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Research Article

Nanomedicine: Techniques, Potentials, and Ethical Implications

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Nanotechnology is concerned with materials and systems whose structures and components exhibit novel physical, chemical, and biological properties due to their nanoscale size. This paper focuses on what is known as nanomedicine, referring to the application of nanotechnology to medicine. We consider the use and potentials of emerging nanoscience techniques in medicine such as nanosurgery, tissue engineering, and targeted drug delivery, and we discuss the ethical questions that these techniques raise. The ethical considerations involved in nanomedicine are related to risk assessment in general, somatic-cell versus germline-cell therapy, the enhancement of human capabilities, research into human embryonic stem cells and the toxicity, uncontrolled function and self-assembly of nanoparticles. The ethical considerations associated with the application of nanotechnology to medicine have not been greatly discussed. This paper aims to balance clear ethical discussion and sound science and so provide nanotechnologists and biotechnologists with tools to assess ethical problems in nanomedicine.

INTRODUCTION

Significant technological advances across multiple scientific disciplines continue to be proposed and validated. A revolution in health care and medical technology looms large on the horizon on the basis of the discipline of nanotechnology. Reports and articles often distinguish between nanoscience and nanotechnology. *Nanoscience* refers to the fundamental study of phenomena and the manipulation of matter at the atomic, molecular, and supramolecular level, where properties differ significantly from those at a larger scale. As such, nanoscience forms the knowledge base for nanotechnology. *Nanotechnology* refers to the design, characterisation, production, and application of structures, devices, and systems that have novel physical, chemical, and biological properties by controlling shape and size at the nanometre scale. Integration with other length scales will often be important to technological applications. In this paper we use the term nanotechnology as a collective term encompassing the various branches of both nanoscience and nanotechnology.

Nanotechnology research has progressed rapidly over the last few years. Nanotechnology has become an interdisciplinary science where the disciplines of physics, chemistry, molecular biology, health sciences, and engineering collaborate, share knowledge, and build up a research culture across traditional disciplinary boundaries. Funding for nanotechnology has increased dramatically and nanotechnology has become a buzz word and is currently very visible compared to other fields of research. The vision of nanotechnology is to advance broad societal goals, such as improved comprehension of nature, increased productivity, better health care and to extend the limits of sustainable development and human potential [1]. A lot of developments in nanotechnology take years, but researchers and politicians claim that the process itself can lead to a new industrial revolution [2].

This paper focuses on the application of nanotechnology to medicine, the field known as nanomedicine, with its promise of improved therapy and diagnostics. Present-day nanomedicine exploits fields such as nanoscale surgery, tissue engineering, and certain types of targeted drug delivery [3–5]. In this paper we consider the use and potential of emerging nanoscience techniques in medicine, and we discuss specific ethical questions that these techniques raise. These ethical considerations are related to risk assessment in general, somatic-cell versus germline-cell therapy, the enhancement of human capabilities, research into human

embryonic stem cells, and the toxicity, uncontrolled function and self-assembly of nanoparticles and nanosystems.

We will show that even though ethical problems in nanomedicine may be more complex than ethical problems in medicine and biotechnology in general, for example the toxicity of nanoparticles resulting from their nanoscale size [6, 7], fundamentally the same general ethical principles are at stake, such as respect for autonomy, beneficence, nonmaleficence, and justice. These ethical principles have been used for ethical assessment in biomedicine for years, and they form part of several different ethical theories, including the bioethical theory of Beauchamp and Childress [8]. This means that even though nanomedicine raises concrete ethical issues that are more complex than those raised by existing technology, a reasonably sound knowledge base has already been acquired in the field of bioethics that can be extended to nanomedicine.

In the following, we consider the use and potential of emerging nanoscience techniques in medicine, such as nanosurgery, tissue engineering, and targeted drug delivery, and we discuss specific ethical questions that these techniques raise.

SURGERY AT THE NANOSCALE

Traditional surgical instruments such as scissors, clamps, and so on may be replaced by nanotechniques. Even though developments in nanotechnology may take years, the journey towards nanosurgery has begun. Few years ago, robot-controlled microsurgery emerged, eliminating the minimum space requirement for manual instrument manipulation and the limitations of the vision of the human eye [9, 10]. And nanosurgery at the level of individual living cells or organelles has already been performed [11, 12]. Promising nanosurgery techniques include the use of AFM with a nanoneedle and femtosecond laser surgery. In the following, the status, potential, and ethical implications of these techniques are analysed.

Nanosurgery using atomic force microscopy (AFM) with a nanoneedle

A Japanese research group [11, 13] has performed analyses and surgery on living cells at nanoscale resolution using AFM and a modified AFM probe. AFM is a type of microscopy in which a probe is scanned across the sample to obtain information about its surface. The information gathered from the interaction of probe with the surface can be as simple as physical topography or as diverse as the physical, magnetic, or chemical properties of the material. The general AFM probe is designed as a 3 μm pyramid with $\sim$ 30 nm end radius on the end of a cantilever which bends as the topography or other properties of the sample change. The bending of the lever is detected by a laser beam detection system and the information is transmitted to a computer, which generates a map of the topography or other properties of interest.

The properties of the cell surface were investigated by contacting and indenting the cell surface with an AFM probe in the shape of an ultrathin nanoneedle. Conventional pyramidal AFM tips are $\sim$ 3 μm in length, but since the height of a plated living cell is 5–10 μm, Obataya et al [11, 13] made nanoneedles that are 6–8 μm in length and 200–300 nm in diameter. Obataya et al [11, 13] investigated the mechanical response during insertion of the nanoneedle in living cells. The nanoneedle penetrated both the cellular and nuclear membranes and was accurately inserted in the nucleus. This new technique has several advantages over the traditional microinjection of proteins, peptides, and genetic material into living cells using microcapillaries. Damage stemming from the use of microcapillaries due to the shape of the capillaries and the inaccuracy of the displacement is problematic in relation to the manipulation of many cell types. The advantages of the AFM system are the accuracy of the needle and that the ultrathin needle does not cause fatal damage to living cells. It has been suggested that the technique could be used to investigate cell activity, to induce controlled differentiation, or to perform therapy on living cells. But Obataya et al emphasise that they call the technology nanosurgery or cell surgery. In this case they are not thinking about direct therapy on an individual cell. What they call "cell therapy" is therapy involving the donation of intact and functional cells to a patient. For example, cell surgery technique could be used to induce cell differentiation from stem cells to prepare healthy cells by manipulation using a nanoneedle.

