nuts and wholegrains) or in nutritional supplements (Hijová et al. 2019) |
| Include probiotic foods, such as live yoghurt, or certain cheeses, encourage the proliferation of beneficial bacteria (such as Lactobacillus) (Barathikannan et al. 2019) |
| Avoid antibiotics if at all possible. The adverse effects (e.g. obesity) of some antibiotics on the gut microbiome are well known (Leong et al. 2018) |
| Include extra-virgin olive oil and other foodstuffs containing polyphenols, improve the function of beneficial bacteria (Prieto et al. 2018) |
| Use probiotic supplements in tablet form, such as spirulina, may help (Li et al. 2019) |

Health surveillance based on microbiota activity is essential in older people. For instance, use of antibiotics, which is so common in the elderly, may adversely affect gut microbiota and this has an overall effect on health and function (Henrickson 2019, Desselberge 2018). It is known that diet modifications, which are specific for older individuals, can have an impact on the gut microbiome and affect physiological and/or pathological mechanisms. The instance of sarcopenia has already been mentioned but there are other physiological functions in older people which are affected (e.g. mitochondrial abnormalities, inflammation markers, insulin resistance) (Casati et al. 2019).

Therefore, practical advice (Table 29.3) for improving the health of the gut microbiome may have a positive effect (Kim and Jazwinski 2018).

## 29.10 Hormetic Interventions for Better Functioning

Hormesis is a dose–response, non-linear occurrence, meaning that a low dose of a stressor can result in benefit, whereas a higher dose may result in damage (Calabrese et al. 2015). During hormesis, mild stressful challenges invoke a stress response and up-regulate defence and repair pathways, with a subsequent overall improvement in function. Hormesis is induced when the challenge is of sufficient magnitude, appropriate quality, and it is perceived as a novelty by the organism. Routine and monotony do not, as a rule, invoke a hormetic response. The assessment and response to the new challenge leads to adaptation and thus, eventually, improvement of function within the environment where the challenges have originated from. In this way, there is a direct link between external challenging information and internal physical or biological changes (Rattan and Kyriazis 2019).

Within a clinical setting, hormesis has several applications which may help improve overall health. Hormesis is gaining increasing interest due to its role in

upregulating several parameters involved in a variety of organs and systems, and it is based on a 'positive stress' principle, i.e. low exposure to a given stimulus upregulates the stress response with a consequent positive effect, whereas excessive exposure results in adverse effects. For instance, hormetic interventions may be used against infections (Weis et al. 2017), in neuroprotection and mental disease, such as in schizophrenia (Calabrese et al. 2017), in nutrition in ageing (Martel et al. 2019), in improving sarcopenia (Musci et al. 2019), and in other aspects of the ageing patient (Kyriazis 2017, Calabrese et al. 2018). The modern literature on hormesis is continually expanding, and there is a large number of papers explaining the process. Examples of hormetically-inspired advice (i.e. ever-changing daily tasks, presenting new challenges every day and positively stressing the organism without causing excessive stress, pleasantly stimulating hurdles), which can be used in a practical, everyday setting include (Kyriazis 2016): physical stimulation (various exercises in changing environments, with different level of activity), social stimulation (ever-changing daily routine, a mixture of personal and virtual activities), and nutritional stimulation (with nutrients or compounds that can positively stress the organism, such as hormetins).

## 29.11 Personalised Medicine and Molecular Pathological Epidemiology

During the past several years, another new concept in health and ageing has been taking form. The concept is that effective therapies against age-related degenerative conditions cannot be based on simple reductionist models, involving only medications or general therapies applied to all. Instead, a more comprehensive and complex approach needs to be employed, targeting the patient as a distinct individual. The combination of several of the factors discussed here, such as adaptation to a digital environment, microbiome composition, availability of clinical resources, genetic and epigenetic factors, drug and prescription variables, individualised hormetic reactions, social and emotional responses, and many others, make each patient unique. Therefore, in order for good health to flourish, we need to develop strategies which see each patient as a unique entity.

