Bioethics and health in international context

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Introduction to the symposium

This symposium was quite a special event, being a joint action of the French and Dutch Academies. It was actually triggered by President Chirac, who showed a personal interest in bioethical problems. In his speech[1] last year in Amsterdam at the Academy during his official State visit to the Netherlands, the President mentioned a large range of issues with ethical aspects, varying from environmental issues to the cloning of human embryos. The President also hinted at the differences in opinion between France and the Netherlands and the need to be in constant dialogue, but he also emphasized that the two countries share common basic values and have a common cultural heritage. Descartes and Huygens are the most celebrated exponents. There are differences between the two countries in tolerance toward abortion and euthanasia, and also toward the protection of human life and dignity, if that life concerns an embryo of not more than 8 cells. We should be aware, of course, that we are dealing with problems of wide impact and scale, far transcending any limited French-Dutch discussion. But we should begin somewhere, and why not start among friends.

In planning the joint French-Dutch symposium, it soon became clear that we should have a clear goal and it was decided to focus on ethical aspects of medicine and human health. It was agreed to plan two one-day symposia, one in Amsterdam in 2001, and one in Paris in 2002. The present meeting concentrates on ethical and legal aspects of scientific developments in the field of genomics, including the consequences of knowledge about individual genes. The central issue of the morn-

ing session was internationalisation, while the afternoon session was devoted to various aspects of pre-symptomatic genetic screening.

Ethical questions have no national boundaries, but legislation has. If humankind cannot agree on general principles, on a supranational or global level, then legislation will reflect local preferences and conflicts will arise. One country may produce goods or medicines, the production of which is banned in other countries. But the distribution of products follows a different set of laws, often based on international free-trade agreements. Thus different ethical interpretations may lead to far-stretching economic advantages and disadvantages. This does not only apply to products ready for trading, but also to scientific research that is the prerequisite for technological and medical advances. Different ethical interpretations may deprive countries from contributing to cutting-edge research, and cause migration of their best scientists and industrial research activities. Different patent policies, e.g. concerning the patentability of genetic sequences, can have disastrous effects as well, and it is important that international agreements will be reached. This is also true for the intellectual property rights on genome sequences of natural organisms, including human beings. Such data – insofar as they do not infringe on the privacy rights of individuals – should ideally be in the public domain and archived as part of the human intellectual heritage. A high-level political commitment was voiced by President Bill Clinton and Prime Minister Tony Blair in June 2000 when the 'complete' human genome sequence was announced: they publicly supported the idea that the results of the human genome project should be freely available. But there are controversies, and high and conflicting interests are at stake.

The afternoon session was devoted to the consequences of the increased knowledge about individual gene sequences that is becoming available. No one can be blind for the rapid technological improvements leading to an explosive growth of knowledge about individual genes. No doubt this knowledge will generate fantastic new possibilities to treat or prevent diseases with genetic components in entirely new ways, such as by repair of defective genes or by complementing defective components in the metabolic pathways by engineered products. And why not prevent defective life from the start by selecting embryos on the basis of their genetic constitution? No one questions the value and admissibility of genetic screening for fatal monofactorial diseases, such as the untreatable Huntington's disease, and few question abortion policies or even embryonic selection based on the result, but should we extend those policies to selection based on the colour of hair, eyes or skin, or the presumed propensity for becoming homosexual or becoming an intelligent being? What ethical principles should guide us here? How should we judge the selection of an embryo, carried out in the Unites States, and reported[2] in October

2000, on the basis of the possibility that the child can donate cells from its umbilical cord to his older sister and save her from a fatal anaemia?

But there is more. In The Emerging Technologies Outlook Project [3] of the Institute for the Future, based on the opinion of many specialists, the prediction is made that within five years solid-state sequencing of thousands of proteins on a single gene chip that will cost 30 dollar cents will be possible. Individual genome sequencing will be possible 'with the ability to map relevant portions of an individual's genetic make-up at a price point that's practical for medical or other applications, probably occurring around 2005.' In Science of 19 October 2001 K. Jain writes [4] about the development of micro-arrays for 'gene spotting'. The Californian firm Affymetrix produces chips that can pack 400,000 different oligonucleotides on a single array, or 40 sequences for each of 10,000 genes. Jain says: 'In the not-to-distant future, microchips can be incorporated into hand-held diagnostic instruments for use at the patient's bedside or in the doctor's office.' One may even buy self-diagnostic units and find the interpretative software on Internet. No one doubts that these techniques will help integrated health care and make individualized therapy possible. But what shall we do with knowledge about our individual propensity to develop cancer at a later age or get early heart attacks? Of course we can adjust our diets and way of living accordingly. But should we tell it to our medical or life insurance company? We cannot withhold this kind of knowledge that influences the statistical probabilities for our medical costs or the statistical probability for our life span. But can we prevent the insurance companies to request this kind of knowledge or to collect it themselves? How do we protect those that become uninsurable? One thing is sure: we cannot let the medical specialist decide to collect the data or not, and let him or her guard and protect the data as well. The data will become available, whether we like it or not.

Finally, I wish to add a few words in writing, after reflection upon a symposium day with its formal and informal discussions. I distance myself from the topic of the day, but I know I keep close to the heart of my medical colleagues Hans Galjaard and Piet Borst. Is the protection of an 8-cell embryo not a moral non-issue in a world where every day 40,000 children under five years of age die of treatable disease and malnutrition?[5] Can we morally justify the use of genetic knowledge for the costly development of a medicine for a rare Western disease in a world where every half minute someone dies of Plasmodium falsiparum malaria,[6] for the treatment of which we cannot spare the research and development funds?

References

1. Discours de Monsieur Jacques Chirac, Président de la République, devant l'Académie Royale Néerlandaise des Sciences, Amsterdam, Pays-Bas, Lundi 28 Février 2000, Présidence de la République, *Service de Presse* (http://www/elysee.fr)
2. *Volkskrant* and *NRC-Handelsblad*, 4 October 2000
3. *Technology Horizons: The Next 20 Years. The Emerging Technologies Outlook project*, Report S-678, Dec. 1999, Institute for the Future, Menlo Park, California (http://www.iftf.org)
4. K.K. Jain, Biochips for gene spotting, *Science* 294 (2001) 621-625
5. H. Galjaard, *De 'maakbare' mens*, Afscheidscollege Erasmus Universiteit, Rotterdam, 7 May 2001
6. *Oxford Handbook of Clinical Medicine*, Oxford University Press, 2001

Internationalisation of norms and regulations in health care

Jean-Didier Vincent

New therapies and their ethical implications in an international context

Summary

My opening remarks will address the difficulty in separating basic research and possible medical applications in terms of bioethics. One of the reasons is that human diseases and health care are generally given as the principal research objective, even if in many cases they are far removed from the research, and thus serve only as a pretext to obtain a grant. In this respect, certain media tend to perpetuate this confusion.

The use of embryonic stem cells in therapeutic research will be examined in relation with the Universal Declaration on the human Genome and human rights and the recommendations from the intergovernmental bioethics committee at unesco on the one hand, and on the other hand, with the various national regulations of legislation, for example, on the question of importation and exportation of embryonic cells to or from countries where embryo research is forbidden. I shall look at these issues taking into account novel 'alternative technology' in particular concerning adult stem cells. The problem of embryonic stem cell lines and germ lines will also receive special attention. Finally I shall try to give an overview on the current bioethical debate and governmental positions in different countries concerning the use of embryos in general with respect to medical applications (cloning, grafts, etc).

The new therapies give rise to major interrogations from the public and the profound anxiety which is sustained by preformed opinions and a blind respect for life based on a 'sacred' and 'untouchable' image. There is a remarkable contrast between public opinion riddled with irrationality and the development of research in molecular biology and cellular genetics. The fear that industrial use of this new knowledge exclusively for profit will lead to uncontrollable excesses is particularly expressed in the hasty reactions to the notion of 'patenting of life'. Another cause of trouble is the difficulty in separating the cognitive purposes of basic research and its possible medical applications: human diseases and health care are generally given as the principal research objective, even if in many cases they are far removed from the research and thus are mainly used as a pretext for obtaining financial support.