Femtosecond laser surgery

Femtosecond near-infrared (NIR) laser pulses can be used to perform surgery of nanometre-sized structures inside living cells and tissues without creating damage. The intratissue nanoprocessing is achieved by the generation of high light intensity (10^{12} W cm^{-2}) by diffraction-limited focusing of the radiation of an NIR (λ = 740 and 800 nm) femtosecond laser on a subfemtolitre volume [12, 14]. The energy delivered by the laser pulses breaks down chemical bonds at the targeted site, vaporising the tissue without causing side effects such as heating of surrounding tissue. The concept "femtosecond laser" refers to the duration of the laser pulses, which is in the scale of femtoseconds.

The energy of the short pulses of femtosecond lasers is so high that instead of destroying the tissue by heat generation (like standard lasers) the photons vaporise the tissue, and the result is a clean hole without necrosis of adjacent tissue [3]. According to König [14], the use of femtosecond laser pulses has the advantages of minimal ablation threshold, low transfer of optical energy into destructive mechanical energy, and the absence of thermal damage to surrounding structures compared to the nanosecond pulses used in conventional microsurgery. König [14] performed a minimum cut-size of 110 nm into the human chromosome 1 and was able to perform chromosome dissections within living cells. And using the femtosecond laser, Tirlapur and König [12] could completely knock out an individual plastid (a cytoplasmic organelle in plants bounded by a double membrane that carries its own DNA, eg, chloroplasts) or part of the organelle without affecting adjacent organelles or the viability of the cell. Potential medical applications include the

use of femtosecond laser microscopes in eye surgery and neurosurgery, tissue engineering, laser-assisted in vitro fertilisation (IVF), and gene therapy [12, 14].

Yanik et al [15] used femtosecond laser surgery to cut individual axons in the roundworm C. elegans, which is about 1 mm long as an adult. They showed that these axons functionally regenerate after the surgery.

Risk assessment

To sum up, the potential medical applications of nanosurgery techniques using AFM with a nanoneedle and femtosecond laser surgery are predicted to include cell therapy, eyesurgery, and neurosurgery, tissue engineering, laser-assisted IVF, and gene therapy. However, if these nanosurgery techniques are going to be used in the future for the treatment of disease and IVF, one should balance the potential benefits and potential harms of these techniques. Future medical applications of nanosurgery techniques require a *risk assessment*.

According to Beauchamp and Childress the evaluation of risk in relation to probable benefit is often labeled *risk-benefit analysis*. They say that the term *risk* refers to a possible future harm, where harm is defined as a setback to interests, particularly in life, health, and welfare [8]. Statements of risk are both descriptive and evaluative. They are descriptive in as much as they state the probability that harmful events will occur, and they are evaluative in as much as they attach a value to the occurrence or prevention of the events [8]. Commonly in the field of biomedicine, the term *benefit* refers to something of positive value, such as life or health. The risk-benefit relationship may be conceived in terms of the ratio between the probability and magnitude of an anticipated benefit and the probability and magnitude of an anticipated harm. Use of the terms risk and benefit necessarily involves an evaluation. Values determine both what will count as harms and benefits and how much weight particular harms and benefits will have in the risk-benefit calculation [8]. The terms harm and benefit, defined as stated above, are ethically relevant concepts. Ethical obligations or principles about not inflicting harm (nonmaleficence) and promoting good (beneficence) are generally accepted [8]. The ethical principles of beneficence and nonmaleficence form part of several different ethical theories. For instance, they are the foundation of the utilitarian theory, which says that ethically right actions are those that favour the greatest good for the greatest number. Another example is the Hippocratic Oath, which expresses an obligation of nonmaleficence and an obligation of beneficence: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them" [8]. So clearly risk-benefit analysis is an ethical issue. According to Beauchamp and Childress, the balancing of the general ethical principles of nonmaleficence and beneficence is not symmetrical, since our obligation not to inflict evil or harm (nonmaleficence) is more stringent than our obligation to prevent and remove evil and harm or to do and promote good (beneficence). Our obligation of beneficence requires taking action (positive steps) to help prevent harm, remove harm, and promote good, whereas our obligation of nonmaleficence only requires intentionally refraining from actions that cause harm [8].

In the case of nanosurgery we need to compare the risk-benefit ratio of nanosurgery techniques with the risk-benefit ratio of already established microsurgery techniques. As described above, nanosurgery techniques using AFM with a nanoneedle have several advantages over traditional microinjection of proteins, peptides, and genetic material into living cells using microcapillaries. Damage stemming from the use of microcapillaries due to the shape of the capillaries and the inaccuracy of the displacement is problematic in relation to the manipulation of many cell types. The advantages of the AFM system are the accuracy of the needle and that the ultrathin needle does not cause fatal damage to living cells. The use of femtosecond laser pulses has the advantages of minimal ablation threshold, low transfer of optical energy into destructive mechanical energy, and the absence of thermal damage to surrounding structures compared to the nanosecond pulses used in conventional microsurgery. This indicates that the risk-benefit ratio of nanosurgery techniques is smaller than the risk-benefit ratio of already established microsurgery techniques. However, the exact risk-benefit ratios need to be based on detailed experiments.

Risk and benefit identifications, estimations, and evaluations are all stages in risk assessment, though, the next step is *risk management*, which can be defined as "the set of individual or institutional responses to the analysis and assessment of risk, including decisions to reduce or control risks" [8]. While risk-benefit analysis may seem like a technical issue, in which risks and benefits are defined, quantified, and compared, the definition of risk and benefits and the evaluation of how much risk is acceptable (risk management) is clearly an ethical issue. For example, risk management in hospitals includes establishing policies aimed at reducing the risk of medical malpractice suits [8].

