Chapter 12
Ethical Implications of Nanomedicine: Implications of Imagining New Futures for Medicine

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12.1 A Historical Introduction

Nanomedicine is seen as one of the most exciting prospects amongst all the potential application of emerging nanosciences and technologies. Sophisticated and exquisitely finely focused instrumentation is providing new understandings of processes of the body and mechanisms of disease. These in turn should open up increasing possibilities for more precise diagnosis and monitoring, and for therapeutic or prophylactic interventions, at the scale of genes, proteins and cells of our bodies. Many of the anticipated benefits of nanomedicine remain as future prospects, and at times there here has been a regrettable tendency to exaggerate. Yet nanotechnologies are beginning to emerge from their initial discovery and exploratory phase. In 6 years since 2008, successive annual *Clinam* European conferences on clinical nanomedicine have reflected a growth in nanomedical techniques, products and clinical trials [1]. This is evidence that this field of nanotechnology is beginning to show at least the first fruits of its promise.

As the scope and influence of nanotechnological applications in medicine increases, there is a corresponding responsibility to consider their ethical and social implications. Ten years ago concerns were expressed at the gap between the rapid development and ethical assessment [2]. But since then numerous studies have explored these questions. A series of European Commission funded projects included a scoping review in 2005 from the Nano-2-Life European Network of Excellence [3, 4], and reports from the NanoBioRaise [5] and NanoMed Round Table [6], Observatory Nano [7] and Deepen [8] projects, and an opinion on nanomedicine of the official European Commission's European Group on Ethics [9].

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Early concerns over potential risks had been raised in a report from the ETC Group in 2003 [10]. A seminal scientific study by the Royal Society and Royal Academy of Engineering in 2004 highlighted how little was known scientifically about the behaviour of nano-sized particles regarding health and the environment. While this was not deemed sufficient to justify what was seen as an over-precautionary call by ETC for a general moratorium, the academies' report was notable for pointing to the need for substantial research into the risk aspects, and also for including ethics in its considerations [11].

The Nano-2-Life and NanoBio-Raise reports noted a gap of legitimation and accountability between researchers and developers and a European general public which was largely unaware of what nanotechnology was [4, 5, 12]. This gap of engagement has begun to be addressed a number of national studies, for example in the UK, Germany and Switzerland and Netherlands, as well as the above EC research projects [13–15].

These activities were energised in part by concerns of governments and the EU, that nanotechnologies might arouse public suspicions and NGO opposition comparable to that experienced with genetically modified food. It was widely acknowledged that nanotechnologies should be opened to public debate as a matter for so-called upstream engagement. For example, stakeholder groups were invited members of a UK Government forum on nanotechnologies which ran for several years [16].

But in general, nanotechnologies have not so far aroused major controversies in Europe. There have been critical reports from NGO groups in particular sectors like food and cosmetics, and the use of nanosilver as an anti-bacterial agent in hospitals [17, 18]. More worrying were a few organised protests of militant groups in France which disrupted a national programme of public debates, and a series of deeply disturbing letter bomb attacks in Mexico, which seriously injured scientists [19]. Such militant opposition does not seem to represent general public attitudes. From the various studies mentioned above, the prospects for nanomedicine so far seem to have met with a broad approval among the wider European population, but with some concerns and at times some useful insights.

For example, a public engagement study for the UK Engineering and Physical Sciences Research Council (EPSRC) [20] asked people about specific nanomedical research priorities. General support was expressed for most applications of nanomedicine, but tempered by concerns about long terms risks and what may happen when the medical research goals enter the domain of large commercial corporations. But its participants also brought important human insights that nanotechnological solutions might sometimes be too sophisticated. Nanosilver surface coatings in hospitals might be less useful than simply doing more ordinary cleaning. Implanted theranostic devices could become too 'smart' if they did not allow control by either the patient or a doctor.

Because the technologies are themselves evolving, ethical reflection is inevitably work in progress. This chapter surveys some of the main ethical and social issues which have emerged to date. Eight themes will be considered: cross-cutting issues, diagnostics, remote monitoring, targeted drug delivery, theranostics, regenerative

medicine, risk and uncertainty, and the relationship of nanomedicine to notions of human enhancement. Three types of questions may arise, running as threads through these themes. In some cases there may be ethical issues with the techniques themselves. There will be ethical and social implications from their uptake by individuals and societies, including possible unintended consequences. Thirdly some more fundamental questions are asked about the values, goals and presuppositions that accompany the technical drivers of nanomedicine.

12.2 Generic and Cross-Cutting Ethical Issues

The first generic question often asked is whether applying nanotechnologies to medicine raises any 'new' ethical issues. The EC European Group on Ethics observed that, notwithstanding the revolution it promised, nanomedicine did not raise issues in biomedical ethics that had not been encountered and considered before [8]. While there was no dramatic new question for the European Commission legislative bodies to face, it did not mean that there are no ethical issues to consider. Nanotechnologies tend to be 'enabling technologies' which provide novel means to existing medical objectives, like rapid point-of-care diagnostics or targeting drug delivery to diseased cells. As is often the case, such new technologies may raise old problems in new ways, or amplify existing issues, or shed new light on them. As the Royal Society report noted, the important thing is to address them, whether new or not [10].