In this respect, politicians on the one hand, and mass media on the other hand tend to perpetuate this confusion. The potential to apply genomic research to improve human health will be influenced as much by the social environment and political context as by the research progress per se. In addition to stimulating informed dialogue on the ethical, legal and social issues, therefore, it is very important:

1. To enhance public debate on societal concerns by explaining the potential benefits of research advances and by countering antitechnology activist pressures;
2. To establish public confidence by defining the appropriate balance of professional standards and regulation.

Views on bioethics differ among and within countries for cultural, economical and political reasons.[1] The cultural differences should not be harmonized and guidelines should therefore not be coercive but rather permissive and encourage an informed debate between three partners: the politician parliament and government, the 'experts' and the public. The media have a major role today in these debates – to influence and to be influenced by – they must avoid both confusion and sensationalism. With regards to descriptions of potential promise and harm we shall consider in order the two major domains of research: genetics and stem cells.

I. Genetics

Three new issues come from genetic research:

Pharmacogenetics
Many research-based pharmaceutical companies believe it is possible to learn why some people respond well to medicines while others don't, or why some patients experience side effects. Many medicines only work in a subset of patients. Often it takes weeks or months to find out if a new medicine will work for a patient. That can be frustrating and costly. Genomics will help to better identify which patients will respond to a medicine, so that the right patient will get the medicine he or she needs.

Scientists have found that when individuals have a certain genotype, or pattern of dna at a gene, they may not be able to metabolise certain medicines. They will then be more likely to experience adverse reactions if given those medicines, or be at a higher risk for developing drug interactions. In addition, some forms of a gene may cause medicines to be metabolised very rapidly. This means that if patients have these forms and receive a medicine that is metabolised in that pathway, they may not respond because the medicine will be removed too rapidly from the body. The major ethical risk is that certain patients will be excluded from a given therapeutic protocol. These patients therefore fall into the situation of an orphan disease and could be abandoned by therapeutic research.

Genomic therapies
The problems are more economical than ethical. Basically a transgene is not different from classical medicine and the tests are submitted to the same issues concerning informed consent and the protection of the person. Nevertheless, since we are creating genetically modified organism (gmo) some procedures have to be followed. In ec each country applies its own legislation on its territory. In France, genomic therapy is submitted to the 'Commission du Génie Génétique' (ogg) and the 'Commission du Génie Biologique'. In the uk, the gene therapy advisory committee (gtac) must obligatorily be advised. Furthermore, when the product is utilised outside the national territory it is obligatory to advise the mea (Medicine European Agency). Ethical problems are mainly related to the cost of genomic therapies. Are these going to be reserved for rich people or for groups of patients more influential than others? Can we envisage the use of genomic therapy for increased comfort or for reasons of aesthetic or age? What role will the market play in making choices? Similar problems concern the so-called orphan diseases.

Orphan medicinal products

Major ethical problems come from the financial cost of genetic research on illnesses which concern very few patients. This is emphasised in underdeveloped countries where many orphan diseases are present and where public support for research is absent. The criterion for designation of an orphan drug is that the prevalence of the disease does not exceed 5 for 10,000. The evaluation is made by the committee for orphan medicinal products (comp) in London which correspond with the 'Orphan Drug Act' in the usa and a similar institution in Japan.

I shall now move on to the domain of cellular therapies which implies the use of stem cells and raises many ethical questions.

II. The stem cells

Stem cells are cells which have the ability to develop into more than one form of human tissue. They may be totipotent (such as the early embryo cells, able to develop into all the different types of cells needed for a complete and functioning organism), pluripotent (such as embryonic stem cell lines, able to give rise to most types of tissue but not capable of bringing a functioning organism into existence) or multipotent (being able to give rise to a limited number of tissue types). These later stem cells are still present in the adult human body, but their potential to develop is less than those of pluripotent embryonic stem cells, which form the focus of the discussion in my talk. Examples of adult stem cells are certain bone marrow cells that give rise to all blood lineages but can turn also into liver cells or cardiac muscle cells. Neural stem cells give rise to neurones and glial cells but can turn also into heart, lung or liver cells. However, for preparation of tissues for transplantation, adult stem cells do not offer of such wide potential to researchers as embryonic stem cells and the ethical issues they may raise are not the same concentrate on embryonic stem cells. Since adult stem cells do not raise specific and major ethic concern I shall consider exclusively the embryonic stem cells.

As referred in table 1, embryonic stem cells may be derived from the embryo at the preimplantation stage of its development. The extraction procedure will end the ability of that particular embryo to develop through implantation in the uterus. The removal of the cells, then, brings the existence of the embryo to an end. The embryo-derived cells are not in themselves an embryo – they cannot develop into a human being; they are therefore just like any other human tissue.

Table 1

Three categories of embryos can be used:

1. 'From abortion: cell lines used over many years without any restriction
2. Embryos resulting from in vitro fertilisation (ivf) and which are no longer the object of parental projects thus become susceptible for research use 'for medical purposes' within a frame work which must be legally defined (when such a law exists): more than 70 cell lines are now available
3. Embryos which can be created by transferring a somatic nucleus into an enucleated ovocyte (isn t). It corresponds to the so-called therapeutic cloning.

Nevertheless es cells can be kept alive and will proliferate more or less indefinitely. They afford the possibility to differentiate and to grow in spare cells or tissue (and may me in the future in entire organs) for grafting into human hosts whose organs are impaired or destroyed. One major question remains: *Is it acceptable to use ES cell* research for therapeutic purpose? A majority of scientists takes the view that the benefits which might flow to humanity from this form of research are so great that it is important that is be allowed to proceed. Nevertheless, some scientists (in majority women) remain opposed.

Concerning 3, as far as transplant rejection is concerned, this risk could be avoided by preparing the stem cells from 'embryos' created by nuclear transfer (transfer of a nucleus from the patient's own cells). In this process, sometimes called 'therapeutic cloning', there is a reprogramming of the donor cell nucleus in the recipient egg, yielding again totipotent embryo cells. The tissues derived from such stem cells would then be autologous to the recipient and not subject to immune rejection. Some committees have raised restriction on the term of 'human embryo' applied to the product of isn t. If it is clear that it the isn t embryo has not a sexed origin in contrast with the ivf embryo, it would be unethical and dangerous for future i.e. in the case of a transgression of the interdiction of reproductive cloning, can we reasonably refuse the status of human being to this product?

Finally, the benefits from embryonic stem cell technologies may also entail some risks, which will have to be carefully weighed. One risk may be uncontrolled proliferation of the transplanted cells and another may be transmission of infectious agents, but the latter risk would be smaller with embryo stem cells than with adult stem cells. Embryo stem cell research could indeed lead to substantial progress in the treatment of various diseases which are listed in table 2:

Table 2

Possible indications for es cells
– Nervous diseases
– Neurodegenerative diseases: Parkinson, Alzheimer, multiple sclerosis.
– Tissues derived from es cell lines to replace the nervous tissue cells which are lost damaged
– Production of various neurotransmitters
– Production of myelin
– Heart infarction
– Bone and cartilage diseases
– Cancer and immune diseases
– Diabetes

III. Existing provisions on genomics and embryonic cells

1. International level
   a. Intergovernmental Bioethics Committee (icbc) at the unesco (2001)
   b. Council of Europe: Convention for the Protection of Human Rights and dignity of human being (1997) – Additional protocol on the prohibition of cloning human being (1998)
   c. Charter of fundamental Rights of the European Union (Nice 2000) – Opinion No. 15 from the European Group on Ethics in Science and new Technologies (ege) (Nov. 2000)

2. National level
   a. Prohibition
      Ireland, Germany, Austria, Hungary, Poland, Norway, Tunisia, Switzerland, Italia, Latin America
   b. Use of supernumerary embryos authorized
      Canada, Sweden, Finland, Spain
   c. Countries envisaging authorization of the creation of embryos for research purposes
      uk, Japan, the Netherlands, Belgium, usa

Recommendations of the Intergovernmental Bioethics Committee (IGBC), May 2001 – UNESCO

At the international level
Encourage Member States, according to the relevant provisions of the Universal Declaration on the Human Genome and Human Rights, to hold debates on the ethical issues raised by the use of embryonic stem cells in therapeutic research, involving all actors concerned, so as to adopt national regulations or legislation, for example, on the question of the import and export of embryonic cells from or to countries where embryo research is forbidden.