Somatic cell therapy versus germline therapy

If nanosurgery techniques are to be used for gene therapy in the future, it is not simply enough to make a general risk assessment and respect the informed consent of the human subject. In the case of gene therapy, we need to differentiate between somatic gene therapy and gene therapy on germline cells. By using gene therapy on germline cells the genetic changes not only affect the individual treated, but also his/her offspring. Germline therapy is not allowed in many countries. In 1996 the European Council agreed to the Convention on Human Rights and Biomedicine—a convention for the protection of Human Rights and the dignity of human beings with regard to the application of biology and medicine. This convention forbids gene therapy on germline cells: "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostics or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendant" [16]. As a result, an interesting ethical debate is going on about the perils and deficiencies of the convention. Ethicists [16] have pointed out that the convention stands

for a misleading interpretation of "human rights" as sort of "natural rights" supposedly independent of any human decision and grounded in allegedly immutable "human nature." According to Mori and Neri [16] the convention represents the idea that human rights have to be grounded in God or natural law, as opposed to being declared as rights by human beings who assert some normative conclusions based on rational argument. In this latter sense, human rights are not immutable and can change when rational arguments compel us to abandon traditional positions. Mori and Neri [16] believe that the approach of the convention is too rigid to govern a research field in rapid evolution; a more flexible and selective approach is required.

Since the aim of the convention is to further the realisation of human rights, Mori and Neri [16] ask which human right is supposed to be involved and whose interests or needs this right is designed to protect and guarantee? The answer is clear: the right refers to "the right to a genetic inheritance which has not been artificially interfered with," and the right is designed to protect future generations. The point is, as noted above, that when germline therapy is used, the genetic changes affect not only the individual treated but also his/her offspring, so if mistakes occur they are irreversible. An experiment with germline therapy could be seen as tantamount to a clinical experiment on unconsenting subjects, who are the affected members of future generations. So one can argue that this procedure is in conflict with the principle of respect for the autonomy of future generations.

However, Mori and Neri [16] believe that the content of the interest of future generations should be illuminated. Future generations could, for instance, have an interest in the eradication of disease-causing genes. The fundamental question asked here is whether there are situations where germline genetic manipulation is justifiable? For example, are there cases where the beneficence obtained by germline therapy is primary and where the principle of beneficence out-balances the principle of respect for the autonomy of future generations? Wivel and Walters [17] see two possible cases. First, such manipulation may be justified when both parents are afflicted with a recessive autosomal disorder, so that 100% of their offspring would be expected to have it. This is an exceptionally rare situation. More common is the case in which both parents are heterozygotes for a recessive genetic disorder. These parents have a 75% chance of having a phenotypically normal child, and screening can be carried out during pregnancy, followed by selective abortion if the foetus is found to be homozygous for the mutant allele. Germline genetic modification is seen as an alternative to screening and selective abortion. Wivel and Walters [17] view such monogenic deficiency diseases as Lesch-Nyhan syndrome, Tay-Sachs disease, and metachromatic leukodystrophy as candidates for this type of genetic therapy. In these cases, the beneficence obtained by use of germline therapy can be perceived as primary. But this does not mean that possible risks and possible irreversible mistakes should not be considered.

Mori and Neri [16] conclude that human rights should not be interpreted as imposing on us morally unsustainable obligations, such as the obligation to abstain from curing people. In contrast, human rights and hence the convention should be interpreted so that they are not immutable and can be changed when rational arguments compel us to abandon traditional positions. As an example, Mori and Neri [16] mention the prospect of in utero gene therapy for homozygous alfa-thalassemia and adenosine deaminase (ADA) deficiency, where the possibility of inadvertent germline modifications cannot be definitely excluded.

Enhancement of human capabilities by nanosurgery

Until now we have focused on potential medical applications of nanosurgery. But will surgeons of the future only use nanosurgery techniques to restore and maintain *normal* function? Or will they produce *suprahuman* capabilities (so-called transhumans)? Satava [18] points out that it may be possible through surgery at the nanoscale to "provide "suprahuman" capabilities, such as the ability to see in the infrared or ultraviolet portion of the spectrum … or see in the dark using implanted ultrasound sensors." Many writers have sought to draw a sharp line between gene therapy and enhancement in order to protect therapeutic procedures from the moral taint of genetic enhancement, which is often associated with eugenics, "playing God," creating perfect people, and so on. Maintaining this distinction allows one to acknowledge the negative connotations of genetic modifications while endorsing the positive aspects. But the distinction between therapy and enhancement is blurred. One could argue that the goal of therapy is to treat an existing disease, while the goal of enhancement is to exceed the boundaries of normalcy and health. But many ordinary medical interventions that are designed to prevent disease actually enhance normal human functioning. For example, vaccinations enhance the immune system by causing it to produce cells and antibodies thereby increasing its ability to fight diseases. Furthermore, many socially acceptable medical interventions, such as cholesterol-lowering drugs, cardio-pulmonary resuscitation, and hormone replacement therapy, are designed to prevent, forestall, or counteract the normal aging process. One reason why it is so difficult to define "genetic enhancement" is that the concept of "enhancement" is based on some understanding of what constitutes a normal healthy human being [19]. Although scholars continue to use the phrase "genetic enhancement," the reflections above indicate that we do not have a clear idea of what constitutes genetic enhancement and what constitutes a normal healthy person. But there does seem to be some kind of consensus among writers that "enhancement" refers to improving capacities such as intelligence, longevity, memory, and so on [20–22]. Even though the discussion of genetic enhancement often has the character of science fiction without reference to scientific facts, we have to take into account that several philosophers, such as Bostrom [23], are celebrating the prospect of radically improving our human capabilities and thus transforming our

humanity through genetic engineering, while other philosophers, such as Habermas [24], are worried about the consequences of genetic enhancement for our identity and self-understanding [21].

The future theoretical possibilities for enhancement of human capabilities give rise to a moral dilemma with regard to the enhancement of offspring: on the one hand, it seems natural for parents to give their children the best possible opportunities; on the other hand, their choice of crucial properties gives parents a power over the lives of their offspring that might threaten the basic principle of human freedom. Genetic enhancement would cause the birth of children whose genetic makeup would have been intentionally designed by other human beings. According to Habermas [24] this would substantially alter the preconditions of "natural" reproduction, by eliminating the contingency or "chance" aspect of one's coming into existence to such a degree that the freedom of the future human being would be violated. This might deeply alter the moral self-understanding of the human species and influence future generations [21, 22].

So, Habermas [24] operates with a right to an unchanged genetic makeup. But our main concern is why human genetic makeup or genetic integrity ought to be protected. What is the special moral status of DNA? In our opinion it is hard to claim that DNA has a fundamental intrinsic value in itself without further justification. Besides, germline gene therapy should not be singled out as the only factor able to alter the genetic constitution of future generations. For instance, medical x-rays on occasion undoubtedly induce mutagenic changes in patients' germline [25]. Habermas [24] emphasises that the crucial thing about interfering with germline DNA is the irreversibility of the procedure. The child would be in a position where he/she cannot say "yes" or "no," that is, give informed consent to the procedure. So according to Habermas genetic enhancement on germline cells among other things contradicts the principle of respect for autonomy.

