Introduction

Human Genetics as Fundamental and Applied Science

Human genetics is both a fundamental and an applied science. As a fundamental science, it is part of genetics – the branch of science that examines the laws of storage, transmission, and realization of information for development and function of living organisms. Within this framework, human genetics concerns itself with the most interesting organism – the human being. This concern with our own species makes us scrutinize scientific results in human genetics not only for their theoretical significance but also for their practical value for human welfare. Thus, human genetics is also an applied science. Its value for human welfare is bound to have repercussions for theoretical research as well, since it influences the selection of problems by human geneticists, their training, and the financing of their research. Because of its continued theoretical and practical interest, human genetics offers fascination and human fulfillment unparalleled by work in fields that are either primarily theoretical or entirely practical in subject matter.

Science of Genetics

Genetics is based on a powerful and penetrating theory. The profundity of a theory depends on the depth of the problems that it sets out to solve and can be characterized by three attributes: the occurrence of high-level constructs, the presence of a mechanism, and high explanatory power [1]. In genetics, the high-level "construct" is the gene as a unit of storage, transmission, and realization of information. Since the rediscovery of Mendel's laws in 1900, genetic mechanisms have been worked out step by step to the molecular level – deciphering of the genetic code, analysis of transcription and translation, the function of gene-determined proteins, the fine structure of the genetic material, and DNA sequences outside of genes. The problems of regulation of gene activity in the development and function of organisms are currently a principal goal of fundamental research. So far, the explanatory power of the theory has not nearly been exhausted.

How Does a Science Develop?

Kuhn (1962) [10] described the historical development of a science as follows: In the early, protoscientific stage, there is substantial competition among various attempts at theoretical foundation and empirical verification. Basic observations suggest a set of problems that, however, is not yet visualized clearly. Then, one "paradigm" unifies a group within the scientific community in the pursuit of a common goal, at the same time bringing into sharper focus one or a few aspects of the problem field, and suggesting a way for their solution. If the paradigm turns out to be successful, it is accepted by an increasing part of the scientific community, which now works under its guidance, exploring its possibilities, extending its range of application, and developing it into a scientific theory.

This concept of a paradigm has three main connotations:

1. It points to a piece of scientific work that serves as an "exemplar," suggesting ways in which a certain problem should be approached.
2. It delimits a group of scientists who try to explore this approach, expand its applicability, deepen its

theoretical basis by exploration of basic mechanisms, and enhance its explanatory power.
3. Finally, while an elaborate theory must not – and, in most cases, does not – exist when a paradigm is initiated, its germ is already there, and a successful paradigm culminates in the elaboration of this theory.

This process of developing a science within the framework of a paradigm has been described by Kuhn as "normal science." The basic theory is taken increasingly for granted. It would be sterile at this stage to doubt and reexamine its very cornerstones; instead, it is applied to a variety of problems, expanded in a way that is comparable to puzzle solving. From time to time, however, results occur that, at first glance, defy explanation. First, this leads to attempts at accommodating such results within the theoretical framework by additional ad hoc hypotheses. These attempts are often successful; sometimes, however, they fail. If in such a situation an alternative paradigm is brought forward that explains most of the phenomena accounted for by the old theory as well as the new, hitherto unexplained phenomena, a scientific "revolution" may occur. The new paradigm gains support from an increasing majority of the scientific community, it soon develops into a new – more explanatory – theory, and the process of normal science begins anew.

This portrayal of scientific development has been criticized by some philosophers of science [11]. The concept of "normal" science as outlined above does not appeal to some theorists. Working within the framework of a given set of concepts has been denounced as dull, boring, and in any case not as science should be. According to these philosophers, scientists ought to live in a state of permanent revolution, constantly questioning the basic foundations of their field, always eager to put them to critical tests and, if possible, to refute them [15–18]. Many scientists actively involved in research, on the other hand, have readily accepted Kuhn's view; he has apparently helped them to recognize some important aspects in the development of their own fields.

Central Theory of Genetics Looked at as a Paradigm

While Kuhn's concepts were developed on the basis of the history of the physical sciences, his description well fits the development of genetics. Up to the second half of the nineteenth century, the phenomena of heredity eluded analysis. Obviously, children were sometimes – but by no means always – similar to their parents; some diseases were shown to run in families; it was possible to improve crops and domestic animals by selective breeding. Even low-level laws were discovered, for example Nasse's law that hemophilia affects only boys but is transmitted by their mothers and sisters (Chap. 5, Sect. 5.1.4). However, a convincing overall theory was missing, and attempts at developing such at theory were unsuccessful. In this situation, Mendel, in his work *Versuche über Pflanzenhybriden* (1865) [12] first improved a procedure; he complemented the breeding experiment by counting the offspring. He then interpreted the results in terms of the random combination of basic units; by assuming these basic units, he founded the gene concept – the nuclear concept underlying genetic theory (Chap. 1, Sect. 1.4).