a. At the European level, the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine of 1997 does not resolve the matter of the permissibility of embryo research and leaves each country responsibility for legislating on this matter, while stipulating two conditions: the prohibition of producing human embryos for research purposes and the adoption of rules designed to assure adequate protection for the embryo (6 countries only including Denmark). An Additional Protocol to the Convention on the Prohibition of Cloning Human Beings was approved in 1998 and took effect on 3 January 2001 in five Member States (Georgia, Greece, Slovakia, Slovenia, Spain).

b. The Charter of Fundamental Rights of the European Union, adopted in Nice, France, in December 2000, expressly prohibits eugenic practices and reproductive cloning, but does not comment explicitly on embryo research. In a Resolution of 7 September 2000, the European Parliament stated its opposition to the creation of supernumerary embryos and to therapeutic cloning. More recently, the European Group on Ethics in Science and New Technologies to the European Commission (ege) adopted Opinion No. 15 of 14 November 2000 on the ethical aspects of human stem cell research and use, in which it states that 'stem cell research based on alternative sources (spare embryos, fœtal tissues and adult stem cells) requires a specific Community budget', while pointing out that 'it is up to each Member States to forbid or authorise embryo research'. On the other hand, the Group considers 'ethically unacceptable' the creation of embryos with donated gametes for the purpose of deriving stem cells, and 'premature' the creation of embryos by somatic nuclear transfer.

At the national level
a. Research on human embryos is expressly prohibited in some countries

Ireland where Article 40, par.3, of the Constitution implicitly prohibits research on the embryo by stating the right to life of the 'unborn child' equal to that of the mother. In *Germany*, the Law of 13 December 1990 on Embryo Protection regards as an offence the fertilization of an ovum for purposes other than its reimplantation in the donor; it takes the same position on the fertilization of a larger number of ova than can be implanted. The situation is similar in *Austria*, where Law No. 275 of 1992 authorises the creation of embryos only for reproductive purposes. In *Hungary* (Law No. 1xxix of 1992) and *Poland* (Law of 7 January 1993 as amended on 30 August 1996), the life of the unborn child must be respected and protected from its conception. In *Norway*, the Law No. 56 of 5 August 1994 prohibits research on embryos and bans their use for any purpose other than reimplantation in the donor. In *Tunisia*, the National Medical Ethics Committee has stated its opposition to all experimentation on the embryo which is regarded as a 'potential person' (Opinion No. 1 of 12 December 1996) and also to any form of cloning (Opinion No. 3 of 22 May 1997). In *Switzerland*, the Constitution (1999) prohibits the use of medically reproduction for research purposes and the fertilization of more ova than are capable of being immediately implanted (Art. 119,2c). In *Italy*, the bill on medically assisted reproduction specifically prohibits the creation of embryos for research purposes and the early splitting of the embryo for therapeutic or research purposes. The Italian National Committee on Bioethics has opposed reproductive cloning, but was unable to reach a consensus on matters relating to the use of supernumerary embryos and on therapeutic cloning (Opinion of 27 October 2000).

As far as Latin America is concerned, in *Brazil* Law No. 8974/95 on genetic engineering prohibits the production, storage and manipulation of human embryos with a view to their use as biological material. *Peru* specifically prohibits the fertilization of human ova for purposes other than reproduction, and human cloning (Law No. 26.842). The right to life from the moment of conception is recognised in Peru by the Children and Adolescent Code (Law No. 27.337), in Costa Rica by Law No. 7739 of 1998 and in *Ecuador* by Article 49, par. 1, of the Constitution (1998).

b. In some countries, the use for research purposes of embryos *donated* by persons following a treatment against sterility and not intended for implantation (supernumerary) is permitted. In general, the conditions imposed are the prohibition of research after the 14th day of existence of the embryo and the consent of the couple that supplies the embryo. That is the case, for example, in Canada, Sweden (Law No. 115) and *Finland* (Law No. 488/1999). In *Spain* (Law No. 35/1988), research on supernumerary embryos is permitted under rigorous restrictions, but their creation for this specific purpose is prohibited. In September 2000, the Observatory of Law and Bioethics of Barcelona did, however, express its support for the creation of

embryos for research purposes, both by donation and by cloning techniques. In *Australia*, the law varies between different states and territories and, in some; law does not regulate the subject. For such cases, the Australian National Health and Medical Council has formulated guidelines (The Ethical Guidelines on Assisted Reproductive Technology, par. 6) which, although not legally binding, are influential.

c. Some countries are envisaging authorisation of the *creation* of embryos for research purposes. In the *United Kingdom*, since 1990 the Human Fertilization and Embryology Act authorises the use of supernumerary embryos for restricted research purposes – in particular concerning reproductive medicine and for the diagnosis of genetic and chromosomal disorders – and the production of embryos for these purposes. On 22 January 2001, the House of Lords passed a law (already approved in December 2000 by the House of Commons), which permits the cloning of human embryos to derive stem cells, thus allowing the possibility of therapeutic cloning. In November 2000, *Japan* adopted a law prohibiting reproductive cloning and prescribing the adoption of guidelines, which should permit the use of stem cells derived from supernumerary embryos. In the *Netherlands*, a bill is currently being prepared, which prohibits the production of embryos for research purposes, with many exceptions. However, the bill authorises research into stem cells obtained from supernumerary embryos. In *Belgium*, similar bills are being debated in the Senate. In *France*, the bioethic bill of 1994 which prohibits embryo research is under review. Importation of es cell lines is neither authorised nor prohibited. In accordance with advices from Conseil d'Etat and ccne a revision of the law has been proposed by the government and will be submitted at the Parliament.

d. In the usa although the Federal financing of such activities is prohibited, the authorization of research on the embryo is left to the discretion of each state. To this date, nine states prohibit such research. However, in a number of states, there is effectively no control over private research of this sort. In 1999, the National Bioethics Advisory Commission recommended that Federal regulations should permit research into embryonic stem cells obtained from supernumerary embryos. However, it remains opposed to therapeutic cloning and to the deliberate production of embryos for the purpose of obtaining stem cells. In August 2000, the National Institutes of Health issued guidelines on the circumstances in which Federally supported scientists might engage in such research. One of the conditions to be met is that no such scientist might destroy an embryo to derive cells: this will have to be done by privately-funded scientists, who will then pass the cells on to their publicly-funded colleagues. On august 9, 2001, us President George W. Bush announced his

decision to allow federal funds to be used for research on existing human embryonic stem cell lines as long as prior to his announcement (1) the derivation process (which commences with the removal of the inner cell mass from the blastocyst) had already been initiated and (2) the embryo from which the stem cell line was derived no longer had the possibility of developing as a human being. us President's criteria that must be met:

1. The es cells must have been derived from an embryo that was created for reproductive purposes.
2. The embryo was no longer needed for these purposes.
3. Informed consent must have been obtained for the donation of the embryo.
4. No financial inducements were provided for donation of the embryo.

Table 3

List of human es cell lines (at varying stages of development) that meet the eligibility criteria (from the nih Human es Cell Registry)

Bresa Gen. Inc	Athens Georgia usa	4
Cy Thera Inc	San Diego ca usa	9
es cell Internation	Melbourne Australia	6
Geron Inc	Menlo Part ca usa	7
Göteborg Univ.	Sweden	19
Karolinska Inst.	Stockholm Sweden	6
Tata Inst.Fund.Res.	Bangalore India	3
Reliance Life Sci.	Munbaï India	7
Technion Univ.	Haïfa Israel	2
uc	San Francisco ca usa	2
Madison Alumin Research Foundation	Madison, Wisc usa	5
	Total	69

IV. The debate

Moral and religious positions

The respect of human life: what means respect? It starts from its commencement to its conclusion but when is commencement? Modern international human rights principles, beginning with the Universal Declaration of Human Rights of 1948, attach fundamental significance to the human being and respect for his or her

dignity as such. Such principles themselves reflect longstanding debates amongst philosophers and scholars of every cultural tradition in the world.