Theories based on targeting a personalised treatment which depends on the needs of a specific patient, such as Precision Medicine (Mohler et al. 2015) and Molecular Pathological Epidemiology (MPE) (Ogino et al. 2013), describe how disease may affect each patient in a unique manner, and therefore it could be impossible to devise generalised strategies that can be effective in everybody, although strategies for specific small groups of patients could still be possible to achieve. In addition, we are now becoming increasingly aware that each patient exhibits distinctive disease profiles based on an interaction of those diverse biological, social and technological factors mentioned above. In other words, each patient is unique in his/her disease profile, an issue conceptualised as the 'Unique Disease Principle' (Ogino et al. 2012).

This requires the employment of a specific approach, namely, precision medicine. Precision medicine is a relatively novel medical model, which basically customises health care provision tailored to each patient, taking into account that patient's genetic and epigenetic profile, environment and socio-cultural aspects (Olivier et al. 2019).

Epidemiological approaches combined with pathology are better able to explore health and disease taking into account molecular, individual and population health. A related discipline, Molecular Pathological Epidemiology is now being deployed, in order to achieve the goal of personalised medicine (Hamada et al. 2017). We are now experiencing the dawn of a new medicine which may be able to deliver effective and appropriate healthcare solutions.

## 29.12 Conclusions

In this chapter, I have argued that health is not merely the absence of disease, and it is not a generally positive situation of wholeness, nor a state of complete physical, mental, and social well-being (WHO definition). From a practical point of view, health is not dependant on wellbeing but on function. People may not feel well, but can function appropriately for their circumstances, therefore they should be considered healthy. This function is specific to each individual, at any given time, at any given environment, and it is not the same for every age group or for every person irrespective of their changing situations. The capacity to adapt to changing external and internal circumstances (Huber et al. 2011) is a useful definition of health, but it needs further clarification. I have argued that **health is good function with respect to a certain environment**, an environment which may change continually. This begs the question whether healthy ageing can be achieved. If ageing is time-related dysfunction, and we are in a position to offer therapies which overcome that dysfunction, then yes, healthy ageing can be achieved, and chronic degeneration may become less relevant in practice.

In this discussion, I highlighted some issues which support healthy ageing by promoting high levels of functioning across several domains, such as physiological, psychological, emotional, technological and societal. Invoking currently available assets both from the patient and from the healthcare provider point of view, helps foster greater resilience and adaptation of the patient to new adversities or challenges (Cosco et al. 2017). Health in a clinical setting therefore, depends on many diverse variables, and involves changing our thinking to embrace new concepts as these develop through an ever-changing modern technological environment.

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# Part IV
# Conclusions

# Chapter 30
# How is 'Health' Explained Across the Sciences? Conclusions and Recapitulation


**Jonathan Sholl and Suresh I. S. Rattan**

**Abstract** In this concluding chapter, we gather the various contributions of this volume and attempt to extract some of the many key insights and challenges raised when it comes to the project of explaining health across the sciences. These insights were distilled down into a selection of the central concepts and issues defended or discussed by the authors, and were organized into a table to see, at a glance, where the attention was given. Reflecting on these insights will go some way towards addressing the question of whether these explanations can be brought together into a coherent or unifying framework or whether we are simply stuck with mutually exclusive views about the multifaceted phenomenon of 'health'.

**Keywords** Health explanations · WHO · Positive and negative health · Homeostasis · Robustness · Adaptation · Aging and healthspan · Unified and integrative theories

## 30.1 Introduction

The overarching aim of this volume was to gather a wide variety of scholars working in many different fields and nudge them to develop novel reflections on the notion of 'health'. These reflections, it was hoped, would then lead to interesting insights into the interdisciplinary project of 'translating' the vague notion of 'health' into more scientific and scholarly terms. In other words, the aim was to better determine how health is being *explained* or described in these different fields. In order to help condense and organize these wide-ranging contributions, we have composed a table to help visualize, at a glance, some of the points of emphasis (Table 30.1). This chapter will try to extract what we feel are some of the more interesting and