A second generic question relates to implicit values in nanomedicine. The 'enabling' concept does not represent the full story. Nanomedical innovations are not just neutral devices or tools, with no ethical significance. They are considered to be 'value-laden'. This means that the diagnostics, devices and drugs which are being enabled by nanotechnologies all, to some extent, embody certain values, visions and tacit assumptions about future medicine and healthcare. The innovators could be said to be co-producing values and artefacts at the same time. This is indeed inevitably the case for early stage innovation. But it is the task of ethical reflection, social analysis and public engagement to check that the values of technical experts are ones which cohere with ethical views in the wider society [21, 22]. Often, underlying changes of value are difficult to see at the time. The NanoMedRound Table report drew attention to the perspective that nanotechnologies are enabling technologies within a wider progressive reshaping of medicine through technologies in general, whose values and goals need to be duly examined [6].

It is important to consider how these changes relate to our understandings of the human person, of society, and of the role and limits of medicine. By nature, nanomedicine seeks to measure and intervene in the body at the most reduced scales. In doing so, it brings together disciplines with different contexts and concepts – physical and materials sciences, engineering, biotechnology, neurosciences, informatics and medicine. Applying an inherently reductionist focus from the analytical sciences to complex systems in the human body may create some conceptual tensions to the broader practices of medicine. The focus on biological functions at the

smallest levels needs also to be duly related to our wider understandings of human beings, derived from culture, religion and ethics, and to concepts like human dignity, personhood, divine image, autonomy, and so on. What is the moral status of human beings, considered in relation to normal adult life, to the earliest (embryonic and/or foetal) and last weeks and months of life, and to people being subjects in medical research, or of novel or experimental medical treatments?

To take one example, at the end of life, no guarantees can be made of life quality into extreme old age, yet breakthroughs inspired or enabled by nanomedicine may mean that many more people will in future survive into a final, frail stage of life. How should we handle the ethical decisions arising from longer average life spans? Is human dignity only associated with a certain quality of life? Or is it something which is intrinsic to a human being, wholly independent of one's state of bodily health or capability? What is it that makes life worth living – is it only the possession of certain faculties, or is it something fundamental in being human, regardless of our frailty? These are old questions, but ones which nanomedicine may amplify in particular ways.

Again, as technologies develop at the brain-machine interface, these renew long-standing discussions about the relationship between one's identity, the mind/brain and the body. In pursuit of nanomedical solutions, how far should we develop devices which promote direct brain-machine interactions, or apply external or internal controls to the brain? Is our human responsibility or autonomy modified if we have a neurotransplant? Should technologies devised and permitted in a strict medical context then be applied without limit to non-medical interventions?

The Nano-2-Life review noted that, whilst welcoming the many new possibilities to treat disease and alleviate suffering, medicine should not be reduced to engineering solutions. In applying techniques derived from nanosciences, it is important not to lose sight of the wider values of medicine and health care which see the patient as more than mal-operating functions. Materials scientists and bioengineers may make very good devices to help, but they may not be the best doctors to treat the whole person, or to help people face the point when a condition is beyond even the best human ingenuity to treat [7].

A third type of cross-cutting ethical issues relates to social justice. In a world of much inequity, how far should we promote advanced nanomedical technologies, if the likelihood is that they will favour only a few who can afford them, or only those countries with the relevant innovation and regulatory infrastructure? For optimal cases, nano-based therapies may be cheap, or may achieve a net saving in long term healthcare costs. But for some applications, the additional expense of sophisticated therapies may place further financial strain on health care systems. These in turn pose further dilemmas for those responsible for apportioning stretched resources. If nano- and other technologies find medical treatments for hitherto intractable problems, medicine is likely to become constrained less by untreatable conditions, and more by the lack of resources to treat everyone. The situation is more acute, when considered in wider global terms. So much could be done to alleviate suffering on a very wide scale by much more basic health provisions than nanotechnology. There is thus also an opportunity cost, both in ethics and resources, in concentrating on developing high-tech medicine. Do we have the appropriate balance?

12.3 Diagnostics, Information and Predictive Medicine

One of the most far-reaching impacts of nanomedicine is likely to be in the area of diagnostics. It is foreseeable that nano-enabled 'lab-on-a-chip' devices may be able to perform a rapid genome analysis on a simple blood sample, for example. If the equipment could become affordable, what has hitherto been an expensive specialist analysis could become routinely used in a family doctor's surgery. Similarly, nanoscale methods and devices could act as 'biomarkers' to monitor chemical changes in the body's metabolism that would be early indicators of developing a disease conditions, long before the physiological appearance of the normal symptoms. Such rapid point-of-care diagnostics could greatly extend the scope of information available to doctors and patients about health status, both in the range of conditions, and the range of people.