Since the rediscovery of his work in 1900, Mendel's insight has served as a paradigm in all three connotations: it provided an exemplar as to how breeding experiments should be designed and evaluated, it resulted in the establishment of a scientific community of geneticists, and it led to the development of a deep and fertile scientific theory. A special problem that has not been answered satisfactorily, in our opinion, concerns the question of why acceptance of Mendel's paradigm had to wait for as long as 35 years after these experiments were published. It would be too simplistic to blame academic arrogance and shortsightedness of contemporary biologists who did not want to accept the work of a "nonacademic" outsider, even if this factor may indeed have been one of the components for this neglect. We believe rather that the many new biological discoveries in the 35 years following Mendel's discovery were of such a revolutionary nature as to qualify as a scientific crisis in the Kuhnian sense and therefore required a completely new approach.

Soon after the rediscovery of Mendel's laws in 1900, however, an initially small, but quickly growing group of scientists gathered who developed genetics in an interplay between theory and experiment and launched the major scientific revolution of the twentieth century in the field of biology.

Human Genetics and the Genetic Revolution

Meanwhile, the biological revolution of the nineteenth century – evolutionary theory – had been accepted by the scientific community. One major consequence was

the realization that human beings had evolved from other, more "primitive" primates, that humans are part of the animal kingdom, and that the laws of heredity which had been found to apply for all other living beings are also valid for our species. Hence, Mendel's laws were soon applied to traits that were found in human pedigrees – primarily hereditary anomalies and diseases. Analyzing the mode of inheritance of alkaptonuria – a recessive disease – Garrod (1902) [5] clearly recognized the cardinal principle of gene action: genetic factors specify chemical reactions (Chap. 1, Sect. 1.5). This insight also required 30 years before being incorporated into the body of "normal" science.

Elucidation of inheritance in humans did not begin with Mendel's paradigm. Many relevant observations had been reported before, especially on various diseases. Moreover, another paradigm had been founded by F. Galton in his work on *Hereditary Talent and Character* (1865) [6] and in later works: to derive conclusions as to inheritance of certain traits such as high performance, intelligence, and stature, one should measure these traits as accurately as possible and then compare the measurements between individuals of known degree of relationship (for example, parents and children, sibs, or twins) using statistical methods. This approach did not contain the potential for elucidating the mechanisms of heredity. On the other hand, it seemed to be much more generally applicable to human characteristics than Mendelian analysis; pedigree analysis in terms of Mendel's laws was hampered by the fact that most human traits simply could not be classified as alternate characteristics, as could round and shrunken peas. Human characteristics are usually graded and show no alternative distribution in the population. Moreover, the phenotypes are obviously determined not only by the genetic constitution but by external, environmental influences as well – the result of an interaction between "nature and nurture" (Galton). Therefore, naive attempts at applying Mendel's laws to such traits were doomed to failure. For traits that are regarded as important, such as intelligence and personality, but also for many diseases and mental retardation, there was only the choice between research along the lines suggested by Galton or no research at all. Investigations on genetic mechanisms would have to await elucidations of the genetics of other, more accessible organisms. Under these circumstances, scientists chose to follow Galton. This choice had not only theoretical reasons; it was strongly influenced by the desire to help individuals and families by calculating risk figures for certain diseases, thereby creating a sound basis for genetic counseling. More important, however, was the concern of some scientists about the biological future of the human species, which they saw threatened by deterioration due to relaxation of natural selection. The motives for their research were largely eugenic: it seemed to provide a rational foundation for measures to curb reproduction of certain groups who were at high risk of being diseased or otherwise unfit.

History of Human Genetics: A Contest Between Two Paradigms

The two paradigms – Mendel's gene concept and Galton's biometric approach – have developed side by side from 1900 up to the present; many present-day controversies, especially in the field of behavior genetics but also those concerning strategies in the genetic elucidation of common diseases, are immediately understandable when the history of human genetics is conceived as a contest between these two paradigms. This does not mean that the two paradigms are mutually exclusive; in fact, correlations between relatives as demonstrated by biometric analysis were interpreted in terms of gene action by Fisher in 1918 [4]. Some human geneticists have worked during some part of their career within the framework of the one paradigm, and during another within the framework of the other paradigm. By and large, however, the two streams of research have few interconnections and may even become further polarized because of highly specialized training for each group, epitomized by the biochemical and molecular genetic laboratories for the one and the computer for the other group.