Furthermore, as mentioned above, Habermas [24] operates with a so-called "right to chance," which is violated if parents intentionally alter the genetic makeup of a future child. But future parents also intentionally choose their partners for reproduction. So, again our main concern is what constitutes the special status of DNA.

It should also be noted that important issues of justice are connected to genetic enhancement [26–28]. For instance, if it is possible to improve normal characteristics by nanomedicine, who should be offered "the treatment"? Should it be those who are better off? Or do we have a moral responsibility towards those who are worse off? In this case, the principle of just distribution of goods in society is at stake. But how to distribute health goods and services is a very complicated issue, not only with regard to the discussion about enhancement of capabilities by nanosurgery, but in health care in general. This issue is connected to the societal implications of nanotechnology, such as the prioritising and commercialisation of science, public trust and transparency in relation to new technologies, and the question of who should gain from nanotechnology. For instance, do we have a responsibility for developing countries? [29]. However, further work on these issues exceeds the scope of this paper.

TISSUE ENGINEERING

Historically, synthetic materials have not served as adequate implants. For example, the current average lifetime of an orthopaedic implant, such as a hip, knee, ankle, and so on, is only 15 years. Conventional materials, that is, materials with constituent dimensions greater than 1 micron, do not invoke the proper cellular responses to regenerate tissue that would allow these devices to be successful for long periods of time. In contrast, nanophase materials may be a successful alternative, thanks to their ability to mimic the dimensions of the constituent components of natural tissues like proteins. Nanophase materials are defined as materials with constituent dimension less than 100 nm in at least one dimension. Materials investigated to date include nanophase ceramics, metals, polymers, and composites. Data has also emerged suggesting that nanophase materials may be optimal materials for tissue engineering applications. This is not only due to their ability to simulate the dimensions of the proteins that make up tissues, but also because of their higher reactivity to the protein interactions that control cell adhesion and, thereby, the ability to regenerate tissues [30].

Strategies in tissue engineering may be divided into the following two categories: (1) in vivo tissue engineering by cell injection and (2) ex vivo tissue engineering by cell expansion on supporting material. Tissue engineering in vivo by cell transplantation is typically performed by intravenous administration of cells in suspension. The vision is that these cells will engraft in the organ (eg, spleen or liver), proliferate extensively and reconstitute organ function [31]. If tissues are engineered ex vivo, cells are expanded in vitro on a supporting material that acts as a template for growth [32]. Autologous cells are preferred as source material for tissue engineering, since they will not evoke an immunologic response. These cells are often found within the organ itself, isolated, expanded in vitro and transplanted (injected) back into the patient. Limited cell engraftment and limited cell survival remain major problems with these techniques [31]. Furthermore, many patients with end-stage organ disease are unable to yield sufficient cells for expansion and transplantation. Since stem cells are pluripotential (they have the ability to differentiate into several cell types) and are able to replicate indefinitely, they may be an alternate source of cells from which the desired organ can be derived. However, if the stem cells are allogeneic, their clinical application may be limited because they can be rejected by the patient's immune system. Therapeutic cloning may represent a way of producing cells which can differentiate into all cell types and replicate indefinitely while not being rejected by the immune system. Therapeutic cloning entails the isolation of embryonic stem cells from an embryo created by transplantation of a nucleus from a somatic cell to an enucleated egg. The resulting in vitro

expanded stem cells are perfectly matched to the patient's immune system. But obtaining, purifying, and expanding stem cell cultures and the control of permanent differentiation processes are issues that still need to be worked out [33, 34].

Many parenchymal cells are anchorage-dependent and require specific environments that often include the presence of a supporting material to act as a template for growth. Therefore both in vitro expansions of cells for cell injection and ex vivo tissue engineering need suitable substrates for adhesion and proliferation. These scaffolds require mechanical strength, interconnected channels, and controlled porosity or pore distribution to allow diffusion of nutrients to the transplanted cells [32]. For ex vivo tissue engineering, cells may be seeded on to polymer matrices, expanded in vitro and then implanted. Ultimately, the cells become incorporated into the tissue or organ of implantation as the polymer biodegrades. The polymer serves as a scaffold or a template to guide cell organisation and growth. Some of the materials used as scaffolds are synthetic polymers (polymers of glycolic acid) or natural material such as collagen [34].

Experimental efforts are currently underway for tissue engineering involving virtually every type of tissue and every organ of the human body. Various tissues are at different stages of development [33]. For instance, in the field of liver therapies, hepatocytes have been incorporated into biocompatible support materials to make an implantable device which has been tested in rat models. The biocompatible material promotes the cell attachment, survival and function of the transplanted hepatocytes. Furthermore, initial studies in animal models have demonstrated the feasibility of the survival of dissociated cells delivered by vein injection or directly injected into the spleen and liver. However, cell engraftment and survival are limited [31]. So, at present, cell transplantation and implantable constructs have only limited clinical use [31, 34, 35]. An ethical analysis of tissue engineering in general requires a risk analysis as described above in relation to nanosurgery, and informed consent should be obtained from both the cell-donor and the participant in the clinical trial [36]. But the use of embryonic stem cells for tissue engineering and therapeutic cloning also raises some specific ethical issues.

Ethical issues in embryonic stem cell research

The ethical issues in stem cell research depend on the source of the stem cells. Somatic stem cells originate from the umbilical cord or the spinal cord. The use of somatic stem cell for therapy raises the very same ethical issues as the other somatic medical interventions we have talked about. These ethical issues include informed consent (the principle of respect for autonomy), risk analysis (the principles of beneficence and nonmaleficence), and the question of who should be offered the treatment (the principle of justice). But the use of embryonic stem cells for tissue engineering and therapeutic cloning also raises some specific ethical issues. In most cases, human embryonic stem cell lines are derived from a culture of a preimplantation embryo produced by IVF. These are mostly embryos in excess of those required for reproduction and donated by couples who have undergone IVF treatment. These embryos probably have the potential to develop into human beings. It is this developmental potentiality that marks them out as different from other cellular donations and which lies at the heart of the ethical sensitivities involved in research into embryonic stem cells [37].