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**Table 30.1** Key concepts and issues presented in or defended by the authors, with details of descriptions or examples illustrating these concepts/issues

| Key concepts/issues | Chapter # | Primary focus, examples |
|---|---|---|
| WHO: for/neutral | 8, 10, 11, 13, 17, 19, 20, 21, 22 | Holistic definition as useful, on the right track, a place to start |
| WHO: critical of | 1, 3, 6, 7, 15, 24, 29 | Holistic/complete view is too demanding, hard to quantify, promotes medicalization |
| Negative health | 3, 5, 8, 10, 12, 25 | Absence of disease, pathology, infection, deformity |
| Health as positive/presence | 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 16, 17, 19, 21, 22 | Holistic account (WHO-inspired), presence of specific properties, abilities, qualities, biomarkers |
| Homeostasis (traditional) | 5, 6, 8, 13, 14, 17, 19, 20, 26 | Localized balance: molecular, cellular, systemic |
| Ability to adapt | 3, 4, 5, 6, 7, 8, 12, 13, 15, 16, 17, 19, 24, 26, 28, 29 | Dynamic view of homeostasis, allostasis, general adaptability, homeodynamic space |
| Ability to adapt (biological) | 1, 2, 3 | Adaptability more specifically biological or evolutionary, health as "derivative of adaptation" |
| Robustness, resilience, stress resistance | 4, 5, 6, 7, 9, 14, 15, 20, 28, 29 | Systems or networks tolerating perturbations, "ability to adequately adapt and respond to homeostatic perturbations" or stressors |
| Natural selection, fitness pressures (over time) | 1, 2, 5, 14, 20 | Selection pressures weaken with time, central for adaptation/adaptability (relating to aging) |
| Aging, lifespan, healthspan | 1, 2, 3, 4, 5, 6, 9, 14, 15, 16, 17, 20, 25, 26, 27, 28 | Health understood in the context of aging/temporality or trajectories, aging as a constraint or limitation to health, overlap or separation of lifespan and healthspan, positivities and potential through aging |
| Hormesis | 4, 5, 8, 15, 20, 21, 24, 25, 28, 29 | As pathway to achieve robustness, resilience, adaptability, longevity, health |
| Localized health/field | 5, 7, 8, 11, 12, 14, 17, 20, 22, 23, 28 | Healthy mouth, blood, sexuality, immune system, public health, neuroimmunology, microbiome, mental health, model organisms |

(continued)

**Table 30.1** (continued)

| Key concepts/issues | Chapter # | Primary focus, examples |
|---|---|---|
| Defining, explaining health in general | 2, 4, 5, 6, 13, 15, 16, 18, 19, 21, 24, 29 | Health is the/a: "capacity to anticipate biological, chemical and physical stresses and to be able to recover successfully from such challenges", "age-specific adaptation", "dynamic response of the whole organism to any challenge that could mobilize the body's resources at various levels and extents", "good function with respect to a certain environment" |
| Advising/illustrating an integrative, unifying, holistic view | 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 27 | "Synthetic mindset", biopsychosocial model, subjective and objective health measures, integrating parts into whole, unifying theoretical framework, integrative health measures/biomarkers/indicators |
| Distinguishing, classifying types of explanations | 6, 8, 19, 23 | Reductionist versus holistic, top-down versus bottom-up, robust, multidimensional, invariant |

promising insights contained in this volume and suggest where future work could be carried out. What follows is thus only a selection of ideas as we could not discuss every contribution on its own terms.

## 30.2 Extracting Insights

### *30.2.1 Assessing the WHO Amid Negative and Positive Views of Health*

One rather unexpected result was that, when pressed to extend insights about a specific body part, function, or scientific field to the notion of 'health' itself, one of the most common perspectives mentioned was the WHO's definition of health. Now, while this definition was called upon repeatedly, at times just to start the discussion and at others to defend it, it was also heavily criticized in several contributions. But, if it is so terribly flawed, as has been pointed out ever since its formulation, why would so many contemporary scientists or philosophers persist in discussing it? Without wading into speculations, one possibility is simply that it is at least a well-accepted way to say something 'more' about health than just that it is marking the absence of disease. While a 'negative' view of health was only rarely mentioned or defended, the WHO's definition was often used to signal the need to develop a 'positive', 'integrated' or even 'holistic' view. The whole challenge, of course, is in spelling

out what this consists in, but it was still the majority view that such an approach is needed, however it is realized. For instance, Murphy, Donovan and Smart (Chap. 7) point out that developing a 'positive' view of mental health requires clarifying what healthy mental capacities are and distinguishing them from the other fuzzy concept coming from the WHO: 'well-being'.

As we will see, perhaps more technical concepts, like resilience or robustness, could be helpful. However, since they tend to serve specific scientific purposes in a given field the question is whether they can allow for generalizations about something so complex, and so personally, socially and culturally embedded, as is the phenomenon of health. Hence, the WHO's definition provides a common and easy starting point to discuss 'health' at higher levels of complexity.