In the first decades of the last century the biometric paradigm of Galton appeared to be very successful. Genetic variability within the human population was believed to be established for normal traits such as stature or intelligence as well as for a wide variety of pathologic conditions such as mental deficiency and psychosis, epilepsy, and common diseases such as diabetes, allergies, and even tuberculosis. Mendelian analysis, on the other hand, seemed to be confined to rare hereditary diseases; the ever repeated attempts at expanding Mendelian explanation into the fields of normal, physical characteristics and common diseases

were usually undertaken without critical assessment of the inescapable limitations of Mendelian analysis. The first major breakthrough of Mendelian genetics was the establishment of the three-allele hypothesis for the AB0 blood groups by Bernstein in the 1920s [2] (Chap. 5, Sect. 5.2.2). Further progress, however, had to await the development of genetic theory by work on other organisms such as *Drosophila,* bacteria, and viruses, especially bacteriophages.

The advent of molecular biology in the late 1940s and 1950s had a strong influence on human genetics and, indeed, brought the final breakthrough of Mendel's paradigm. A major landmark was the discovery by Pauling et al. in 1949 [14] that sickle cell anemia is caused by an abnormal hemoglobin molecule.

The foundation of human chromosome research in the late 1950s and early 1960s (Chap. 3, Sect. 3.1) came as a second, important step. At present, most investigations in human genetics have become a part of mainstream research within the framework of genetic theory. The human species, regarded by most early experimental geneticists as a poor tool for genetic research, is now displaying definite advantages for attacking basic problems. Some of these advantages are the large size of available populations, the great number and variety of known mutants and chromosome anomalies, and the unparalleled detailed knowledge of human physiology and biochemistry in health and disease. The improved understanding of human genome structure and its variability (Chap. 2) by the completion of the human genome project, by new sequencing and array technologies, and by efforts to identify all functional elements in the human genome sequence (Chap. 4), further facilitates both basic and applied research in human genetics.

One would expect that such breakthroughs have led to the establishment of Mendel's paradigm as the only leading paradigm in human genetics. This, however, is not the case. In spite of the fact that genetic theory is now pervading many fields that seemed to be closed to it, the paradigm of Galton – biometric analysis – has attained an unsurpassed level of formal sophistication over the past decades. The availability of software tools has greatly facilitated the development and application of biometric techniques. Moreover, in some fields, such as behavior genetics, the application of genetic theory – Mendel's paradigm – is still hampered by severe difficulties (Chap. 23), and here biometric methods have dominated for a long time. In the same field, however, they are most severely criticized and subject to controversial discussions about ethical issues and possible discrimination.

Progress in Human Genetics and Practical Application

The achievements of molecular biology and chromosome research have not only altered human genetics as a pure science, but have also brought marked progress in its application for human welfare. At the beginning, this progress did not appear very conspicuous; the diagnosis of hereditary diseases was improved, and many, hitherto unexplained malformations were accounted for by chromosome aberrations. The first practical success came in the early 1950s when the knowledge of enzyme defects in phenylketonuria (Chap. 1) and galactosemia led to successful preventive therapy by a specific diet. However, a breakthrough on a much larger scale was achieved when the methods of prenatal diagnosis for chromosome aberrations and for some metabolic defects were introduced in the late 1960s and early 1970s (Chap. 25, Sect. 25.2). Suddenly, genetic counseling could now be based not only on probability statements but, in an increasing number of cases, on certainty of individual diagnoses. This scientific development coincided with a growing awareness in large parts of the human population that unlimited human reproduction must not be accepted as a natural law but can – and should – be regulated in a rational way. Introduction of oral contraceptive agents signaled this awareness. The chance to avoid the births of severely handicapped children is now accepted by a rapidly increasing proportion of the population. At the same time, better knowledge of pathophysiological pathways is improving the chances for individual therapy of hereditary diseases, including the promise somatic gene therapy by introduction of genes into cells of functional tissues (see Chap. 27). Applications of human genetics as a practical tool to prevent suffering and disease have found wide resonance and have now one of the most rewarding approaches in preventive medicine. In many countries, the politically responsible bodies have already created, or are now creating the institutions for widespread application of the new tools.