The main question is what status human embryonic stem cells have compared to new-born children. This problem arises from the fact that development from embryo (fertilisation) to human being is a continuous process. Interpretation of the value of human life is part of a world view. Some would say that human life has the status of a potential person from conception, so embryonic stem cells deserve to be protected from avoidable harm. Since embryonic stem cells have moral status or dignity, they should not be destroyed in research for the sake of basic science or for the sake of trying to develop new therapies. But a more liberal view would be that human embryos have an important moral status or dignity only after their biological individuality has been established and only after the completion of implantation. On this view, we can defend research into embryonic stem cells, which offers great promise for basic science in the short term and may help to provide new approaches to therapy in the long term. An even more liberal view would be that the circumstances of a human embryo's creation do not affect its moral status while it is in vitro, so we can defend research into embryonic stem cells. As can be seen, the ethical dilemma centres around the fact that embryonic stem cells are derived from a potentially viable embryo, which means it centres around the question whether or when this embryo has a moral status or dignity which should be respected.

The conservative view, which holds that human life should be protected from conception, that is, the protection is absolute, is represented in the regulation of research into embryonic stem cells in the following countries: Ireland, Italy, Norway, and Austria. In these countries, research into embryonic stem cells is not allowed. The liberal view which holds that human worth must be graduated in accordance with the development of the foetus, that is protection of human life is relative, is represented in the regulation of embryonic stem cell research in the following countries: Belgium, Great Britain, and Sweden. In these countries research is allowed into embryonic stem cells left over from IVF and embryonic stem cells derived for research. Denmark, Finland, Greece, Holland, Spain, and Hungary represent a middle position; in these countries research is only allowed into embryonic stem cells left over from IVF [38].

Given that ethical problems centre around the status of the embryo, we need to investigate whether there are ways of getting around the embryo. According to Evans [39] cells for transplantation therapies, as well as for in vitro studies, can be isolated from aborted foetuses, and embryonic germ cell lines (pluripotential stem cell cultures that are closely related to embryonic cell lines) can be isolated from 5–9-week-old foetal gonads. In these cases there is no

potential for development at the time when the cells are derived.

One large paradox remains, however. Why have ethical issues in connection with embryonic stem cell research received so much attention compared to the ethics of discarded blastocysts left from IVF? We need to be consistent in these two cases. If embryonic stem cell research is ethically problematic because of the moral status of the embryo, then it is equally problematic to discard blastocysts left over from IVF.

DIAGNOSTICS AND TARGETED DRUG DELIVERY BY NANOPARTICLES

Future applications of nanotechnology may include the use of nanosystems or nanoparticles for the detection of early disease and the delivery of therapeutic agents. The vision is that nanoparticles may be able to seek out a target within the body (eg, a cancer cell) and perform treatment. The treatment delivered by the nanoparticles may be that of releasing a drug in a localised area, thus minimising the potential systemic side effects of generalised drug therapy as in, for instance, chemotherapy [3, 18, 40].

There are numerous engineered constructs, assemblies, architectures and particulate systems used for diagnostics and targeted drug delivery, whose unifying feature is their nanometre-scale size range (from a few to 250 nm). These include polymeric micelles, dendrimers, polymeric and ceramic nanoparticles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes, and liposomes. First, therapeutic and diagnostic agents can be encapsulated, covalently attached, or adsorbed on to nanocarriers. These approaches can overcome drug solubility issues, particularly in view of the fact that large numbers of the new drug candidates emerging from high-throughput drug screening initiatives are water insoluble. Second, by virtue of their small size and by functionalising their surface with synthetic polymers and appropriate ligands, nanoparticulate carriers can be targeted to specific cells and locations within the body after intravenous and subcutaneous routes of injection. Such approaches may enhance therapeutic effectiveness and decrease side effects. Some of these carriers can be engineered in such a way that they can be activated by changes in the environmental pH, chemical stimuli, or by the application of an external heat source. Such modifications offer control over particle integrity, drug delivery rates, and the location of drug release, for example, within specific organelles. Some are being designed with the focus on multifunctionality; these carriers target cell receptors and deliver simultaneously drugs and biological sensors [41].

But if nanoparticles are to be used for targeted drug delivery, we need to be aware of the toxicity of nanoparticles resulting from their nanoscale size. Materials in this size-range may approach the length scale where their properties differ substantially from those of bulk materials of the same composition, allowing them to perform exceptional feats of reactivity, for instance. Possible undesirable results of these capabilities are harmful interactions with biological systems and the environment with the potential to generate toxicity [6, 7]. So we need to perform a risk-benefit analysis as described above.

The prospects of uncontrolled self-assembly of nanosystems

Although some of the nanosystems used in drug delivery may be pre-manufactured, Satava [18, 40] points out that many may need to be created by self-assembly. The scientific challenge will then be to control these self-assembling processes [18, 40].

In his book, *Engines of Creation*, Drexler [42] describes the fear of the uncontrolled spread of self-assembling nanoparticles. But to evaluate the realisation rate of self-assembling nanoparticles, we should look at the state of the art. Current research into the self-assembling of nanostructures deals with the self-assembly of, for instance, carbon nanotubes and rodcoil polymers. The idea behind self-assembly is that molecules always seek the lowest energy level available to them. If bonding to an adjacent molecule accomplishes this, they bind. The forces involved in self-assembly are generally weaker than the bonding forces that hold molecules together, because they correspond to weaker aspects of Coulombic interactions and may be compared to hydrogen bonds that hold the hydrogen atoms in one molecule of liquid water together with the oxygen atom of the next [43]. So when we focus on present research into the self-assembling of carbon nanotubes, there may be a relatively long journey to the uncontrolled self-assembly of nanoparticles. That is why we believe that science fiction looms in the background when Drexler [42] describes the threat of nanotechnology leading to the uncontrolled spread of self-replicating nanosystems or nanoparticles in environment. This kind of approach to the evaluation of nanoscience techniques should be avoided, so we can have a debate founded on sound science, where the actually documented risks of nanotechnology are taken seriously, instead of a debate based on public fear and scepticism caused by predictions spiced with science fiction.

The significance of feedback mechanisms for controlling the function of nanoparticles

Haberzettl [3] points out that nanoparticles used in drug delivery may get "out of control" in the absence of feedback mechanisms to control their function. To take this into account, it may be possible to develop nanoparticles which are biodegradable or composed of naturally occurring substances which can be eliminated from the body through the natural mechanisms of metabolism and excretion. Alternatively, nanoparticles could have "homing" devices which would allow them to be collected and removed after performing the desired function [3].