Amongst modern philosophers, there is an active debate about the philosophical foundation for research into, and use of, embryonic cells precisely because of the potential of the human embryo to develop into a human being with the unique and special qualities inherent in that status. Such debates are not confined to a religious and spiritual context. Philosophics of no religious opinion, and humanists approaching the issues in a wholly secular way, have expressed the need for the development of principles to guide the ethical permissibility of embryonic stem cell research and use.

Is embryo research compatible with religious beliefs as to *sanctity* of human life? Large range of opinions among different religions: for example, in the case of Islam, the use of embryos for therapeutic or research purposes may be acceptable provided that it takes place before the point at which the embryo is ensouled, i.e. from the 40th day after fertilization (cf. Aristotle).

Some branches of Christian thought (*in the Protestant tradition*) regard full human status as something which is acquired gradually, and which might therefore not be present in the early embryo. Protestant theology, however, is very diverse, and it is more difficult to find a single source of authority on this issue to which reference might be made. It is, infect, part of the Protestant ethos that moral questions are determined by the individual conscience, and there is therefore room for a variety of stances on this point. *Protestant thought, therefore, may accept that this is an issue on which Christians may have very differing views, with these differing views being compatible with Christian beliefs.*

In Judaism, the Biblical and Talmudic law holds that the full status of a human being is not present at the moment of fertilization, but is acquired after a period of post-implantation development. An important feature of Jewish thinking in this area is that embryos outside the womb, in analogy to gametes, have no legal status unless parental intent gives them life potential by implantation and pregnancy. An embryo made for ivf treatment and maintained *in vitro* without potential for implantation could therefore be donated and used for therapeutic research. This would be in line with the life-saving duty, which is a strong one in Judaism.

The most strongly argued opposition to the use of embryos for therapeutic or research purposes is to be found within the Roman Catholic tradition. In the Catholic view, a human being comes into coexistence at the time of fertilization, and the embryo is therefore considered as a human individual having the right to its own life. An individual embryo should therefore be given the opportunity to develop into a mature human being. It is an implication of this position that it is necessary to strictly control the fertilization of ova *in vitro, and it is impermissible to use supernu-*

merary embryos for therapeutic purposes. This is because the life of that embryo is sacred and it cannot be ended by any human agency.

The status of the embryo

The ethical legitimacy of performing human embryonic stem cell research depends, in large measure, on the status which is attributed to the embryo. Although there are other considerations having a bearing on the ethical question – such as the consent of the 'owners' or creators of the embryo (the parents) –, the categorising of the embryo is crucial to the question of what can be done with it. Much of the ethical debate in this area has been taken up with the question of just what the embryo is. If the embryo is a human being (or person), then our treatment of it is limited to that which we are allowed to do to other human beings. If, by contrast, it is no more than a collection of human cells, – when there are far fewer restraints on our handling of it. Mid-way views on the embryo allow for varying degrees of restraint on its use.

It is clear that the human embryo has a unique status in biological terms. Unlike any other cluster of living cells, it has the capacity to develop into a functioning complex organism that will be substantially differentiated from the entity it once was. This difference may be described as the embryo's potential – the potential to become a fully developed human being. That is, of course, only a biological fact, but it is a biological fact in the face of which we stand in moral awe. In so far as our ethical notions depend upon the valuing of human life, then the human embryo demands respect as the source of the human life to which we attach such significance. But how far should this respect go? What respect is due to surnumary embryo is it actually different of a gamete which is also 'potentially' a human being?

Therapeutic cloning leads to an embryo which can develop as a human being and therefore has to be admitted in the human community. How can we differentiate concerning the dignity attached to human person a cloned or 'normal' human being? Arguments about whether the human embryo can be considered a person have been prolonged and marked by a failure to reach agreement. In one view, personhood begins with the fertilisation of the ovum by the sperm; from that moment on, the infant, to the child, and later to the adult human being it will become. To end the life of the embryo, then, amounts to an ending of the future life of the infant and, indeed, of the child and the adult. Personhood in this view is an ethically significant quality, which human beings have at every stage of their lives, beginning with the embryo and surviving until death brings it to an end.

This view of personhood has been challenged by those moral philosophers who see personhood as being dependent on an ability to experience those features of life which lend to life its value and meaning. From the biological point of view, personal

individually can be attributed to the embryo only after the day in its early development when division into normal twins is not possible any more (up to 13 days after-fertilization). Embryos are therefore entitled to respect, but would not enjoy the personhood.

A major subject of debate is that of the potentiality of the embryo. The human embryo has the potential to become a person even if it is not yet a person. For this reason, the defenders of a protected embryo status argue that it is wrong to do to the embryo anything that will prevent it from fulfilling this potential. Opponents of this view argue in turn that the potential to become a thing does not give one that status which goes with having become that thing. Ova and sperm are components of the zygote, which later becomes an embryo and then a fœtus, but that does not mean that they can enjoy the status appropriate to a zygote or a fœtus until that stage of development has been reached. We do not accord fœtal status to sperm; why, then, accord human being status to an embryo? Moreover, an embryo resulting from *in vitro* fertilization, but which will not be implanted in an uterus, has no potential to develop into a human being. The same applies to 'embryos' made by nuclear transfer, which should not be implanted for the purposes of human reproductive cloning.

Creation of embryos for research

The creation of human embryos specifically for research purposes is to be distinguished from the research use of embryos which have been created with a view to their implantation but which have not been able to be implanted and have therefore become supernumerary. In the case of the specially created embryo, the act of creation is intended to fulfil a purpose, which is unrelated to any interest which the created organism might have; in the case of the supernumerary embryo, the organism has not initially been seen as a means to another end, but has created as an end in itself.

Is there any justification for allowing the creation of human embryos in order to derive form them stem cells, which will be used for therapeutic purposes? If the embryo is considered to have a status which goes with personhood, then this would offend the principle prohibiting the instrumentalization of persons. If it is not considered to have such a status, however, there may be no objection to its use for the benefit of others and the potential gains should be weighed against any damage that such a use would entail to any recognised value. Assuming that the embryo is not to be given the status which goes with personhood, it would be permissible to use the embryo for purposes which did not demean it. It would clearly be unacceptable for human embryos to be used for purposes which would reflect contempt for the class of embryos in general (given that some human embryos,

those that are either implanted or are to be implanted, are accorded particular respect and protection). If we cherish human life, then we must cherish all manifestations of the body; hence the universal habit of according reverence to human remains and the widespread ethical prohibitions against the causal abuse of the human body. To endorse any use of the human embryo which was not consistent with a reverence for human life would be widely regarded as wrong. Those who believe that therapeutic research on embryos is ethically permissible, might argue that the creation and use of a human embryo outside the context of human reproduction does not necessarily undetermine the attitude of respect for the human body and human dignity, provided that the purposes involved in such creation and use are purposes which we would recognise as beneficial ones. Medical uses fall into this category. In this view, it would appear to be quite consistent with an attitude of respect for human life to allow the use of human embryos at an early stage of development, well before the stage at which anything resembling a self can be said to come into existence. Such use promises to provide the possibility of the relief of a great deal of human suffering, a goal that in no sense calls into question respect for the human body.

Nuclear transfer provides an alternative way of creating human 'embryos' with the purpose of deriving stem cells, although at present this technique is unproven. This is a form of cloning, but it is not reproductive cloning, as the resulting 'embryo' is not created for implantation. Because of its purpose, it is sometimes called 'therapeutic cloning'. The attraction of this method of producing embryonic stem cells lies in the fact that these cells would be compatible with the cells of the donor of the nucleus. This presents major possibilities for autologous transplantations, in which the problem of rejection is largely overcome.

Note

1. Most of my data comes from the proceedings of the intergovernmental bioethics committee (2nd session May 2001) and from the report by Michel Revel and Alexander Mc Call Smith at the 7th session of cib (unesco).

Sjef Gevers

International standard setting in the field of bioethics

Introduction

Internationalisation is a development with a strong impact on most domains of life and most sectors of society. Health care, medical practice and biomedical research are no exception to this. The same holds for the law, also where it relates to – and tries to regulate – health care and medicine. To a growing extent, the legal norms to be applied to health care have an international background, or are even developed at the international level. In the final analysis, I do not believe that we have much influence on this development, in the sense that we could stop it, even if we would like to do so. The internationalisation of health law is inevitable. At the same time, it cannot be denied that some parts of health law are less under international influence that others, and there we may decide to hasten the pace of internationalisation or – on the contrary – to slow it down. Secondly – and here is much more to decide – the question is what kind of international standards we are looking for: do we want full harmonisation of national laws, or rather a framework of common principles for national legislation? Should we only codify existing consensus and stimulate further debate, or should we try to go further? Do we prefer effective legal safeguards, or standards with first of all a symbolic meaning?