Effects of Practical Applications on Research

These practical applications have led to a marked increase in the number of research workers and the amount of work within the past decades. From the beginning of the twentieth century up to the early 1950s, human genetics had been the interest of a mere handful of scientists for most of whom it was not even a full-time occupation. Many of the pioneers were trained and worked much of their lifetime as physicians in special fields of medicine, such as Waardenburg and Franceschetti in ophthalmology, and Siemens in dermatology. Others were interested in theoretical problems of population genetics and evolution and chose problems in human genetics as the field of application for their theoretical concepts, most notably J.B.S. Haldane and R.A. Fisher. Still others had their point of departure in physical anthropology. This heterogeneous group of scientists did not form a coherent scientific community. For a long time, there was almost no formal infrastructure for the development of a scientific specialty. There were almost no special departments, journals, and international conferences. This lack of focus resulted in a marked heterogeneity in quality and content of scientific contributions.

All this has changed. Departments and units of human and medical genetics are now the standard in many countries; universities and medical schools offer special curricula, many journals and other publications exist, and numerous congresses and conferences are being held. Human genetics is now an active and vigorous field which continues to grow exponentially.

Dangers of Widespread Practical Application for Scientific Development

This development, however, satisfactory as it is, has also a number of potentially undesirable consequences:

(a) Research is promoted primarily in the fields of immediate practical usefulness related to hereditary diseases; fields of less immediate practical importance may be neglected.
(b) Initially the contact with fundamental research in molecular genetics and cell biology was not intensive enough. This may have led to a slowdown in the transfer of scientific concepts and experimental approaches from these fields. Fortunately, this has changed with the advent of recombinant DNA techniques and many other methods. The speed with which results of basic research are being transferred into practical application has increased significantly.
(c) As in other sciences, certain topics may evolve to a mainstream research where vast human and financial resources are being invested, drawing it off other areas, which are then neglected in spite of their great importance. For example, at present the immense activities to unravel complex disorders by high-throughput assays have resulted in a decreased interest in studying monogenic Mendelian disorders although their detailed analyses may provide invaluable insights into consequences of mutations and their associated pathophysiology (see Chap. 4, Sect. 4.1).
(d) Much medical research applies established methods to answer straightforward questions. Many studies collect data with new techniques. Individual results are often not of great import, but the ensemble of such data are the essential building blocks for the future progress of normal science. Much of such work is being carried out in human and medical genetics and is quite essential for many medical and anthropological applications. However, there is continued need in human genetics to develop testable hypotheses and try to test their consequences from all viewpoints.

Human geneticists must not neglect the further development of genetic theory. Basic research is needed in fields in which the immediate practical application of results is not possible but might in the long run be at least as important for the future of the human species as current applications in diagnostic and preventive medicine.

Advantages of Practical Application for Research

The needs of medical diagnosis and counseling have also given strong incentives to basic research. Many phenomena that basic research tries to explain would simply be unknown had they not been uncovered by study of diseases. We would be ignorant regarding the

role of sex chromosomes in sex determination had there not been patients with sex chromosomal anomalies. Phenomena such as spontaneously enhanced chromosome instability in Fanconi's anemia or Bloom's syndrome with all its consequences for somatic mutation and cancer formation (Chap. 3, Sect. 3.7) were discovered accidentally in the process of examining certain patients for diagnostic reasons. Genetic analysis of the "supergene" determining the major histocompatibility complex in humans contributes much to our fundamental understanding of how the genetic material above the level of a single gene locus is structured, and how the high genetic variability within the human population can be maintained (Chap. 6, Sect. 6.2.5). However, research in this field would certainly be much less active had there not been the incentive of improving the chances of organ transplantation.

Whether we like it or not, society pays increasing amounts of money for research in human genetics because we want to have practical benefits. Hence, to promote basic research, we must promote widespread practical applications. To guarantee progress in practical application for the future as well – and not only in the field of medicine – basic research needs to be supported. This is also the only way to attract good research workers and to maintain – or even improve – scientific standards. This paradox creates priority problems for all those concerned with research planning.

Human Genetics and the Sociology of Science

The discussion above should have demonstrated that human genetics – as all other sciences – has not developed in a sociological vacuum, following only the inherent logical laws of growth of theory and experimental testing. Human genetics is the work of social groups of human beings who are subject to the laws of group psychology and are influenced by the society at large in their attitudes toward research and their selection of problems. Unfortunately, sociological investigations of group formation and structure in human genetics have not been carried out. Another group active in the foundation of molecular biology, that which introduced the bacteriophages of *Escherichia coli* into the analysis of genetic information, has been studied extensively [3]. We know from this and from other examples that, during a phase in which a new paradigm is being founded, the group that shares this paradigm establishes close within-group contacts. The normal channels of information exchange such as scientific journals and congresses are superseded by more informal information transfer through telephone calls, e-mail communications, preprints, and personal visits. Within the group, influential personalities serve as intellectual and/or organizational leaders. Outside contacts, on the other hand, are often loose. When the acute phase of the scientific revolution is over, the bonds within the group are loosened, and information is again exchanged largely by normal channels of publication.