This is seen as part of a major shift from the evidential medicine based on observable symptoms, to a predictive, pre-symptomatic, 'information based' medicine, in which the early indications of an incipient disease state could be picked up early, perhaps years before the symptoms were observed. The hope is that it should then be possible to address the condition long before it takes serious hold in the body. This may delay or reduce the onset, or even prevent it altogether.

A goal of this pre-symptomatic approach to medicine is to move beyond addressing clinical symptoms, or families known to be at risk of a particular disease, to be able to pick up indications in people who would consider themselves healthy. A core assumption in such knowledge-based medicine is that information is taken to be a universal good. In many cases having more specific and relevant information about the condition of a patient will indeed be of much benefit. But is this always the case? When examined more closely, the value of the information is highly context-dependent.

Three questions arise:

(a) How useful is information about our present and future health status?
(b) What preventive interventions are justified within the body, based on what level of diagnostic and especially pre-symptomatic information, and on what levels of probability?
(c) To whom should my health status information be known, other than myself?

Consider four types of preliminary indication of a medical condition that might be obtained using nano-enabled diagnostics. The first two are situations where the knowledge gives a clear and unambiguous diagnosis.

1. As the doctor, if you have an indication, you know what to do, but you don't usually know early enough. For example in atherosclerosis, the first indication may be a heart attack 'out of the blue'. If doctors and patients only knew that the condition was developing, actions could be taken that might delay the condition, or make it much less serious, or in the best cases could prevent it from developing altogether. Here, there is a strong ethical case for pre-symptomatic information, for knowing in advance.

2. In the second case, the disease will certainly develop, but there is nothing that can be done to prevent it. It is relatively uncommon to know with such certainty, and usually it is on the basis of genetic information. Huntington's disease is the classic case, where a late-onset highly distressing, terminal degenerative disease can be detected by a simple genetic test. If the defect is found, the outcome is unavoidable. The offer to test members of families in which the disease is known to run leads to two typical reactions. Some choose to have the test – to remove the uncertainty and know one way or the other – to have prior warning of what will indeed happen, or to have the relief of knowing that they and their children will be free of the disease. Others choose not to have test, not wishing to know any earlier in their lives whether so devastating and unpreventable degradation is about to happen to them.

   The other two situations are probabilistic. The diagnostic information only indicates an increased *propensity* to developing a certain condition, but it is not certain that it will develop significantly. Perhaps it is not clear that the level is sufficient for the condition to take hold, or the test or biomarker shows a positive indication of only one of several factors all of which need to come into play before the disease really develops. Some of these other factors may be known, but others may as yet be unknown. What the doctor can tell a patient is that they have a greater than average *probability* of developing the particular condition, perhaps a lot higher in some cases, but not that they will necessarily get it. Again there are two types.
3. The condition might never develop, but there is nothing that can be done, if it did. This is a probabilistic version of case 2. The worth of having the information is even more problematic.
4. In case 1, the doctor or patient can do something about it, but the condition may never actually develop. This presents a real challenge as to what to do. It will depend on the nature of what can be done – the degree of invasiveness to one's body, the restriction or disruption to one's daily life, activities and expectations, the risks involved. If the actions were a simply change of diet or getting more exercise, this might not pose much of a problem. If a much more invasive and profound intervention is involved, like a mastectomy or prostate removal, or if the procedure or treatment itself carries a significant risk, the patient is left with a dilemma. Moreover, if the indication now entails starting to take pharmaceutical drugs for the rest of one's life, there are likely to be side-effects of the drugs when taken on a long term basis.

These examples are given to illustrate the complex range of contexts into which the information provided by nano-diagnostics would be received by doctors, patients and their families and carers. Pre-symptomatic information may be very beneficial in many situations, but not in all. In case 1, the information may well be life-saving, whereas in case 2 it may be an advanced warning of one's death. In cases 3 and 4, the information is only probabilistic. It is not a foregone conclusion that such information is necessarily a benefit. The predicted condition may still never happen. People are likely to vary in their attitude. For some, the knowledge of the probability

would represent prudent foreknowledge and some actions they could take, just in case. But for others it would just be more stress to one's life, and they would rather get on with living and face the situation if it arises.

Advanced knowledge of a future disease or condition also carries the personal problem of admitting to oneself that one is now an 'ill' person. Does a person in their 30's, who feels perfectly healthy and otherwise in the prime of life, now want to start lifelong preventive medicine, for a condition that might normally only appear in their 70's? And if it is not certain that it would develop, at what percent probability and what degree of seriousness of outcome, does one judge that it is indeed worth beginning such a course of action?

None of these are new issues in medicine. But what is different is their *scope*. Hitherto such questions were typically faced by families which carried a serious genetic disease, for which a test existed, but they were not often experienced in the wider population. The new situation that nanomedical diagnostics is likely to open up is that the range of testable medical conditions, and the availability of testing within the population, will be very much wider. The sorts of dilemmas indicated in the examples above are likely to become much more commonplace.