In this paper I will elaborate on this. What are the scope and limits for developing international standards in the field health law, and in particular bioethics? Which lessons can we learn from the past? The next question then is how – taking account of past experience – we may proceed in the future. Where to find the right balance between too little and too much international standard setting?

Scope and limits

First of all a few words about the concept 'international standards'. At the international level there is no machinery that is comparable to the national legislative process. In some regions, there may be supra-national organisations with the power to lay down binding rules for their member-states, like the European Union; however, this is an exception rather than a rule. In fact, most of the standards developed internationally are guidelines, recommendations, declarations etc. However, although they are not law in a strict legal sense, they may have moral authority and obtain direct legal significance if incorporated in national legislation or referred to in court decisions. Binding international standards are primarily to be found in treaties, such as the international conventions on human rights which are law for the countries that ratified them; even then however, proper enforcement may not take place, so that in practice their moral authority may be as important as their legal status. Sometimes, one has the impression that that kind of international law can only exist by virtue of its weakness. In spite of these weak spots, there is an increasing need for international standards in the health field, be it only as a common framework for the elaboration of national law. The reasons are obvious and do not need much comment. The first is that the increased mobility of persons, goods and capital across frontiers calls for international cooperation, in particular in case of the deliberate creation of a common market, like in the European Union. More and more, this applies also to health care, as we all know. Some sub sectors of the health care system – like the marketing of drugs and medical devices, or medical research – are already so much internationalised that it is simply ineffective to regulate them only at the national level. The second reason is that many health issues are related to the fundamental values enshrined in international human rights instruments. This holds in particular for the problems raised by the rapid development of biomedical sciences. There is an international consensus that the life sciences should develop in a manner respectful of human rights. The Convention on Human Rights and Biomedicine, adopted by the Council of Europe in 1996, is a direct result of this.

In spite of the need for international standards, it is difficult to reach consensus on them also at the level of common principles. Here I am talking not so much about the down-to-earth rules establishing common markets and free trade, but about the rules trying to elaborate human rights in the field of biomedicine and bioethics where basic values are at stake.

First, there is the problem of whether there is room at all for universal principles given the social and cultural differences between countries. Although it can be hard to accommodate the search for common principles with cross-cultural or cross-

national variation, I do not believe that in the long run this is an insurmountable obstacle, and the function of international standards is precisely to bridge this variation. Even if there is disagreement, it takes place within a common normative framework which presupposes at least some degree of universality; in the final analysis, a denial of the possibility of universal standards would amount to a denial of all law. But of course, the more disagreement there is, the more difficult it will become to develop a common framework, and the more international standards are likely to reflect the bare minimum, instead of being more progressive.

A second, related problem has to do with the level of generality. To the extent that a principle is framed in more general terms, it will cover more cases; at the same time it will become less conclusive in a specific situation. This raises the dilemma whether one should only adopt the more specific rules on which there is agreement, or moving beyond them to a higher level of generality. The latter would be less problematic, if institutions would exist empowered to apply the standards to contested cases and to see to it that they are being enforced. Unfortunately, on this point (adjudication and enforcement) international law is only poorly developed.

The discussions preceding adoption of the Convention on Human Rights and Biomedicine, the most important attempt so far to develop common legal norms on bioethics, show ho difficult it is to reach agreement on different issues like embryo research, germ line gene therapy, or non therapeutic research with incompetent persons. Lack of agreement on substantive issues can also result in ambiguity concerning basic concepts, like 'everyone' or 'human being'. The protection provided by the Convention to human life before birth, for instance, depends to a large extent on how this concept (i.e. 'human being') will be interpreted at the national level. Furthermore, several principles laid down in the Convention have a high degree of abstractness, whereas an international judicial complaint procedure is lacking; on the other hand, further elaboration of the Convention may take place through protocols to it. On the whole, I believe that the Biomedicine Convention is a great step forward. Even if many countries outside Europe will not ratify it, it is an important regional document, and apart from its legal significance it has given a strong impulse to the international debate on bioethical issues.

Two cases

What other lessons are there to be learned from past experience? Let me reflect briefly on two examples: the unsuccessful attempt to develop a Council of Europe Recommendation on medical examinations preceding employment and private insurance, and the controversies concerning recent international standards in the field of human subject research.

Due to developments in the biomedical sciences, in particular genetics, medical examinations may increasingly be used as an instrument to select candidates for employment or for private insurance or pension schemes. In the competitive, deregulated economy of today this is likely to give rise to social exclusion (if not discrimination) on the basis of future health prospects. At the same time, medical examinations for these purposes have a growing potential to interfere with individual human rights, like the right to private life. This, as well as the free movement of persons and services across national frontiers, calls for convergence of national laws, first of all to limit the extent to which such medical examinations can be requested, secondly to provide protection to the basic rights of citizens where these examinations still take place. For this reason, in 1995 the Council of Europe set up a Committee of Experts with the task of preparing a draft recommendation in this field. At the end of 1996, the Committee submitted such a draft for consideration by the Public Health Committee and – finally – the Council of Ministers. At the national level, attempts to legislate on medical examinations had already evoked fierce opposition from employers and the insurance industry. When the draft was discussed in the Council of Europe, several member states voiced strong criticism partly reflecting the arguments of private industry, partly reflecting the differences between national laws and social security systems. In the final analysis, three years later, it was decided that there was insufficient support for a recommendation. The Committee of Experts was allowed to publish its conclusions, but only under their own responsibility in the form of a report. In my opinion, this field is an example where – unfortunately – international standards are lacking while they are urgently needed. It is significant that it was not even possible to reach agreement on a recommendation (which is not a binding legal instrument after all). The Biomedicine Convention has only partially made up for this in providing (in Art. 12) that tests which are predictive of genetic diseases or serve to detect a genetic predisposition may only be performed for health care purposes or for health care related research. Obviously, if it is sometimes possible to reach a compromise and to legislate on controversial issues at the national level, it is much more difficult to do so in an international context. May be the time was not yet ripe to address this issue at the international level, where the 'window of opportunity' (in political and social terms) would seem no less important than at national level.

The second example – human subject research – demonstrates that instead of too little, there may be also too much international standard setting. The number of (draft) international standards concerning human subject research is steadily increasing. Looking at international standards relating to all human subject research (and not only clinical drug trials), there is first of all the Declaration of Helsinki which was recently revised by the World Medical Association (wma). Further-

more, also the Council for International Organisations of Medical Sciences (cioms) is now updating its 1993 International ethical guidelines. At the European level – apart from the recent European Union Directive on good clinical practice in clinical trials on medicinal products – the Council of Europe Steering Committee on Bioethics (cdbi) has recently made public a draft additional Protocol to the Convention on Human Rights and Biomedicine on biomedical research. There are considerable differences in the status, scope and contents between these documents. This may create confusion, in particular where they do not support and complement each other. This is illustrated by the diverging rules on the protection afforded to persons who are not capable to give consent to participation in research. The proposed cioms guidelines, for instance, include a provision dealing with (research) interventions that do not hold out the prospect of direct benefit to an (incompetent) individual (Guideline 5); it requires that the risk of such interventions should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. However, 'slight or minor increases above such risk may be permitted when an ethical review committee is persuaded that the object of the research is sufficiently important'. According to the explanatory text 'the meaning of this standard is inferred from what various research ethics committees have reported as having met that standard', including 'the performance of additional lumbar punctures or bone-marrow aspirations in children having conditions for which such examinations are regularly indicated in clinical practice'. Unfortunately, this would seem to set hardly any limits to the interventions that can take place in non-therapeutic research with incompetent persons.