Similar developments can be observed in the field of human genetics. For example, in Chap. 6 (Sect. 6.2.5) we sketch the groups active in the elucidation of the major histocompatibility complex and in the assignment of gene loci to chromosome segments (Sect. 6.1).

Of similar influence on population genetics has been the first "big science" research project in human genetics – the Atomic Bomb Casualty Commission (ABCC, now the Radiation Effects Research Foundation, RERF; www.rerf.or.jp) project that was launched in the late 1940s in Japan by American and Japanese research workers to examine the genetic consequences of the atomic bombs in Hiroshima and Nagasaki (Chap. 10). In later years, this project led, for example, to comprehensive studies of the genetic effects of parental consanguinity. The second endeavor of this type is the "Human Genome Project" – the attempt at analyzing and sequencing the entire human genome by coordinated international cooperation (see Chap. 44). Today many research efforts are being conducted and can only be accomplished in large, international consortia, as for example the ENCyclopedia Of DNA Elements (ENCODE) project (www.genome.gov) or the Functional Annotation of the Mammalian Genome (FANTOM) project (fantom.gsc.riken.jp).

Many, if not most of the more interesting developments in the field were not initiated by investigators who would declare themselves human geneticists, or who worked in human genetics departments. They were launched by research workers from other fields such as general cytogenetics, cell biology, molecular biology, biochemistry, and immunology, but also from clinical specialties such as pediatrics, hematology, ophthalmology, and psychiatry. A common theme running through many recent developments has been the

application of nongenetic techniques from many different fields such as biochemistry and immunology to genetic concepts. On the other hand, techniques originally developed for solving genetic problems, especially for molecular studies of DNA, are being introduced at a rapidly increasing rate into other fields of research, for example in both medical research and practical medicine. In fact, most recent progress in human genetics comes from such interdisciplinary approaches. The number of research workers in the field has increased rapidly. Most did not start as human geneticists but as molecular biologists, medical specialists, biochemists, statisticians, general cytogeneticists, etc. They were drawn into human genetics in the course of their research. This very variety of backgrounds makes discussions among human geneticists stimulating and is one of the intellectual assets of the present state of our field. However, such diversity is also a liability as it may lead to an overrating of one's small specialty at the expense of a loss of an overview of the whole field [8]. With increasing complexity of research methods, specialization within human genetics has become inevitable. However, this brings with it the danger that the outlook of the scientist narrows, whole fields are neglected, and promising research opportunities remain unexploited.

Human Genetics in Relation to Other Fields of Science and Medicine

The rapid development of human genetics during recent decades has created many interactions with other fields of science and medicine. Apart from general and molecular genetics and cytogenetics, these interactions are especially close with cell biology, biochemistry, immunology, and – with many clinical specialties. Until recently, on the other hand, there have been few if any connections with physiology. One reason for this failure to establish fruitful interactions may be a difference in the basic approach: genetic analysis attempts to trace the causes of a trait to its most elementary components. Geneticists know in principle that the phenotype is produced by a complex net of interactions between various genes, but they are interested more in the components than in the exact mechanism of such interactions. At present, genetic analysis has reached the level of gene structure and the genetic code; a final goal would be to explain the properties of this code in terms of quantum physics. A malevolent observer might compare the geneticist with a man who, to understand a book, burns it and analyzes the ashes chemically.

The physiologist, on the other hand, tries to read the book. However, he often presupposes that every copy of the book should be exactly identical; variation is regarded as a nuisance. To put it differently, physiology is concerned not with the elements themselves but with their mode of interaction in complicated functional systems (see Mohr [13]). Physiologists are more concerned with the integration of interacting systems than with the analysis of their components. The analysis of regulation of gene activities by feedback mechanisms, for example, the Jacob-Monod model in bacteria, and some approaches in developmental genetics of higher organisms have taught geneticists the usefulness of thinking in terms of systems. On the other hand, methods for molecular analysis of DNA have been introduced into physiology at an increasing scale. Genes for receptors and their components, for example for neurotransmitters, and genes for channel proteins are being localized in the genome and analyzed at the molecular level. Hence, the gulf between physiology and genetics is now being bridged. With the increasing interest of human geneticists in the genetic basis of common diseases and individual genetic variation in response to influences such as nutrition and stress, genetic concepts are increasingly influencing the many branches of medicine that, in the past, have profited relatively little from genetic theory. Molecular biology is developing increasingly into a common basis for many branches of science, and most biomedical scientists are nowadays becoming better acquainted with the principles of genetics. A field of molecular medicine is emerging.