### *30.2.2 Homeostasis: Traditional and Nuanced*

That being said, these more technical concepts (e.g. homeostasis, robustness, resilience) were quite often appealed to in order to explain healthy functioning, either in a localized context or to provide a more general definition of health. Like the WHO's definition, 'homeostasis' was often used as a foil in order to develop a more dynamic account, usually framed in the general sense of the 'ability to adapt', and sometimes appealing to more recent concepts, such as allostasis, robustness, or homeodynamic space. The use of such concepts is not surprising either since they can be situated in a long history of attempts to differentiate normal or healthy physiology from the pathological (which has been one of the proposed benefits of homeostasis ever since its formulation). This volume, then, further supports the claim that such physiological concepts remain central to clarifying what health is.

### *30.2.3 Health as Evolutionary Adaptability*

Relatedly, other technical concepts coming from the biological sciences, such as fitness and adaptation, were also used to explain health, but were in the minority and generally confined to more explicitly evolutionary accounts of health. In these accounts, fitness was often appealed to not only to describe key aspects of health, such as age-dependent adaptability, but also to explain why it is so rare to maintain health indefinitely. As both Kirkwood (Chap. 1) and Arnold et al. (Chap. 2) point out, while our bodies were programmed for survival, the need to survive forever was never a high priority for natural selection, and thus we observe the entire process of deterioration and damage accumulation that characterizes 'aging'. In this sense, evolutionary explanations come in different forms: partly explaining *why* health is observed (e.g. as a component of what ensures fitness or longevity), and partly explaining what

health *is* (e.g. some form of adaptability). If health really is 'derivative' of adaptation (Arnold et al., Chap. 2), then perhaps it is odd that adaptation was not a more central concept in the other chapters.

### *30.2.4 Health and Adaptation in the Context of Aging, Healthspan and Hormesis*

In line with the previous point, we also observe an interesting reliance on either the field of aging research in general, or specific concepts stemming from it, such as hormesis or homeodynamics (the former initially coming from toxicology but now often discussed in the context of aging modulators). This observation, like some of the others, is likely due to a selection bias since many of the authors asked were known by one of the editors through their work on or interest in precisely these issues. Nevertheless, the importance of aging research in particular for explaining health may be underappreciated. For example, Lenart, Scheringer and Bienertová-Vašků (Chap. 16) argue that we need a thoroughly temporal understanding of how phenotypes are cumulatively formed into 'phenotypic trajectories' (the sum of interactions between genotype, environment and aging) if we are to clarify health and disease. Similarly, Nehlin and Andersen (Chap. 15) try to specify how molecular biomarkers could be used to identify broader 'health trajectories'. One of the interesting implications of these approaches is that perhaps our typical understanding of health as a 'state' is misguided and we would benefit from thinking about health in terms of processes, trajectories, or arcs. If so, the notions of 'health' and 'healthspan' could become much more intimately linked. As mentioned, the concept of hormesis, often discussed in the context of aging, may also help to integrate physiological descriptions with social and environmental factors so as to clarify in what sense an environment can be healthy or health-promoting; for instance, by providing appropriate levels of stressors or challenges (Agathokleous and Calabrese, Chap. 21).

Relatedly, one of the recurring ways to describe health in a clinical context was in terms of adaptability. The ability to adapt to and thrive from stressors, be they on the chemical, cellular, systemic, physiological, psychological, or interpersonal level, seems crucial to not only explain what health is but how it can be promoted or enhanced. Now, while there is much research examining whether the modulation of specific molecular pathways can ultimately result in improved health, the research presented in several contributions suggests that such attempts are likely misguided due to the complex nature of biological systems and the aging process (Vaiserman and Lushchak, Chap. 27). While one could develop cocktails acting on multiple pathways, a potentially more promising alternative is that of implementing more systemic lifestyle interventions, generally based around the notion of 'hormesis' (Kyriazis, Chap. 29). Moreover, while there does not appear to be a law of nature preventing indefinite life or health extension, there is perhaps an interesting tension between the notion that health is about change and adaptation, whereas 'life extension' seems to

aim for unchanging, or at least the indefinite maintenance of, certain appearances or capabilities (Stambler, Chap. 26). Further research into this link between interventions working through the principle of hormesis and overall health seems both necessary and promising.