In this respect, the draft Council of Europe Protocol provides much more protection to persons not capable of giving consent. Research that has not the potential to produce results of direct benefit may only be carried out on them if it entails minimal risk and minimal burden for the individual concerned (Article 18). According to Art. 20, research bears minimal risk if it is to be expected that it would result, at the most, in a very slight and temporary negative impact on the health of the person concerned; for the burden to be minimal, it is required that it is to be expected that the symptoms or unpleasantness will be, at the most, temporary and very slight.

The recent eu-directive (on good clinical practice in pharmaceutical research) contains still other provisions on this point. It has raised controversy, because it seems to exclude any non-therapeutic research with incapable adults, while at the same time being rather liberal as far as similar research with children is concerned. How confusing the international situation is, is demonstrated by a recent report of the Human Rights Committee on compliance by the Netherlands with the un Covenant on Civil and Political Rights; in this report the Netherlands are required

to completely remove persons unable to give genuine consent from any medical experiments which do not directly benefit them!

In my view, taking account of the fundamental rights at stake, the legal response to the internationalisation of biomedical research should be developed as part of international human rights law, for instance as a further elaboration of the Convention on Human Rights and Biomedicine. Additionally, other international guidelines can play a useful role, provided they are elaborated in a transparent way, and do not go below the level of protection provided by international human rights law. However, before elaborating and publishing their 'own' standards, international organisations should really ask themselves what the 'added value' is of their contribution in terms of further convergence and better protection. A mere proliferation of standards is of no use to anybody, and may even lead to 'shopping' between different international documents.

The balance between the national and the international level

Taking all this into account, what about the main question, i.e. where and how to strike the balance between national and international standard setting? Again I will focus not on the more mundane issues like harmonisation of safety and quality standards, but on issues where basic values are at stake.

First of all, I do not believe it makes sense to attempt to harmonise the field of bioethics completely. Apart from the fact that that is impossible to achieve, some variety between countries is not necessarily bad. If there is spontaneous convergence in the future, that is to be welcomed, but one should not try to impose international norms if they run counter to deeply held national beliefs, unless there is a strong reason to do otherwise. If we try to refrain form legislating morality at the national level, we should certainly do so at the international level. Abortion and euthanasia can be mentioned as an example. Looking at national laws, there is a lot of diversity on these issues. Maybe this will change in the future (I expect it will). However that may be, for the foreseeable future the existing diversity should be respected. This is not to say, of course, that countries may try to prevent for instance abortion by encroaching on other fundamental freedoms of their citizens, like freedom of expression or freedom to travel to another country (see the controversy concerning the Irish abortion policy).

On which issues should we try to develop international standards? My answer would be: when the fundamental values articulated in particular in human rights law cannot be protected equally well by leaving the matter to national law. In other words: where the internationalisation of biomedical research, health care and society at large require international action to prevent infringements on or even gradual erosion of these fundamental values. The two cases discussed before, i.e. the protection against discrimination and encroachments on privacy in the event of medical examinations, and the protection of subjects in biomedical research, meet this criterion in my opinion. Other examples can be mentioned, such as the commercialisation of organ transplantation. Basically, this is a plea for the subsidiarity principle. However, I would prefer a qualified subsidiarity principle: it is not enough that a certain issue can be regulated somehow at the national level, what is decisive is that better protection can be achieved by addressing the matter at international level. If so, an international response to the issue is called for.

How may international standards in the field of bioethics best be developed? Here also we should adopt a differential approach. Some issues are so basic and so much agreed upon – for instance that there should be no trafficking in human organs – that full harmonisation is possible. With regard to most issues, however, the appropriate way would rather be to try to reach agreement on a framework of common principles with the possibility of elaborating parts of it in more detail later on. The Biomedicine Convention which allows for further more detailed norm setting through protocols is a good example of this. Such a gradual, incremental approach will in particular be necessary when we try to develop legally binding instruments, as I think we should at least where there is the kind of necessity mentioned before. Sometimes it will simply be impossible to achieve the kind of normative framework which is needed. Medical examinations are an example I have already mentioned. Embryo research is another one. Given the internationalisation of biomedical research international standards are required; at the same time there is basic disagreement on the degree of protection to be granted to the embryo-in-vitro. In such a case, there is nothing better to do than to try to 'muddle through', for instance – like the Biomedicine Convention does – by setting common standards and allowing national legislation to deviate from them, be it only partially and under certain conditions. However, even where international standards are more likely to codify consensus than to solve conflicts, in the long run they will do more and support the slow convergence of national approaches.

References

1. *Draft additional protocol to the Convention on Human Rights and Biomedicine, on Biomedical Research*, cdbi, Council of Europe, Strasbourg 2001.
2. Gevers, J. *Bioethics: the development of international standards, in: Bioethics research: policy, methods and strategies, Proceedings of a European Conference* (Rome 23-25 November 1995), European Commission, Report eur 17465 en, p. 129-135.
3. Gillon, R. Biomedical ethics in Europe – a need for the pobs? *J. Med. Ethics* 1993, 3-4.
4. Heinze, E. Beyond parapraxis: right and wrong approaches to the universality of human rights law, *Neth. Quarterly of Human Rights*, 1994, 369 .
5. Human Rights Committee (72nd session), *Considerations of reports submitted by state parties under art. 40 of the Covenant*: The Kingdom of the Netherlands, Geneva, 20 July 2001.
6. *Medical examinations preceding employment and private insurance: a proposal for European guidelines*, Council of Europe, Strasbourg 2000.
7. Roscam Abbing, H.D.C. The Convention on Human Rights and Biomedicine: an appraisal of the Council of Europe Convention, *European Journal Health Law* 1998, 377-378.

Govert den Hartogh

Should we welcome supranational regulation of bioethical issues?

These days the Dutch parliament discusses a draft-law concerning the use of embryos in medical research and practice. The law allows under some conditions the use of spare embryos in research. For the time being it forbids the intentional creation of embryos. It also forbids reproductive cloning. A proposed temporary ban on therapeutic cloning has been lifted by amendment. Some weeks ago a well-known biologist wrote an alarming note for a Dutch newspaper informing us that a Temporary Committee of the European Parliament, called the Committee on Human Genetics and other New Technologies of Modern Medicine, proposes in it's final report new legislation prohibiting all embryo research and (in accord with a ep resolution of 7 September 2000) all forms of cloning. The law could count, the biologist said, on a majority in the European parliament, and European law overrules national law. So the efforts of the Dutch minister of health care and the Dutch parliament had all been in vain. As it turns out, he has been ill informed, for the restrictions proposed by the Fiori-committee would only have had direct application to research paid for from European funds. (At the conference we also learnt that the committee's final report had been rejected the day before by the parliament by a large majority.) Nevertheless the case alerted the Dutch public to the question whether it is desirable to have, not only resolutions and recommendations, but also binding European rules on such controversial bioethical issues.

These issues are at present being discussed all over the world, and most of the arguments used in any discussion will return in each, at least in liberal-democratic countries. Many of the arguments will end in some plea for legal regulation, and

legal regulation will be proposed and implemented in many cases. But though the arguments are the same, the conclusions drawn by legislative authorities are not. Legal regulations on bioethical issues within the member-states of the eu, for example, show some stark differences. So should we aim at overcoming these differences by introducing binding eu-regulations? Why should we want to create such uniformity? I believe that the basic drive for this is a commitment to moral truth. If the right to life implies an absolute prohibition to kill the innocent, even when the aim is to end a dying patient's unbearable suffering, the recent Dutch and imminent Belgian legislation on euthanasia and phycian-assisted suicide are morally unacceptable, hence if we can use legal means to prevent the Dutch and the Belgians from implementing their immoral laws, we should do this. We do no longer accept state sovereignty to be an excuse for the violation of basic human rights. The eu exemplifies the strongest forms of supranational authority in the contemporary world. So why not use this powerful instrument to make the world somewhat safer for morality?

The arguments which are actually used do not explicitly appeal to this motive, but I believe they all presuppose it. Most of these arguments appeal to external effects of the legal arrangements within one country on medical practice in other countries. For example, members of the Fiori committee have pointed to the danger of researchers moving to the countries with the least restrictive rules concerning stem cell research. It is doubtful whether such a brain drain will actually happen on any significant scale or whether it should be considered objectionable as such, the eu being committed to the free movement of labour. So the argument derives whatever force it has from the assumption that the morally high ground is occupied by the more restrictive legal regimes. Suppose that at some point in the future it can be predicted that medical doctors will move to countries which still do not allow euthanasia or physician-assisted suicide in any form. Would anyone accept this as giving us even the slightest reason to impose the Dutch or the Belgian rules on Ireland and Poland?