If nanoparticles are going to be used in the future for the detection of early disease and the delivery of therapeutic agents, one ought to balance the risk to nonmaleficence of the nanoparticles getting "out of control," the possible beneficence obtained by the treatment of serious disease, and the

question of respect for the autonomy of the patient. The ethical considerations of nonmaleficence, beneficence, and respect for autonomy are in conflict and we must consciously determine which considerations should have most weight.

HOW TO ANALYSE THE ETHICAL ISSUES IN NANOMEDICINE

As shown when we take potential ethical problems in nanomedicine as our point of departure, we deduce that general ethical principles, such as respect for autonomy, beneficence, nonmaleficence, and justice, are at stake (Table 1).

The ethical principles at stake in nanomedicine form part of several different ethical theories. In our argument, we follow the bioethical theory of Beauchamp and Childress, because it contains the relevant principles (Table 1). According to Beauchamp and Childress a dialectical relationship exists between ethical principles and concrete ethical problems. The emergence of new ethical problems provokes a critical analysis and possibly a reformulation of existing ethical principles. Due to the dialectical relationship, this reformulation may provoke a modified view of actual ethical problems. In this way, the examination of ethical problems is a process and not the application of rigid ethical principles [8]. According to Beauchamp and Childress' theory we can use practical ethical problems in nanomedicine as a starting point to analyse the ethical principles that are at stake in the actual case. This analysis may lead to a modification of the ethical principles because of the dialectical relationship between principles and practice.

Beauchamp and Childress believe that the principles of their theory (respect for autonomy, beneficence, nonmaleficence, and justice) find support across different cultures. They claim that the principles are part of a cross-cultural common morality [8]. However, even though these principles are generally acknowledged, this does not mean that there is consensus about what is good and bad. Interesting debates occur when the principles are to be interpreted and balanced in specific historical, social, economic, and political contexts. According to Beauchamp and Childress, no principle ranks higher than the others. Which principles should be given most weight must depend on the context of the given situation. Beauchamp and Childress consider the four principles as *prima facie binding*, that is, they must be fulfilled unless they conflict on a particular occasion with an equal or stronger principle. This type of principle is always binding unless a competing moral obligation overrides or outweighs it in a particular circumstance. Beauchamp and Childress write "some acts are at once prima facie wrong and prima facie right, because two or more norms conflict in the circumstances. Agents must then determine what they ought to do by finding an actual or overriding (in contrast to prima facie) obligation" [8]. This means the agents must locate the best balance of right and wrong by determining their actual obligations in such situations by examining the respective weights of the competing prima facie obligations (the relative weights of all competing prima facie norms). Beauchamp and Childress write "what agents ought to do is, in the end, determined by what they ought to do *all things considered*" [8].

Table 1: A brief formulation of the bioethical principles of respect for autonomy, beneficence, nonmaleficence, and justice.

The two American bioethicists Tom L. Beauchamp and James F. Childress:

The Principle of Respect for Autonomy

(i) As a negative obligation: autonomous actions should not be subjected to controlling constraints by others.
(ii) As a positive obligation: this principle requires respectful treatment in disclosing information, probing for and ensuring understanding and voluntariness, and fostering autonomous decision-making.

This principle does not count for persons who are not able to act autonomously: infants, drug-dependent patients are examples. However, these persons are protected by the principles of beneficence and nonmaleficence [8].

The Principle of Beneficence

(i) One ought to prevent and remove evil or harm.
(ii) One ought to do and promote good.
(iii) One ought to weigh and balance the possible goods against the possible harms of an action [8, 46].

The Principle of Nonmaleficence

One ought not to inflict evil or harm. Or more specifically: one ought not to hurt other persons mentally or physically [8].

The Principle of Justice

Beauchamp and Childress examine several philosophical theories of justice including egalitarian theories which emphasise "equal access to the goods in life that every rational person values (often invoking material criteria of need and equality)" [8]. Beauchamp and Childress propose that "society recognize an enforceable right to a decent minimum of health care within a framework for allocation that incorporates both utilitarian and egalitarian standards" [8]. (Utilitarian theories emphasise "a mixture of criteria for the purpose of maximising public utility") [8].

In the latest edition of their book, *Principles of Biomedical Ethics*, Beauchamp and Childress specify conditions that should be fulfilled for one prima facie principle to weigh heavier than another [8]. They also describe how to specify the principles [8]. Mepham [44] has developed a practical way of applying Beauchamp and Childress' theory called an "ethical matrix." This approach describes how to move from the general level of the principles to the level of practical questions [45].

We believe then that most of the ethical questions raised by nanomedicine so far are covered by Beauchamp and Childress' principles. An example of the application of Beauchamp and Childress' ethical principles as tools for

analysing ethical issues in nanomedicine could be an ethical assessment of the use of nanoparticles for the detection of early disease and the delivery of therapeutic agents. In this actual case, one has to balance the risks of nonmaleficence caused by the nanoparticles getting "out of control," the possible beneficence obtained by the treatment of serious disease and respect for the autonomy of the patient. Here the principles of nonmaleficence, beneficence, and respect for autonomy are in conflict, and the agents must consciously determine which prima facie principles should be set-aside in the actual situation.

Although Beauchamp and Childress' theory is prominent in bioethics, it is, of course, also subject to much philosophical discussion [47–58]. For example, in an attempt to criticise philosophical bioethics in general, Hedgecoe [52] focuses on the bioethical theory of Beauchamp and Childress, because principlism is the dominant way of doing bioethics. Hedgecoe [52] accuses traditional philosophical bioethics of giving a dominant role to idealised rational thought, and of tending to exclude social and cultural factors. He criticises principlism for using abstract universal principles without empirical evidence and for concentrating on developing and justifying theories while paying little attention to the practical utilisation of those theories. Hedgecoe [52] sums up "because of this refusal to come to terms with empirical research in the way in which ethical decision-making actually takes place in the clinic, bioethics faces a difficult gap that must be bridged if it is to remain a relevant and serious discipline." As an alternative to principlism, Hedgecoe [52] defends the position of what is called "critical bioethics," where the results of empirical research feed back to challenge and even undermine the theoretical framework of bioethics.