Fields of Human and Medical Genetics

The field of human genetics is large, and its borders are indistinct. The development of different techniques and methods has led to the development of many fields of subspecialization. Many of these overlap and are not mutually exclusive. The field of *human molecular genetics* has its emphasis in the identification and analysis of genes at the DNA level. Methods such as DNA digestion by restriction endonucleases, Southern blotting,

polymerase chain reaction (PCR), sequencing and many others are being applied. *Human biochemical genetics* deals with the biochemistry of nucleic acids, proteins, and enzymes in normal and mutant individuals. Laboratory methods of the biochemist are being used (e.g., chromatography; enzyme assays). *Human cytogenetics* deals with the study of human chromosomes in health and disease. *Immunogenetics* concerns itself largely with the genetics of blood groups, tissue antigens such as the HLA types, and other components of the immune system. *Formal genetics* studies segregation and linkage relationships of Mendelian genes and investigates more complex types of inheritance by statistical techniques.

Clinical genetics deals with diagnosis, prognosis, and to some extent treatment of various genetic diseases. Diagnosis requires knowledge of etiological heterogeneity and acquaintance with many disease syndromes. *Genetic counseling* is an important area of clinical genetics and requires skills in diagnosis, risk assessment, and interpersonal communication. *Population genetics* deals with the behavior of genes in large groups and concerns the evolutionary forces of drift, migration, mutation, and selection in human populations. The structure and gene pool of human populations are studied by considering gene frequencies of marker genes. In recent years population geneticists have become interested in the epidemiology of complex genetic disease that require biometric techniques for their studies. *Behavioral genetics* is a science that studies the hereditary factors underlying behavior in health and disease. Behavior geneticists attempt to work out the genetic factors determining personality and cognitive skills in human beings. The genetics of mental retardation and various psychiatric diseases are also considered. The field of sociobiology tries to explain social behavior by using biological and evolutionary concepts.

Somatic cell genetics is the branch of human genetics that studies the transmission of genes at the cellular level. Cell hybridization between different species is an important tool for the cartography of human genes. *Developmental genetics* studies genetic mechanisms of normal and abnormal development. This field employs to a large extent model organisms and has a strong emphasis on animal experimentation. *Reproductive genetics* is the branch of genetics that studies details of gamete and early embryo formation by genetic techniques. This area is closely related to reproductive physiology. Due to the growing application of assisted reproductive technologies in couples with infertility disorders this field has recently grown significantly. *Pharmacogenetics* deals with genetic factors governing the disposal and kinetics of drugs in the organism. Special interest in human pharmacogenetics relates to adverse drug reactions. *Ecogenetics* is an extension of pharmacogenetics and deals with the role of genetic variability affecting the response to environmental agents.

Clinical genetics has grown very rapidly in recent years because of the many practical applications of diagnosis and counseling, intrauterine diagnosis, and screening for genetic disease. Most research in human genetics is currently carried out in clinical genetics, cytogenetics, molecular and biochemical genetics, somatic cell genetics, and immunogenetics under medical auspices. Research in formal and population genetics has benefited enormously from the increasing knowledge about genome structure and its variation and the availability of new, cheaper high-throughput sequencing approaches.

Future of Human Genetics

Research methods in science are becoming ever more complicated and expensive, and human genetics is no exception. As a necessary consequence mastering of these methods increasingly requires specialization in a narrow field. Purchase of big instruments creates financial difficulties. Hence, the selection of research problems is often directed not by the intrinsic scientific interest in the problems or the conviction that they could, in principle, be solved, but by the availability of research methods, skilled coworkers, and instruments. Many research projects require large patient cohorts and complex, genome-wide analyses, tasks of a magnitude that can only be performed within international consortia. Such efforts are greatly facilitated by web-based databases (Sects. 29.1–29.3) which provide an easy means for distributing results to the genetic community. Furthermore, such databases ensure that new evolving information can easily be utilized by other persons in the field. For example, data on copy number variation in the human genome and possible consequences for the phenotype are now rapidly assessable in databases (Sects. 29.2 and 29.3) and are thus available for genetic counselors who can use this knowledge to provide their patients with detailed up-to-date information.

However, the tendency toward specialization will inevitably continue, and it is possible that, in this process, important parts of human genetics will be resolved into fields mainly defined by research methods, such as biochemistry, chromosome research, immunology, molecular biology [see 12], or into certain clinical areas. For example, hereditary metabolic diseases or syndromes associated with dysmorphic features and developmental delay are often studied and treated by pediatricians with little genetic training. Several departments of neurology have established their own neurogenetics branches, which are often independent from the respective department of human genetics. However, despite this tendency toward subspecialization, it is important to note that a laboratory performing genetic diagnostic procedures needs trained and experienced personnel, up-to-date equipment, and has to fulfill internationally defined quality standards, which are regulated by law in many countries. Therefore, it is probably not cost-effective to perform genetic diagnostics in small laboratories that offer only a few tests. Therefore, large laboratories performing all important human genetics diagnostic procedures may evolve to organizational structures in which human genetics remains united.