In considering the tests enabled by nanodiagnostics, careful consideration needs to be given to who wants the information, and under what circumstances? A recurring theme in literature, from Greek myths, through Macbeth to Harry Potter, is that having advanced information is something humans do not typically handle well. A considerable re-education may be needed of what people might in future expect from a visit to the doctor. A point-of-care genome analysis may tell her what antibiotic to prescribe for my persistent cough, but when does she tell me that my genome also shows, say, that I have my higher than average risk of colon cancer?

In such cases, at what point should people be told, and what should they be told? In general it is a doctor's duty to tell the patient material information for their health. But how does the doctor allow for the fact that I might prefer not to know, given that even to reveal to me that there *is* information is likely to prompt me to want to know what it's about, or else to worry about what it might be? Important factors will include such things as explaining to the patient about the extent and expectations from a test, and discussing how far they wish a preliminary result to be investigated further. Regulatory bodies have basic principles and guidelines on matters such as consent and confidentiality, see for example in [23], but these may need to be kept under review in the light of advances in nanodiagnostics in the next few years.

There is also an increased relevance to some long-standing ethical questions: to whom the information should be available, other than the patient and the doctor, and who has the right to interpret its implications outside my immediate health context? Insurance companies, employers, the police, or state databases may each consider they have legitimate claims to my data, under certain circumstances. There were serious concerns in the past over insurance obligations. Insurance companies feared people having tests and then taking out large insurance protections based on the result. Some people in families at risk did not wish to have a genetic test, however, not for fear of finding they have a susceptible gene, but for fear of what an insurance company might do with the result. In the UK there is an ongoing moratorium protecting

people who undergo genetic tests from having to disclose the information to insurers, except in the limited cases [24]. The availability of tests has not grown as much as anticipated [25], but nanodiagnostics may change this picture in future.

A further issue is sheer volume of information which may become available, and how it could be handed and interpreted. Already the internet has made far more medical information available to patients, both good and bad, about diseases and treatments. How well can either doctors or patients cope with all the new specific information that may emerge about my health and its implications from nanomedicine? This is likely to change the balance of the doctor-patient relationship. Some people would no doubt welcome being able to take greater charge of their health in a more informed way, but others will prefer to leave most of it to the professionals. This is also dependent on the type of healthcare system and culture which one is in. The British National Health Service and the private healthcare systems of the USA represent two very different situations, for example.

Another practical implication is that a greatly increased degree of personal counselling is likely to be needed, to help families respond to the dilemmas which the additional knowledge may bring. Significant contact time between professional and patient may be needed, first to understand, to let the implications sink in, and then to begin to decide amongst possible options. Experience from genetic counselling suggests that this may require several meetings over a relatively short period of time. Counselling services for rare genetic conditions have needed relatively modest resources. If the dilemmas of pre-symptomatic medicine become commonplace, much greater emphasis will inevitably need to be put on counselling.

This may seem a long way from nanoscale biomarkers as means of monitoring the condition of certain key health parameters. But if the technologies are as successful as expected then, the impacts of success need also to be considered wisely. The complexities discussed above indicate that it would be naive to embrace nanodiagnostics as part of the ‘knowledge economy’, without assessing what knowledge is beneficial and what is not, and under what circumstances it should be given, when, and to whom. Information, as such, is blind to human circumstances. It is up to humans not to be driven only by the logic of data, but to take account also of wider values and considerations. To reveal what would normally be hidden can certainly have important advantages for some areas of medicine, but it may on occasions disrupt more natural patterns of human knowledge. The religions and literature of many cultures suggest that in a person’s life there may a proper time to know, and a proper time not to know, about a future event, like a terminal disease.

12.4 Remote or Personal Monitoring of Health Status

A development closely related to diagnostics is to combine in a nanoscale device both the means to monitor a health parameter in a patient, and a way to transmit the information to another location. Such ‘smart’ nano-scale implants in the body may

allow someone to go home sooner after an operation, if the healthcare professionals at the hospital can continue to follow the patient's recovery remotely. If key biomarkers fall or rise beyond prescribed warning levels, indicating that something is going wrong, this can act as an alert for action to be taken. This might be a local treatment, or bringing the patient back into hospital.

This concept is has considerable attractions. It would both reduce the time the patient is away from home and loved ones, and also free up much needed bed space in the hospital more quickly. In more remote and rural areas, like the Scottish islands, the ability to monitor a patient remotely could be of great benefit if he is 3 h drive away from a main hospital, provided sufficient local infrastructure was also on hand to respond at need. This could be extended to very elderly or chronically ill people, or those with a known susceptibility, like heart or stroke patients at risk of a recurrence. Again, changes in critical parameters could forewarn of the need to take preventative measures.

One downside is that this represents a degree of surveillance by a third party. One's whereabouts, and to some degree, something of one's private activities will be known and followed. Even with benevolent intentions, and restricted to particular professionals, family members and carers, some people may not welcome a sense of their privacy being 'snooped on'. On the other hand, it can provide a sense of security that someone is on hand to help if something starts to go wrong. A weekly video or phone link to a nurse to go through the week's readings can become a welcome reassurance, and a point of regular contact, for people living alone with a long term medical condition.