However, we do not think that this critique of Beauchamp and Childress' theory is well founded. As pointed out above, according to Beauchamp and Childress, a dialectical relationship exists between ethical principles and ethical problems. The emergence of new ethical problems provokes a critical analysis and possibly a reformulation of the ethical principles. Due to the dialectical relationship, this reformulation may provoke a modified view of actual ethical problems [8]. So the principles of Beauchamp and Childress are not rigid, but changeable. In his paper, *A defense of the common morality*, Beauchamp [59] stresses the importance of empirical research for ethical principles. And the first author at this paper is currently in dialogue with Beauchamp, performing a qualitative empirical investigation of the use of the four principles by molecular biologists and physicians in their daily work [60], so as to improve the bioethical theory of principles by bringing it into concord with practice. According to Beauchamp and Childress, there is no straightforward movement from principles to particular judgments. Principles are only the starting points and, as such, general guidelines for the development of norms of appropriate conduct. The principles need to be supplemented by paradigm cases of right action, empirical data, organisational experience, and so on [8]. Beauchamp and Childress state that rights, virtues, and emotional responses are as important as principles for ethical judgement [8]. So to point at the four principles is by no means the final word about the ethics of nanomedicine.

Given the fact that we cannot know what form nanotechnology will take in the future and therefore what kinds of ethical issues will arise, we are confident that the open-endedness of Beauchamp and Childress' theory makes it appropriate for discussing emerging ethical issues in nanomedicine. Due to the dialectical relationship between theory and practice, the emergence of new ethical problems in nanotechnology may provoke a reformulation of the ethical theory bringing it into concord with the future practice of nanotechnology. We are convinced that the open-ended theory of Beauchamp and Childress is sufficiently sensitive to the dynamics of the field of nanotechnology to adequately address emerging ethical issues in the field. The sensitiveness of Beauchamp and Childress' theory can be illustrated by the changes they have made since the first edition of their theory [61]. Beauchamp and Childress have taken their critics into account over the last 25 years by incorporating their comments and suggestions and simultaneously publishing papers to discuss their theory [47, 48, 59].

CONCLUSION

In considering the use and potentials of emerging nanoscience techniques in nanomedicine, such as nanosurgery, tissue engineering, and targeted drug delivery, we have discussed ethical considerations related to this field. These ethical considerations are related to risk assessment in general, therapy on somatic cells versus germline cells, the enhancement of human capabilities, research into human embryonic stem cells, and the toxicity, self-assembly and uncontrolled function of nanoparticles and nanosystems. The analysis of potential ethical problems in nanomedicine shows that even though ethical questions in nanomedicine may be more complex than ethical questions in general medicine and biotechnology, for example the toxicity of nanoparticles resulting from their nanoscale size [6, 7], fundamentally the same general ethical principles, such as respect for autonomy, beneficence, nonmaleficence, and justice, are at stake. These ethical principles have been used for ethical assessment in biomedicine for several years and they form part of several different ethical theories, including the bioethical theory of Beauchamp and Childress [8]. This shows that even though nanomedicine raises ethical issues that are more complex than those raised by existing technology, a reasonably sound knowledge base has already been acquired in the field of bioethics that can be extended to nanomedicine.

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REFERENCES

[1] Roco MC. Broader societal issues of nanotechnology. *Journal of Nanoparticle Research.* 2003;5(3-4):181–189.

[2] Crow MM, Sarewitz D. Nanotechnology and societal transformation. In: Roco MC, Bainbridge WS, eds. *Societal Implications of Nanoscience and Nanotechnology.* Boston, Mass: Kluwer Academic; 2001:55–67.

[3] Haberzettl CA. Nanomedicine: destination or journey? *Nanotechnology.* 2002;13(4):R9–R13.

[4] Emerich DF, Thanos CG. Nanotechnology and medicine. *Expert Opinion on Biological Therapy.* 2003;3(4):655–663.

[5] Freitas RA. Nanotechnology, Nanomedicine and Nanosurgery. 2006. http://www.kurzweilai.net.

[6] Warheit DB. Nanoparticles: health impacts? *Materials Today.* 2004;7(2):32–35.

[7] Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. *Science.* 2006;311(5761):622–627.

[8] Beauchamp TL, Childress JF. *Principles of Biomedical Ethics.* Oxford, NY: Oxford University Press; 2001.

[9] Giorgi C, Sala R, Riva D, Cossu A, Eisenberg H. Robotics in child neurosurgery. *Child's Nervous System.* 2000;16(10-11):832–834.

[10] Adler JR Jr, Murphy MJ, Chang SD, Hancock SL. Image-guided robotic radiosurgery. *Neurosurgery.* 1999;44(6):1299–1307.

[11] Obataya I, Nakamura C, Han S, Nakamura N, Miyake J. Nanoscale operation of a living cell using an atomic force microscope with a nanoneedle. *Nano Letters.* 2005;5(1):27–30.

[12] Tirlapur UK, König K. Femtosecond near-infrared laser pulses as a versatile non-invasive tool for intra-tissue nanoprocessing in plants without compromising viability. *The Plant Journal.* 2002;31(3):365–374.

[13] Obataya I, Nakamura C, Han S, Nakamura N, Miyake J. Mechanical sensing of the penetration of various nanoneedles into a living cell using atomic force microscopy. *Biosensors and Bioelectronics.* 2005;20(8):1652–1655.

[14] König K. Robert Feulgen Prize Lecture. Laser tweezers and multiphoton microscopes in life sciences. *Histochemistry and Cell Biology.* 2000;114(2):79–92.

[15] Yanik MF, Cinar H, Cinar HN, Chisholm AD, Jin Y, Ben-Yakar A. Neurosurgery: functional regeneration after laser axotomy. *Nature.* 2004;432(7019):822.

[16] Mori M, Neri D. Perils and deficiencies of the European convention on human rights and biomedicine. *Journal of Medicine and Philosophy.* 2001;26(3):323–333.

[17] Wivel NA, Walters L. Germ-line gene modification and disease prevention: some medical and ethical perspectives. *Science.* 1993;262(5133):533–538.

[18] Satava RM. Disruptive visions: moral and ethical challenges from advanced technology and issues for the new generation of surgeons. *Surgical Endoscopy.* 2002;16(10):1403–1408.

[19] Resnik DB, Langer PJ. Human germline gene therapy reconsidered. *Human Gene Therapy.* 2001;12(11):1449–1458.