Survival of an established field of science has no value in itself. If a field dies because its concepts and accomplishments have been accepted and are being successfully integrated into other fields, little is lost. In human genetics, however, this state has not been reached yet and it may never get to this point. Many concepts of molecular biology, often in combination with "classical" methods such as linkage analysis, are now being applied to humans. A few decades ago human genetics was a medical field mainly dealing with rare syndromes and prenatal diagnostics. This picture has completely changed as the genetic contributions to common diseases are increasingly being unraveled. For example, genetic counseling is now an integral part of care in families with hereditary cancer diseases (Chap. 14) or neurologic disorders. In addition, data evolving from genome-wide association studies (GWAS) have identified numerous new loci in the genome that may change the susceptibility for diseases or phenotypic features. The effect of these loci may often be only moderate (Sect. 8.1), however, the evolving knowledge may further increase requests for genetic counseling. In future, genetic counseling provided by professionals in the field may have to compete with "direct-to-consumer genetic testing" over the Internet that is already offered by several companies. Such developments are accompanied by growing options for predictive genetic diagnosis, which require standardized procedures for both the counseling session and the molecular genetic testing and which often involve difficult ethical issues. Thus, the tasks in human genetics have changed tremendously over the past decades and new challenges are constantly arising in this rapidly evolving field. Newly evolving technologies, such as whole-genome sequencing (see below), will further expand the future of human genetics. In fact, it can be predicted that human genetics will change medicine, as it has the potential to identify persons with an increased risk for certain diseases and it may provide information about treatment options. These aspects are now often referred to as "personalized medicine" (Chap. 4, Sect. 4.4) and they will likely dominate medicine in upcoming years.

Unsolved and Intriguing Problems

With the rapid increase in knowledge over recent years new and often unexpected problems have arisen. At a time when hereditary traits were defined by their modes of inheritance, the relationship between genotype and phenotype appeared relatively simple. This straightforward relationship seemed correct when some hereditary diseases were shown to be caused by enzyme defects, and when hemoglobin variants turned out to be due to amino acid replacements caused by base substitutions. With increasing knowledge of the human genome, however, many hereditary traits with phenotypes that had been considered identical turned out to be heterogeneous. These were caused either by mutations in different genes or by different mutations within the same genes. However, even mutations that are identical by the strictest molecular criteria sometimes have striking phenotypic differences. Analysis of such genotype-phenotype relationships by the study of genetic and environmental modifiers poses intriguing future problems in human genetics.

The establishment of genotype–phenotype relationships was recently further complicated by two new findings. The first finding represents the unanticipated variation within the human genome (Chap. 2). Future

research will have to elucidate how copy number variants (CNVs) contribute to human phenotypic diversity and disease susceptibility. CNVs are also of interest for a better understanding of the evolution of the genome, as they provide the raw material for gene duplication and gene family expansion. However, in addition to numerical variation there are extensive structural variations, such as inversions or insertions. Their impact on gene function remains to be elucidated. The second finding was the characterization of functional elements by the ENCODE consortium. To date, only 1% of the human genome has been analyzed by various high-throughput experimental and computational techniques; however, the findings revealed an unexpected number and complexity of the RNA transcripts that the genome produces. These findings have challenged traditional views about regulatory elements in the genome and added new insights into the complexity of human genetics, revealing that our understanding of the genome is still far from being complete. In order to address this, the National Human Genome Research Institute (NHGRI) launched two complementary programs in 2007: an expansion of the human ENCODE project to the whole genome (http://www.genome.gov/ENCODE) and the model organism ENCODE (modENCODE) project to generate a comprehensive annotation of the functional elements in the *Caenorhabditis elegans* and *Drosophila melanogaster* genomes (http://www.modencode.org; http://www.genome.gov/modENCODE). These efforts will likely contribute to a better understanding of genome complexity and gene regulation.

At present our understanding of somatic genome variability is very incomplete. Current concepts suggest that erroneous DNA repair and incomplete restoration of chromatin after damage may be resolved and may produce mutations and epimutations. Both mutations and epimutations have been shown to accumulate with age and such an increased burden of mutations and/or epimutations in aged tissues may increase cancer risk and adversely affect gene transcriptional regulation. This may in turn result in a progressive decline in organ function, a phenomenon frequently observed in aging. With the demographic trend of prolonged life expectancy, a better understanding of somatic genome variability and the stability of the genome may grow in importance.