A second implication is the degree of responsibility that is shifted to the home, the patient and the carer. This may be something welcomed. If one has an elderly parent who is living on their own, it could ease some of the stress to know that particular health functions were being monitored. If I am the patient, it might be reassuring for me to keep a regular check on my critical measurements, which become part of the way of life of living with my condition. On the other hand, it can be a considerable additional stress to keep taking or checking a measurement, day in day out, and interpreting what it means if things are not going well.

Looking further into the future, if monitoring health parameters by implants or particles becomes commonplace, there may be pressure to use them for other than medical reasons. Elite sports and military use are examples where monitoring is already done, which are accepted within their special contexts. One could imagine equivalent arguments being put forward for certain occupations, like a pilot or bus driver where many other lives are in one's hands. Technically, it would be a relatively short step to a more general surveillance of performance in a work context, or for an insurer to want to monitor one's risk levels. But this would cross a significant ethical line where the primary beneficiary of people's private health information is no longer the individual him/herself, but various third parties. This may represent another clash between the value of human persons and a merely functional logic to use the capacities which some new nanotechnology may enable. At this point I would argue we lose the precedence of human values at our peril.

12.5 Implants and Targeted Delivery

The flag ship concept of nanomedicine is the notion of targeted drug delivery. Typically a pharmaceutical product is encapsulated in a nanoscale carrier, to which has been attached an array of ligands variously designed to carry the particle through hostile media in the body, to recognise specific diseased cells of the body, or toxins or other malicious entities, and, on encountering them, to release the active ingredient to do its job. It should do this without affecting healthy cells nearby, or other organs of the body. In particular, it is intended to overcome the problem of the introducing chemicals systemically. At present, in order to have a sufficient concentration of the active chemical in the affected organs, it has to be introduced into the whole body, and chemicals powerful enough to attach a cancer cell, say, may impact harmfully in many unintended elsewhere in the body, causing significant side effects. A growing number of targeted pharmaceuticals are in use, and many more are likely to follow.

There is a strong ethical case in favour of nanomedical methods which have a reasonable prospect of addressing the problems of systemic drug delivery. The primary ethical questions are about risk, long term implants, and overclaiming. There are issues of risk in relation to the nanocarrier and its behaviour and ultimate fate in the body. Because of their size, nanoparticles have the potential to pass through barriers of the body and end up in strange places. While the understanding of nanoparticle risks remains relatively poorly developed, a precautionary approach is appropriate. Given the present uncertainties of the technique, targeted delivery is better focused on the more serious or intractable medical conditions, until a body of substantial experience has been accumulated of these therapies in practice. Ongoing and long term monitoring needs to go hand in hand with more fundamental risk studies on different materials and formulations. Carriers that the body will naturally degrade or 'functionalised' particles have been seen as more favourable than pure inorganic materials which would remain largely inert.

This leads to a more general question about implanting nanoscale devices into the human body. This might be to monitor the progression of disease, to deliver therapies in situ, to provide scaffolds for replacing damaged or failing tissues, or to provide external monitoring of our health. How far should we make nano-technically enabled interventions in the body? Should this remain something done exceptionally, under particular conditions, as with macro interventions like hip replacements and stents? Or should we expect this eventually become the normal pattern, in widespread use? The technology may be beguiling. What other important factors need to be taken into consideration, and what takes precedence if conflicts between values arise?

The last point in this section is a tendency for some promoters of targeted delivery to overclaim about their products. For example, video simulations create an almost military scene of unmanned capsules zooming through blood vessels, seeking out their targets, and delivering their payload by precision impact on the affected cells. The military analogy is perhaps unfortunate, but the medical equivalents of collateral damage and wrong targeting of supposedly precision bombing, are relevant issues.

Targeted drug delivery should be a step change improvement compared with system delivery of a pharmaceutical, but risks of unintended consequences remain, say if the intended therapeutic molecule hits the wrong target, or if it has side effects which perhaps the researchers did not look for.

The tendency to exaggerate can sometimes present an ethical problem in itself. Hopes for the benefits of for high tech therapies are raised amongst vulnerable patients, or hard pressed policy makers. At earlier stages in innovation, the prospects claimed by the researcher or a company about a 'breakthrough' under idealised research conditions, with a view to attracting further funding, can raise misleading expectations. In practice, applications will only be realised after a critical review of their feasibility, clinical reliability, economics, and safety, and unfortunately many fail at one hurdle or another. Once approved for clinical use, a technique may work well in some patients but prove less effective in others. Such is the nature of innovation. A degree of modesty is therefore called for, both out of respect for the vulnerability of the human patients and recognition of the finite understanding of the method. At this nano-medical interface, the emphasis needs to be that of the doctor treating a human person, rather than the impersonal logic of technique, however good it may be.