### *30.2.5 Taking a Stab at 'Health' in General*

Perhaps *the* central issue emerging from this volume is the following: what ultimately *is* health? What was rather interesting to observe is how many of the contributions involved attempts to provide a unifying or integrative perspective on health in general. These generalizations seem to be most common, as one would expect, when we turn from the focus on specific parts or functions and look to the insights derived from entire fields or research domains. As a result, we received some very intriguing ways to define health, such as: 'age-specific adaptation' (Arnold et al., Chap. 2); the 'dynamic response of the whole organism to any challenge that could mobilize the body's resources at various levels and extents' (Fülöp et al., Chap. 13); 'a collection of basal optimal values of true relevance for optimal body function' (Nehlin and Andersen, Chap. 15); the 'capacity to anticipate biological, chemical and physical stresses and to be able to recover successfully from such challenges' (Agathokleous and Calabrese, Chap. 21); or 'good function with respect to a certain environment' (Kyriazis, Chap. 29). In this vein, the notions of 'robustness' and 'resilience' were often appealed to, typically in the framework of the 'omics' sciences. For instance, Tacutu and colleagues (Chap. 5), seeking to synthesize genomic, methylomic, transcriptomic, metabolomic, or exposomic levels, argue that 'a healthy system can be described by efficient signalling and communication, decreased uncertainty, increased stability and, ultimately by increased robustness'. While such attempts might not satisfy some philosophers and their love of formalizations and strict definitions, at the very least they point us in the direction that future interdisciplinary research could take.

There were also several contributions coming at the notion of health from the view of what characterizes or is present in healthy individuals. For instance, there was the suggestion to specify the 'parameters', 'indicators', 'factors' or even the various 'biomarkers' that are observed in health at any level of organization (Sholl, Chap. 6; Nehlin and Andersen, Chap. 15). In this line, Rattan (Chap. 4) argues that three central biomarkers (stress response, damage control, continuous remodeling) can help track the higher-level parameters of robustness, resilience and allostatic load, which together comprise a healthy phenotype. Similarly, Karamalegos and colleagues (Chap. 14) suggest that there is no single description of what a healthy microbiome is in terms of comprising this or that species of microbe. But there is nevertheless what they call a 'core of functional reactions' or specific qualities that would have to be part of any healthy microbiome, such as the *diversity* of microbial species, and general *robustness* and *resilience* to stressors. While the latter is focused on explaining health for a specific field, the insights about defining the specific parameters or biomarkers

of health surely generalize to other fields, potentially even to overall organismic health.

One central challenge to any attempt at a coherent definition of 'health', however, was nicely captured by Arnold and colleagues (Chap. 2): any 'unified understanding of health requires the solution of a puzzle with many pieces.' There are clearly *many* explanations for this phenomenon or physiological property we call 'health' and putting them together is a herculean task. Nevertheless, the majority of the contributions either explicitly called for the need to integrate localized descriptions of health (e.g. of cardiovascular, oral or blood health) into descriptions of a healthy body, to put bodies in their social and physical environments, or for the need to develop an account or theory of health that can unify as many of these perspectives as possible. While this aim to situate findings about one body part into a more complex biological whole is rather important, albeit rather dated, the challenge is 'to be holistic with discipline', as Færgeman nicely points out (Chap. 11).

We thereby need to combine structural and functional descriptions and situate these within the dynamic functioning of the whole organism and its countless environmental influences, but this is far from easy to do rigorously and systematically. The difficulty, then, is not just that of linking a specific mechanistic description with broader dynamics, but accommodating with the sheer amount of variables and data that are being produced by the medical sciences and the various 'omics' that are driving current research. Perhaps some fields are better suited to deal with this kind of complexity, as suggested by the contributions on studying health via systems biology (Tacutu et al., Chap. 5), on immunity as a holistically coordinated biological system (Fülöp et al., Chap. 13), on healthy sleep as fundamentally integrating physiology, representations and behaviors (Micoulaud-Franchi et al., Chap. 17), or on how social perspectives start from individuals as embedded in social networks, organizations, communities, nations, etc., with each of these levels providing further explanations as to the health of the individuals within (Zachariae, Chap. 22). While it is in no way clear how to construct such a holistic or integrative account of health, this goal nevertheless appears to be widely shared.