Let the truth triumph! What could be wrong with this as a political aim?

My first comment concerns the notion of moral truth itself. In our usual thinking about truth we accept the law of the excluded third: any statement which is capable of being true is either true or false. But it need not be a form of either moral scepticism or moral relativism to recognize that in the domain of morality, there may exist, not just truth, but truths, plural. Some of our most sophisticated recent accounts of moral truth allow for this possibility. E.g., the moral truth is what, given our considered views of the largest range of moral issues, does the best job of giving a

coherent account of these. Or: the moral truth is the hypothetical outcome of an informed completely uncoerced dialogue. There may be more than one account of our considered views doing an equally good job in creating coherence, or the uncoerced dialogue may allow for several alternative outcomes.

Such 'constructivist' and non-foundationalist accounts of moral truth can be connected with a plausible view of the role of morality in human social life. If the basic function of morality is to make it possible for everyone to live a good life in a mutually adjusted way, it is conceivable that, at least as regards *some* alternative ways of mutual adjustment, there is no definitive reason to opt for one of them. The considerations for and against each of those moralities may be of equal weight, or, more plausibly, incommensurable. Another consequence of such views is that moral truth may be time-indexed: today's truth need not be identical with tomorrows. If we start from the here and now and discover that the best coherent account of our considered views requires a change of mind on a particular topic, this changed view itself (and in particular the experience we accumulate in acting on it) will be part of the data to be fed into our coherentist reasoning of tomorrow. What some people think of as a 'slippery slope' may be the essence of creative moral thought.

It is also worth remarking that many aspects of the moral truth are sensitive to context under any plausible account. Again it is not a form of relativism to accept this. For example, in the discussion about the wisdom of legalizing euthanasia or physician-assisted suicide under certain conditions, considerations concerning the way in which health care services are organized and distributed in a particular country, may make a large difference to the risks of mistake and the dangers of abuse.

Even if we do not accept the foregoing account as a correct view of the moral truth, we can still, even more plausibly, accept it as a correct view of the nature of reasonable moral belief. For the remainder of my discussion I will assume that there is only one correct answer to every specific moral question. This corresponds to the presupposition of the classical discussions of the principle of toleration, e.g. John Locke's one in the *Epistola de Tolerantia*. Locke's views, unlike for example Bayle's, do not depend on any form of religious scepticism. Locke does not deny that there is only one 'narrow path to heaven', but still he argues for tolerance. I will look at his arguments for the toleration of divergent individual beliefs and practices and see to what extent they can be translated into arguments for toleration of diverging legal regimes concerning moral issues.

The first argument which I already hinted at derives from the basic facts of human fallibility. These are central to Locke's view, and they are reinforced by his observation that the selection process of political personnel usually is not geared to picking out the people with the greatest moral wisdom. John Rawls develops these arguments in his account of the so-called burdens of judgment (Political Liberalism, pp. 54 ff.). In thinking about moral issues the relevant evidence is often conflicting and complex, hence hard to assess. Even if we agree about the relevant considerations, we may disagree about their weight. All the concepts we use are vague and subject to hard cases, hence reasonable persons may differ on their application. The way we assess evidence and weigh values is shaped by our total life-experience, which is never all encompassing; 'total experiences must always differ'. Finally, no system of social institutions can realize to the fullest extent the full range of moral and political values. 'There is no social world without loss.'

If we apply Rawls' view to bioethical issues, it is highly relevant that, as I noted, usually the whole spectrum of relevant considerations, of initially plausible views and arguments, will be presented on the public forum in each liberal-democratic society, if only the free press is doing it's job. Weighing these considerations and arguments, and designing a legal regime which recognizes their force as best as possible will be an immensely complex task which therefore will be highly sensitive to the 'burdens of judgment'.

Within each society it will often be necessary to decide on a specific legal regime, because people should be in a position to know how they will be treated, which rights they can claim etc. Considerations of legal certainty require some such decision to be made. But this reason does not extend to the supra-societal level (if you stay within another country you should expect to be treated by its standards) and then fallibilism requires us to accept that the view which carries the day elsewhere is not unreasonable and may even be right. Some people argue that the democratic process as such, even if it is not an implementation of an ideal dialogue, at least is some approximation to it: the chance that a large democratic majority has it right, in their view will be greater than the chance that a single individual has it right. Even if we accept that (to my mind not very convincing) argument, however, it does not follow that the greater the number of people involved in the decision process, the higher its epistemological status. For enlarging the number of decision-makers beyond some point may also strengthen those aspects of the decision process, e.g. the opportunities for logrolling, which also increase its distance from an ideal dialogue. You can expect an earnest exchange of information and argument in a committee of ten, but hardly in a rally of thousands.

Let me quote John Locke in order to introduce my next argument. 'Neither the Profession of Any Articles of Faith, nor the Conformity to any outward Form of Worship…can be available to the Salvation of Souls, unless the truth of the one, and the acceptableness of the other unto God, be thoroughly believed by those that so profess and practise. But Penalties are no ways capable to produce such Belief. It is only Light and Evidence that can work a change in Men's Opinions…'. Generalizing his point from religious faith to moral views: if you coerce a person to live by a truth he does not endorse, such a life has no value whatsoever to the person who lives it. It is also a form of insult and disrespect to an autonomous person who has sincerely, even if fallibly, considered the question how to live. Occasionally this argument can indeed be transferred to the intersocietal level. For example at the present time almost 90% of the Dutch population believes that there are some conditions under which doctors should be legally allowed to grant a patient's request for euthanasia. Demonising the Dutch legal regime on euthanasia as a 'culture of death' and by comparisons with the Holocaust, surely does no justice to the complex issues to which the Dutch policy tries to find an answer, and it is insulting, not only to the Dutch society but also to the large segments of reasonable people within one's own society who are prepared to seriously consider similar answers to similar problems. Most of the time, however, the legislation in force does not so clearly reflect a general conviction shared by a large majority, it may rather depend on highly contingent political matters, e.g. in the maintenance of a coalition government, and therefore occasionally even reflect a minority viewpoint. But in that case another aspect of Locke's argument becomes relevant. For he does not only require an inner persuasion of the mind, but he also requires this persuasion to be formed in the proper way. 'For there being but one truth, one way to Heaven; what Hopes is there that more men would be led into it, if they had no Rule but the Religion of the Court, and were put under a necessity to quit the Light of their own Reason, and oppose the Dictates of their Consciences, and blindly to resign up themselves to the will of their Governors? In the variety and contradiction of Opinions in Religion, wherein the Princes of the World are as much divided as in their secular Interests, the narrow way would be much straitened; one Country alone would be in the right, and all the rest of the World put under an obligation of following their Princes in the ways that would lead to Destruction; and that which heightens the Absurdity, and very ill suits the Notion of a Deity, Men would owe their eternal Happiness or Misery to the Places of their Nativity.' As I already said, in bioethical matters often a decision has to be made, some way or the other, and in such case there is no alternative but to make it by following the usual procedures, and thereby allow it to depend on an accidental balance of power. But that some

point of view for some such reason can command a majority of votes in the European Parliament is hardly a consideration sufficient to legitimise superimposing it on national law. The minimum requirement we should make for 'light and evidence' as a necessary input in the democratic decision making process concerning bioethical issues is that such discussion making is preceded by free public debate. At present there is an intensive ongoing public debate on many issues, in particular as regards medical decision at the end of life, the use of new reproductive technologies and of new insights in genetics. But the main and in some cases almost the exclusive arena of debate is the national community. Surely bioethics take the international literature into account, which for European bioethics means that they often depend on the same standard staple of American books. But the actual engagement of argument and counter-argument which feeds political decision largely takes place in the national media. This is not only the main arena of discussion, but also the sphere in which the experience of living by some particular legal regulation is accumulated and evaluated. It may be a matter to be deplored, but at present there really is no equivalent to these collective learning processes on the community level.