12.6 Theranostics

A special case of implants is the so-called 'theranostic' device (*thera*peutic – diag*nostic*) which would combine a measurement and monitoring role with some kind of therapeutic delivery. The delivery is activated in response to a critical change in level of a parameter which has just been measured. The attraction is not needing to wait before activating the therapeutic response, perhaps to maintain some function like blood sugar levels within a tolerated range, if these were about to drift outside the range. The advantage is that the remedial action is rapid and does not depend on the patient or perhaps a nurse to have to step in, notice the change and activate the response.

It depends, however, on having established a close numerical correlation between what is measured and the degree of therapeutic response. This has to have been established in advance with considerable precision and reliability in order to programme the device accordingly. One problem is applicability and reliability. Can one indeed produce an algorithm so robust, or so flexible, that it applies infallibly to all patients who would present with this condition? It may be possible to tune the device initially for the particular patient, but will the settings continue to be valid as the patient's metabolism changes, with different activities, at different times of day, times in a woman's monthly cycle, etc. To the extent that the device responds automatically, there must be a very high resilience to misleading data. How reliable in engineering terms is the equipment, for example as materials degrade with age, or pump flows become restricted? If modifications became required from time to time, would this be possible?

Conceptually, theranostics relies on the assumption that a necessarily limited set of measurements in a device is sufficient on its own to represent accurately a complex physiological change and to deliver the correct response without human intervention. Such an assumption requires a great deal of trust in the reliability of the design concept, the programming and the engineering. To produce a 'black box' of sufficient flexibility and reliability would seem to be a tall order. Indeed, some companies in this area are reluctant to make devices too automated, in recognition of factors like the variability in patients.

In the UK public consultation on potential research fields in nanomedicine, theranostics received a lower priority than several other nanomedical applications. People expressed concern that scientist might make such a device to be *too* smart. In envisaging theranostic devices implanted in their bodies, people felt they or a doctor should keep some control over the implant and its operation. A degree of human judgement was necessary rather than depending on algorithms and programming. It is another case where human values are needed to modulate engineering logic.

12.7 Regenerative Medicine

One of the most intriguing prospects of nanotechnology is to be able to construct material objects 'atom-by-atom' to any shape or form desired. While its more exaggerated claims have been rightly criticised, one potentially useful application is in regenerative medicine. The isolation of human embryonic stem cells and induced pluripotent cells have opened up many new possibilities to replace lost or damaged cells in vital organs of the body. One aspect is the possibility to regrow nerve cells, for example in spinal cord following an accident, or in the retina in certain cases of blindness. This requires an appropriate tissue scaffold to be grown starting at the nanoscale and building upwards. A number of nanomaterials are being investigated.

While the basic ethical rationale is very good, such techniques run into the serious ethical problems, if they entail the use of cells originally derived via the destruction of human embryos. It is not the place here to rehearse the arguments for and against human embryonic stem cells, but, suffice to say, in some countries and for some individual patients, such technologies would be ruled out unless they could be achieved based on non-embryonic sources of the cells. Fortunately some of the best prospects lie in encouraging the body's own stem cells to regrow, so the ethical problem may be avoidable, but it is important to aware of the issue. Other potential ethical questions would arise if it becomes possible to regrow brain tissue, and in attempts to construct organs by this method outside the body.

12.8 Risk and Uncertainty

The risks associated with the use of nanoparticles and nanoscale implants in the human body have been much discussed. These include the transport of particles to unintended parts of the body, side-effects on the body's metabolism, and the long

term use of implants. Given that there will always be risk associated with these types of interventions, there is an ethical dimension to how one sets a tolerable level risk, and against what criteria. Once scientific data become available, the numerical probabilities and consequences remain as numbers on a page, until it is decided what levels constitute acceptable or unacceptable risks. These are ultimately ethical judgements. To make such judgements will require not only much good research but also much careful engagement with different publics, patients' groups and their carers.

Risk may be calculated with a good deal of reliability in areas of established engineering experience. Nanotechnologies, however, typically go beyond well trodden paths. A second dimension is thus how one handles the inevitable uncertainty associated with novel procedures involving tiny devices in the body. How precautionary should we be? From fields such as genetically modified food, two version of the precaution principle emerged – hard and soft. Hard precaution is the inclination not to proceed if a significant case for a risk of harm can be made. Soft precaution argues that one should proceed unless there is reasonable evidence that there is a risk of significant harm, but which at this point cannot be sufficiently evaluated. In principle both are resolvable by further evidence, one way or the other. In practice, however, some uncertainties are likely to remain intractable, or would take a very long time to assess. In the meantime, patients are longing for treatments to their conditions.

The key question will be at what point it is considered that enough is now known to proceed, or it is concluded that the intended process would entail unacceptable risk. Some general principles are that, in areas of uncertainty, the initial focus should be on applications with a high degree of medical benefit, the more serious diseases, on situations where there is a degree of reversibility or recovery from adverse effects, and where there is an ability to track the fate of nanoparticles or implants. But a strict ethical principle of 'do no harm' may not be achievable. This brings us to a final and fundamental point about the way we handle risk.