### *30.2.6 Forms of Health Explanations*

We have been using the notion of 'explanation' above, but it is important to note that explanations come in many forms. Perhaps the most generic form involves descriptions of an observed state of affairs in terms of causes, mechanisms, pathways, or biological principles. This can then result in specifying a 'why' or 'how' for this state of affairs, but it can also involve specifying the 'what'. In other words, explanations of 'health' can clarify *why or how health is achieved*, but they can also clarify *what health is*. The former kind of explanation would rely on the latter, since to achieve something we need to know what that is. While this distinction remains ambiguous in many of the contributions, we nevertheless observed many attempts to describe what health is, as well as to point out the pathways or mechanisms by

which such health is brought about. Future work could perhaps make this distinction clearer from the beginning, and the various references in these chapters to lifestyle and nutritional interventions could be promising places to start.

While explanations in the medical sciences often take the form of causal explanations, Broadbent and Smart (Chap. 23) point out that a holistic explanation would need to appeal to different parts of the causal process: what they call "illness causation" and "pathomechanism". In other words, the causally relevant external sequence of events leading up to the somatic response (illness causation) and the subsequent mechanisms producing the disease manifestation (pathomechanism). As they show with convincing case studies, placing too much emphasis on the latter can result in ignoring the social and cultural context (which may be the case with some public health approaches to our current Covid-19 pandemic), being both ethically and empirically dubious. While they focus on illness, perhaps similar holistic explanations obtain when it comes to health.

Finally, a further challenge to this project of constructing a unified explanation is more of a conceptual or classificatory one, often pointed out by the philosophical contributions (Konsman, Chap. 8). For instance, Lerner (Chap. 19) suggests that while it is an open question as to whether a unifying account of health can be developed, any approach will have trade-offs to consider: 'either one has a bottom-up approach finding a common denominator that all organisms share or one has a top-down approach which starts with a certain valuable criterion and then one clarifies which organisms fulfil the criterion'. A bottom-up approach may cover most if not all organisms, but at the cost of an overly vague or rudimentary notion of health. A top-down approach may better capture features of complex organisms, but at the cost of excluding aspects of simpler ones. The challenge to any attempt to provide a coherent account of health will thus be threading the needle between broadly inclusive yet vague approaches and ones that are precise yet narrow or restrictive.

## 30.3 Looking Ahead

Ultimately, additional volumes like this are needed to help gather even more explanations and descriptions of health so as to better determine whether there can only be field-specific explanations or whether we can generalize from one field to another. Doing so will help evaluate whether the entire project of trying to translate the vague notion of health into more precise, scientific terms is even feasible. Combining the specificity and detail-oriented strengths of scientists with the philosophical ability to develop more abstract and cross-discipline reflections could be the most fruitful way forward. As mentioned in the preface, while we were able to achieve some level of interdisciplinarity here in terms of the final selection of contributions, another interesting approach could involve having each chapter co-authored by scientists and philosophers.

While it is rather commonplace today to plea for interdisciplinary methods, the discussion of health could not be more in need of such research. This property we call

‘health’ is at the crossroads of many sciences and fields, and clearly draws in social and personal considerations, making it multidimensional, if not altogether disjointed. If there is any hope in explaining what health is, and doing so in a way that expresses some unification or ‘consilience’ across the scientific and humanistic fields, it will require actual and persistent collaboration.

# Correction to: Molecular Biomarkers of Health


**Jan O. Nehlin and Ove Andersen**

**Correction to:**
**Chapter 15 in: J. Sholl and S. Rattan (eds.),**
***Explaining Health Across the Sciences*,**
**Healthy Ageing and Longevity 12,**
**https://doi.org/10.1007/978-3-030-52663-4_15**

In the original version of the book, in Table 15.2 of Chapter 15 "micromolar" term was wrongly abbreviated as "Mmol", which has now been corrected. The chapter and book have been updated with the change.

The updated version of this chapter can be found at
https://doi.org/10.1007/978-3-030-52663-4_15



J. Sholl and S. Rattan (eds.), *Explaining Health Across the Sciences*, Healthy Ageing and Longevity 12, https://doi.org/10.1007/978-3-030-52663-4_31

# Index





J. Sholl and S. Rattan (eds.), *Explaining Health Across the Sciences*, Healthy Ageing and Longevity 12, https://doi.org/10.1007/978-3-030-52663-4

**I**



**L**



**M**