[20] Walters L, Palmer JG. *The Ethics of Human Gene Therapy.* New York, NY: Oxford University Press; 1997.

[21] Christiansen K. The limits of Habermas' critique of a liberal eugenics. In press.

[22] Andersen S. *Moral Responsibility Towards Future Generations in Global Ethics and Sustainable Development.* Uppsala, Sweden: Uppsala University Press; 2006. Grenholm C-H, Normunds K, eds. In press.

[23] Bostrom N. In defence of posthuman dignity. *Bioethics.* 2005;19(3):202–214.

[24] Habermas J. *The Future of Human Nature.* Cambridge, UK: Polity Press; 2003.

[25] Smith KR. Gene therapy: theoretical and bioethical concepts. *Archives of Medical Research.* 2003;34(4):247–268.

[26] Green RM. Last word: imagining the future. *Kennedy Institute of Ethics Journal.* 2005;15(1):101–106.

[27] Allhoff F. Germ-line genetic enhancement and Rawlsian primary goods. *Kennedy Institute of Ethics Journal.* 2005;15(1):39–56.

[28] Lindsay RA. Enhancements and justice: problems in determining the requirements of justice in a genetically transformed society. *Kennedy Institute of Ethics Journal.* 2005;15(1):3–38.

[29] Mwase IMT. Genetic enhancement and the fate of the worse off. *Kennedy Institute of Ethics Journal.* 2005;15(1):83–89.

[30] The Nano Science Technology Institute (NSTI). 2006. http://www.nsti.org.

[31] Allen JW, Bhatia SN. Engineering liver therapies for the future. *Tissue Engineering.* 2002;8(5):725–737.

[32] Yang S, Leong K-F, Du Z, Chua C-K. The design of scaffolds for use in tissue engineering. Part II. Rapid prototyping techniques. *Tissue Engineering.* 2002;8(1):1–11.

[33] Hipp J, Atala A. Tissue engineering, stem cells, cloning, and parthenogenesis: new paradigms for therapy. *Journal of Experimental and Clinical Assisted Reproduction.* 2004;1(1):3.

[34] Lalan S, Pomerantseva I, Vacanti JP. Tissue engineering and its potential impact on surgery. *World Journal of Surgery.* 2001;25(11):1458–1466.

[35] Chan C, Berthiaume F, Nath BD, Tilles AW, Toner M, Yarmush ML. Hepatic tissue engineering for adjunct and temporary liver support: critical technologies. *Liver Transplantation.* 2004;10(11):1331–1342.

[36] Lo B, Zettler P, Cedars MI, et al. A new era in the ethics of human embryonic stem cell research. *Stem Cells.* 2005;23(10):1454–1459.

[37] Evans M. Ethical sourcing of human embryonic stem cells—rational solutions? *Nature Reviews: Molecular Cell Biology.* 2005;6(8):663–667.

[38] Walters L. Human embryonic stem cell research: an intercultural perspective. *Kennedy Institute of Ethics Journal.* 2004;14(1):3–38.

[39] Evans M. Ethical sourcing of human embryonic stem cells—rational solutions? *Nature Reviews Molecular Cell Biology.* 2005;6(8):663–667.

[40] Satava RM, Wolf RK. Disruptive visions: biosurgery. *Surgical Endoscopy.* 2003;17(11):1833–1836.

[41] Moghimi SM, Hunter AC, Murray JC. Nanomedicine: current status and future prospects. *FASEB Journal.* 2005;19(3):311–330.

[42] Drexler E. *Engines of Creation: The Coming Era of Nanotechnology.* New York, NY: Anchor Press; 1986.

[43] Ratner M, Ratner D. *Nanotechnology. A Gentle Introduction to the Next Big Idea.* Upper Saddle River, NJ: Pearson Education; 2002.

[44] Mepham B. *Food Ethics.* New York, NY: Routledge; 1996.

[45] Kaiser M. Assessing ethics and animal welfare in animal biotechnology for farm production. *Revue Scientifique et Technique.* 2005;24(1):75–87.

[46] Beauchamp TL, Childress JF. *Principles of Biomedical Ethics.* Oxford, NY: Oxford University Press; 1989.

[47] Beauchamp TL. Principlism and its alleged competitors. *Kennedy Institute of Ethics journal.* 1995;5(3):181–198.

[48] Beauchamp TL. Reply to strong on principlism and casuistry. *Journal of Medicine and Philosophy.* 2000;25(3):342–347.

[49] Degrazia D. Moving forward in bioethical theory: theories, cases, and specified principlism. *Journal of Medicine and Philosophy.* 1992;17(5):511–539.

[50] Ebbesen M. *The Golden Rule and Bioethics. A Reflection Upon the Foundation of Ethics.* Linköping, Sweden: Linköping University Electronic Press; 2002. http://www.ep.liu.se/exjobb/cte/2002/001/.

[51] Engelhardt HT Jr. Critical care: why there is no global bioethics. *Journal of Medicine and Philosophy.* 1998;23(6):643–651.

[52] Hedgecoe AM. Critical bioethics: beyond the social science critique of applied ethics. *Bioethics.* 2004;18(2):120–143.

[53] Holm S. Not just autonomy—the principles of American biomedical ethics. *Journal of Medical Ethics.* 1995;21(6):332–338.

[54] Lustig BA. The method of 'principlism': a critique of the critique. *Journal of Medicine and Philosophy.* 1992;17(5):487–510.

[55] Lustig BA. Concepts and methods in recent bioethics: critical responses. *Journal of Medicine and Philosophy.* 1998;23(5):445–455.

[56] O'Neill O. Practical principles & practical judgment. *The Hastings Center Report.* 2001;31(4):15–23.

[57] Richardson HS. Specifying, balancing, and interpreting bioethical principles. *Journal of Medicine and Philosophy.* 2000;25(3):285–307.

[58] Strong C. Specified principlism: what is it, and does it really resolve cases better than casuistry? *Journal of Medicine and Philosophy.* 2000;25(3):323–341.

[59] Beauchamp TL. A defense of the common morality. *Kennedy Institute of Ethics Journal.* 2003;13(3):259–274.

[60] Ebbesen M, Pedersen BD. Using empirical research to formulate normative ethical principles in biomedicine. *Journal of Medicine, Health Care and Philosophy*. In press.

[61] Beauchamp TL, Childress JF. *Principles of Biomedical Ethics.* 1st ed. Oxford, NY: Oxford University Press; 1979.