Other problems may arise from new technologies, such as next-generation or third-generation whole-genome sequencing (Chap. 4, Sect. 4.4), which will make sequencing of entire genomes possible and affordable within in a short period of time. These possibilities will require new bioinformatic tools and interpretation of sequencing results will greatly depend on whether we understand better the aforementioned relevance of structural and copy number variation and whether we can make sense of the various transcriptionally active regions in the genome. If we succeed, there is no doubt that whole-genome sequencing will change human genetics tremendously. They will, for example, contribute to a better understanding of modifier genes in monogenic diseases and thus explain the frequently observed phenotypic variability. Furthermore, they will contribute significantly to further propel research on complex diseases. However, although the new possibilities of human genetics are fascinating they raise at the same time new ethical issues. For example, in prenatal diagnostic settings tests can now be offered not only for devastating diseases but also for common phenotypic traits. Thus, the consequences of the new technologies and new insights do not have consequences only for human geneticists but also for the entire society.

Possible Function of a Textbook

In his book on *The Structure of Scientific Revolutions,* Kuhn in 1962 [2] described the function of textbooks not very flatteringly: they are "pedagogic vehicles for the perpetuation of normal science" that create the impressions as if science would grow in a simple, cumulative manner. They tend to distort the true history of the field by only mentioning those contributions in the past that can be visualized as direct forerunners of present-day achievements. "They inevitably disguise not only the role but the very existence of . . . revolutions . . ."

Below we shall proceed in the same way: we shall describe present-day problems in human genetics as we see them. The result is a largely affirmative picture of normal science in a phase of rapid growth and success. Anomalies and discrepancies may exist, but we often do not identify them because we share the "blind spots" with most other members of our paradigm group. The "anticipation" phenomenon in diseases

such as myotonic dystrophy is one example (Chap. 5, Sect. 5.1.7). This disease tends to manifest more severely and earlier in life with each generation. Obviously, this observation did not appear to be compatible with simple mendelism. Therefore, it was explained away by sophisticated statistical arguments which we cited in earlier editions of this book. In the meantime, however, anticipation has been shown to be a real phenomenon, caused by a novel molecular mechanism. What we can do is to alert the reader that human genetics, as all other branches of science, is by no way a completed and closed complex of theory and results that only needs to be supplemented in a straightforward way and without major changes in conceptualization. Our field has not developed – and will not develop in the future – as a self-contained system. Rather, human genetics, as all other sciences, is an undertaking of human beings – social groups and single outsiders – who are motivated by a mixture of goals such as search for truth, ambition, desire to be acknowledged by one's peer group, the urge to convince the society at large to allocate resources in their field – but also the wish to help people and to do something useful for human society.

Therefore, we shall emphasize the history and development of problems and approaches. Occasionally, we shall ask the reader to step back, reflecting with us as to why a certain development occurred at the time it did, why another development did not occur earlier, or why a certain branch of human genetics did not take the direction that one would have expected logically. Inevitably, this implies much more criticism than is usually found in textbooks. Such criticism will – at least partially – be subjective, reflecting the personal stance of the authors. Our goal is to convince the reader that a critical attitude improves one's grasp of the problems and their possible solutions – it is not our intention to convince him that we are always right.

We would have liked to give more information on the ways in which sociological conditions within the field and – still more important – the developments in the society at large have influenced the development of human genetics, and the ways in which thinking on these problems has in turn influenced the societies. The eugenics movement in the United States and the *Rassenhygiene* ideology in Germany have had a strong – and sometimes devastating – influence on human beings as well as on the social structure of society at large. Too little systematic research has been carried out, however, to justify a more extended discussion than that presented in Chap. 1 (Sect. 1.8) [17]. Much more historical research along these lines is all the more urgent, as many of the ethical problems – inherent, for example, in the sterilization laws of many countries during the first decades of the twentieth century – are now recurring with full force in connection with prenatal diagnosis, selective abortion and the possibility of germinal gene therapy (Chaps. 25 and 26). Scientists and physicians working in human genetics were actively involved in and sanctioned ethically abhorrent measures in the past such as killing severely malformed newborns and mentally defectives in Nazi Germany – and how will future generations judge our own activities? These are intriguing questions. They show the Janus face of human genetics: it is a fundamental science – guided by a fertile theory and full of fascinating problems. It is also an applied science, and its applications are bound to have a strong impact on society, leading to novel and difficult philosophical, social, and ethical problems.

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