Since risk is inherent to the human condition, we should resist undue demands for certainty and safety, or a culture of blame for techniques which fail. There is a profound difference between negligence, given what you knew but did not act on, and not knowing something which no one had reason to know at the time. Hindsight can be very destructive in this respect. The question is, set against all the other risks of human living and the particular condition of the patient, how much or little risk is tolerable? And, having decided, everyone involved should recognise that no one can guarantee success.

12.9 Human Enhancement

One cannot end a chapter on the ethics of nanomedicine without briefly considering the issue known as human enhancement. All the examples considered so far address using nanotechnologies for explicitly medical goals. A topic of increasing debate in the last 10 years has been whether we should use these, or other technological methods, to enhance the human body beyond its present capacities. Should nanotechnology only 'make humans better', in the sense of treating diseases and injuries, or should we

use it to 'make better humans', by using technology to improve the basic specification of the human body and brain directly?

The first significant study, the 2002 US report NBIC report on 'converging technologies for improving human performances', was optimistic about this latter prospect [26]. A European expert group urged submitting enhancement goals to wider social scrutiny, if our humanity is not to be redefined by a techno-logic driven primarily by technical and economic feasibility [27]. More recent reports are from the UK academies [28] and the Dutch Rathenau Instituut [29] as well as an increasing academic literature and several European Commission studies, some broadly approving, and some more critical ([30–34]). It must be said that only a few technologies exist today. Most of what is discussed in these reports remains as future prospects whose practical feasibility is very uncertain, and some have criticised the field for indulging in too much speculative ethics [35]. The implications are sufficiently far reaching to take the question seriously, however, and we summarise some of the key issues.

The first is the basic ethical issue of whether we should seek to make serious changes to human body and its metabolism. This depends on one's view of the human being and of human technological intervention. Traditional presuppositions hold that there are moral or societal bounds which should act as a restrain on what may otherwise be feasible technically. These limits are drawn from the insights of the religious and cultural traditions, philosophy and theology, the arts and humanities, and the social sciences. Christian thinking for example grounds human nature in God's creation of human beings 'in God's image', although two recent studies considered that this did not mean that enhancements are necessarily prohibited, as such [36, 37]. Traditional views are challenged by transhumanist belief that humans are destined to go beyond our current biological limitations.

It may be helpful to think of this question in terms of three general views. One view sees the human body and its capacities as something 'given' which it is not to be majorly changed. The transhumanist philosophy regards the human body as evolutionary, in principle open to be changed without limit. An intermediate position recognises that humans could be changed in degree but not without limits, not change whatever we regard as our human nature. In summary these are: change nothing, change anything, or draw lines as to limit what may be changed.

The second ethical question is what is meant by the idea human enhancement, and whether enhancements really do enhance? The assumption is made that if I do something that improves some functional capability in my body or brain, it is an enhancement. But on what basis are we to judge whether actually it constitutes an enhancement, beyond a purely subjective view? A focus on improving human performance, for example, seems too limited a criterion, compared with more holistic concepts of the human person. The assumption that to be that little bit faster, stronger, smarter, more retentive, more musical, we are somehow happier and better as humans seems too vulnerable to things going wrong. A better question would be in what sense are we better as human beings by having a particular capacity enhanced? It might indeed be appealing to do certain things better than one could naturally, but would it make the difference between a good life and a poor one? Beyond a certain

basic point of physical survival and necessity, what matters most to humans are their relationships. Wider issues such as love, friendship, creativity and spirituality seem to matter more than functional abilities.

A few examples serve to illustrate that enhancements may not be as straightforward as the term suggests at first sight. Suppose retinal implants would provide a true recovery of sight to some blind people, and this is extended to offer vision into the infrared region for the normal sighted. It is said that this would have considerable safety advantages for night driving, for example. On the other hand, would one use the new capacity to drive faster, and not more safely? And why not simply use some form of spectacles to achieve the same end? Secondly, cognitive enhancing drugs have become used by students concentrating for exams, but the value only exists as long as only a few have the advantage. If all students used it, there would be no competitive advantage, but no one would then dare stop using it. Thus all would become locked into a pointless 'enhancement', and one which would not reflect their true ability. A third example is in the field of sport. There are plenty of examples where the over-amplification of critical functions can be pursued out of proportion to the rest of the body, resulting in significant overall damage. The same harmful imbalances have been observed in genetic engineering of animals for faster growth rate, both by selective breeding and molecular intervention [38]. We may need to consider rather carefully before calling an intervention an enhancement.

A third issue is reliability, risk and regulation. Whereas medical devices and pharmaceuticals are subject to strict and complex testing and regulation, there is little or no regulation of enhancements. There is no comparable system to test and guarantee that an implant or a chemical enhancement both does 'what it says on the packet' and is safe and reliable, and is not a false product of the modern equivalent of the quack doctor. Recent experience of unscrupulous and invalidated stem cell treatments underlines the importance of having a system of regulation and validation.

Safety testing also raises a problem. Riskier medical procedures are justified only for the more serious medical conditions. For enhancement technologies there is no comparable balancing good of saving life or preventing serious suffering. This marks an important distinction between nanotechnologies to address medical conditions and those intended to enhance healthy human beings. In academic debate, some have criticised this distinction, because it assumes ideas of a 'human nature' and what is 'normal' to humans, which are merely human constructs of our times, but which do not have any ultimate grounding philosophically. As observed above, this depends somewhat on one's world view.

In contrast to this, one of the findings of a recent public engagement study was that people do seem to have an implicit sense of normalcy in human capacities, even if it would be hard to pin it down to any sort of definition [39]. In assessing a range of potential human enhancement applications, people often made a distinction: technologies to bring people who are ill or disabled in some way 'up' to the norm, were broadly accepted, but using the same technologies to take healthy people beyond the norm, were viewed sceptically or even objected to. Some special situations were perhaps acceptable, for example, for rescue workers in a disaster to take a drug to do without sleep. But to do this in everyday life was seen as abnormal.

To a first approximation the medical – enhancement distinction seems valid. There are indeed situations where the distinction is blurred, which should be considered on their own merits, rather than invalidating the distinction. As Holm has pointed out, we do not think yellow and red are not valid as colours just because they can blur to form orange [40]. Thus whereas nanomedicine would be generally favoured, enhancements were viewed much more critically.

A last main group of issues of human enhancement are its many social implications. Amongst these are three of particular note. The first is a general point that the various implications of enhancement technologies are too important to be treated just as matters of personal preference, but should be regulated at a societal level in most cases. The second is a deep concern that in practice human enhancement is promoted primarily by and for those who are already in high levels of economic and social advantage. Enhancements would inevitably be available mostly for the rich and priviledged, thereby enhancing their advantages still further. Advocates of enhancements point out that any new technology tends to create new winners and losers, and that one should not object to enhancement on that basis. Many things once considered luxuries are now cheap and widely available, like televisions, mobile phones and computers. But suppose enhancement technologies really did prove to be as good as some claim, this would give those who could afford to use them 'hard-wired' advantages. While those less well-off were waiting for the prices to come down, the rich would get ever further ahead, in what would become a 'nano-divide'. Some argue that to pursue personal human enhancements, without regard for those who miss out, people might be enhanced functionally but diminished in humanity [36].

The final social issue is whether, faced with the issues like poverty, poor health, climate change, and global food security, the idea of human enhancement is largely a distraction for the well-off, and which misses the point. It might be argued that what is wrong with the human condition is not a lack of strength, longevity, intelligence, beauty, athleticism, art, science or even education. It lies in deeper moral and spiritual shortcomings of humanity, individually and collectively, as the world's ongoing conflicts show. However much we 'enhanced' ourselves physically, these inherent human failings would remain because these would seem to lie beyond technical fixes.

12.10 Conclusions and Postscript

This chapter has considered a range of ethical and social issues associated with likely advances in nanotechnologies, primarily as applied to medicine, but also possible enhancements of the human body. The technical logic of nano-enabled medicine always needs moderating with ethical reflection to apply human values to achieve wise solutions. In many cases a good ethical case can be made for the considerable medical benefits, but enthusiasm for new technical solutions should not lose sight of the wider perspective of human values, and the long experience of the

practice of medicine. Nanomedicine needs to maintain a human face. Human enhancement, on the other hand, does not have the ethical benefit of making an ill person better. It depends for its appeal on a more elusive idea of making 'better' humans. It remains to be seen whether it would actually offer significant improvements to the human condition that would outweigh social concerns, risks and practical problems. It also begs the wider question whether the deepest needs of the human condition cannot be met by technology.

Important social and conceptual changes are likely to accompany the application of nanomedicine, especially in pre-symptomatic diagnostic information giving advanced knowledge about our future health status. We think of ourselves as relatively well or relatively ill. But if in the long term, nanotechnologies might eventually make much hitherto unsuspected data about our bodies accessible to us, what now is a well person? If read-outs of genes, chemicals or other parameters will represent almost any body function, may we find that we are all to some extent 'ill', or at least probably ill?

In many cases, such knowledge will be welcome and valuable, and in some circumstances even be life saving. But a sense of proportion is also needed about 'knowledge-based medicine' and our health status. In his witty Victorian English tale, *Three Men in a Boat*, Jerome K. Jerome recounts going to the British Museum library to look up an ailment in a medical encyclopaedia. But out of curiosity he reads on and finds that he seems to show the symptoms for half of the diseases in the book. 'I went into that reading room a happy healthy man. I crawled out a decrepit wreck.' He went to his doctor with a full list of his supposed diseases, and is given a prescription. He goes to the pharmacy and discovers the prescription is for a daily diet of beef steak, a pint of beer, good exercise and early to bed … 'and don't stuff your head with things you don't understand!' [41].

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