That is not to say that we cannot and should not learn from each other. This brings me to my last argument for toleration which cannot be found in Locke's Letter, at least not in an explicit form, but is the core of the argument in John Stuart Mill's *On Liberty*. An adequate learning process requires a variety of learning experiences, and hence of 'experiments in living'. If the way we live is the only way we know of, our conviction that it is the right way will only be 'a dead dogma, not a living truth'. For this reason we should welcome the fact that different countries are at present dealing in different ways with the problems posed by severe suffering at the end of life. Of course, this presupposes a willingness to seriously study the actual experience each of these countries is going through. With the Dutch experiments in partial legislation and public control of euthanasia we have been rather unlucky in this respect. As Margaret Battin shows in an amusing paper, almost all the euthanasia-tourists coming to the Netherlands, whatever their views on arriving, firmly intended to find them confirmed and invariably succeeded. As a result many of their descriptions of the Dutch medical and legal practice are almost inrecognizable to the insider. To put the matter very briefly: any medical practice of actively ending the lives of dying patients in severe and unrelievable suffering, whether it is legalized or not, is open to two risks: on the one hand doctors may sometimes end the lives of patients who did not make an explicit, fully voluntary, and well-considered request. On the other hand doctors may accept free requests of patients who could, with

appropriate care, still have had some lifetime of acceptable quality. The most common criticism of the Dutch experiment with legalization is that it increases the first risk; even the us Supreme Court thought it did. But there is very little evidence that this is true. On the contrary, there is growing evidence that the opposite is true: this risk is greatest in countries in which the practice exists but is not legally recognized in any way. (It is to be deeply deplored that until now we have so very little comparative factual information about these matters, while millions of research money is available for the smallest chance to increase our diagnostic and therapeutic capacities. Do we not want to know the truth?) So it may be that the real dangers involved in the Dutch experiment are of the second type. And in this respect it should also be conceded that the Dutch themselves, however understandably, have been too much on the defensive as regards foreign criticism.

So in arguing that we should apply the principle of subsidiarity to the legal regulation of bioethical issues and that we hardly have any need for European legislation, I do not want to suggest that we should not learn from each other to a far larger extent than we do at present. (I have to confess that in preparing this paper I have been ashamed to realize how little I know of the French discussion and the French experience.) But we should fight our parochialism by enlarging our interest in each other's principles and practices, and not by trying to replace them by uniform supranational standards.

Shouldn't we welcome at least the attempt to define the common ground, as it has been done in the European Convention for Biomedicine and Human Rights? I am not at all denying the importance of the background of shared moral beliefs for the vitality of the intersocietal discussion which I have pleaded for. But this background should be simply allowed to exist, it need not be defined, and surely not by any gremium in which matters are liable to be decided by negotiation as much as by argument. If some view, e.g. on the creation of human embryo's for the purposes of stem cell research, is at present a minority view within every member state, it may have more adherents than a view which is a majority view in some states, and, what is more, we may eventually discover it to be required by the best coherent reconstruction of our shared moral convictions.

Summary of the discussion on internationalisation of norms and regulations in health care

Before lunch there was some time for discussion and debate on the basis of the three presentations given by Prof. Jean-Didier Vincent, Prof. Sjef Gevers en Prof. Govert den Hartogh. The chairman, Prof. Johan Legemaate proposed several items for discussion that had been brought up in the previous lectures. Prof. Vincent for instance had mentioned the influence of the mass media in either creating confusion or clarity among the general public and the impact that may have on the perception of new technologies. The same speaker wanted international guidelines not to be coercive, but permissive. This topic relates to Prof. Gevers lecture in which he asked what kind of standards we should have at the international level. Prof. Gevers pointed to the fact that in certain areas there are many international standards, even conflicting with each other. In general he pleaded for more international standard setting in the field of bio-ethics. Prof. Den Hartogh argued in contrast that there might be a value in having different national approaches.

Prof. Wladimiroff referred to Prof. Gevers lecture about national and international standard setting and his argument for more harmonisation in the field of bio-ethics. He pointed to the flagrant intrusion of the principles of subsidiarity he had experienced the week before, regarding the issue of embryo research at the European level. He asked Prof. Gevers and Prof. Hartogh to comment on this. Prof. Gevers stressed that on neither level one should try to fix morality by law. Nevertheless there is reason to try to achieve consensus on some common principles in some fields. Medical research is a field that according to Prof. Gevers comes into consideration very strongly. We cannot deny the international dimension of medical re-

search it self, after all. Furthermore, human rights might be at stake to some extent. Prof. Legemaate asked whether Prof. Gevers sees differences between his own view and the view of Prof. Den Hartogh. Prof. Gevers affirmed this impression, but he wondered whether this was due to Prof. Den Hartogh's approach. Contrary to what Prof. Den Hartogh suggested, law should not be about moral and philosophical truth. It should be much more modest: practical wisdom or an ethical minimum. This makes it easier to strive for a common framework. Procedural solutions might be an option where substantive answers cannot be given. Prof. Vincent had asked about the status of the embryo. As far as the law is concerned, however, this question, according to Prof. Gevers, need not to be answered immediately at any price. A procedural solution might be sufficient for the foreseeable future, given the impossibility to reach consensus now.

Prof. Den Hartogh did not understand Prof. Gevers position. On the one hand he claims that law is only about minimum standards, on the other hand his motivation to strive for this is a better protection of human rights. According to Prof. Den Hartogh it is the interpretation of what human rights are that is at stake in debates about embryo research, abortion and euthanasia. Prof. Den Hartogh accepts Prof. Gevers first argument for international standardisation, namely the international dimensions of medical practice itself. The human rights issue, per contrast, should be seen as a reason to support the principle of subsidiarity.

Prof. Vincent pointed out again that the status of the embryo is the major issue. The use of embryos from abortion is as unproblematic as the use of cadavers. If an embryo is created for in vitro fertilisation it has an ethically different status from one specifically created for therapeutic use. The parents are the owners of the in vitro created embryo. In case of therapeutic cloning, the embryo is created for the use of the patient who gives the nucleus. The nucleus gives the genetic information for the embryo. That is why the patient should be considered the owner of the embryo. These are ethically important differences. If one cell is taken from the blastocyte the embryo is dead. Duplication can occur until the 14th day; thus personality can only exist after that period. After 14 days the status of human being might be given to the embryo. The biologist should bring such scientific considerations into the debate.

Prof. Tubiana remarked that the bible gives a definition of the embryo. An embryo is always in the uterus of the mother. Isolated cells outside the uterus of the mother are not an embryo. The main criterion for the evaluation of medical technologies according to him should be the question whether it reduces the burden of illness. Therefore scientific knowledge must precede and be a basis for discussion on ethical issues. The question is whether alternatives exist for stem cells. He proposed to sign a resolution about the potential benefit and the need for more research on stem cells.

Prof. Den Hartogh remarked that if you take the ethical position that the main aim is the minimisation of human suffering that does not allow you to avoid the question of the status of the embryo. If the embryo was indeed a right bearer than it becomes ethically problematic to use his body. But Prof. Den Hartogh agreed with Tubianas definition of the status of the human embryo. Prof. Vincent agrees that there is no embryo outside the womb, because these cells have no potential to develop into a human being.

Prof. Meijler from Amsterdam, who was a practising cardiologist before his retirement, disagrees with Prof. Den Hartogh about comparing the issue of embryos with euthanasia. In principle a definition of an embryo can be given, but it is impossible to define the requirements for legitimate euthanasia such as 'unbearable suffering'. You cannot make a law based on vague concepts and on circumstances you cannot define. We cannot even define a procedure and there is no possibility to check afterwards whether euthanasia was rightfully administered. According to Prof. Meijler it is a disservice to the necessary research on human embryos to combine it with the highly debated procedure for euthanasia. Prof. Den Hartogh clarified that he meant to say that the more controversial an issue is, the more reason you have for toleration. He didn't mean to judge the acceptability of an issue. Both issues are debated and there is no clear-cut moral truth. That is why he pleaded for toleration. Still he did not agree with Prof. Meijler's opinion about euthanasia, for there are substantial requirements mentioned in the Dutch law. The question is how much clarity you need to regulate such issues in general. Prof. Vincent stated that science should not become an ideology and that there are some limits to the subsidiarity. Prof. Gevers defined the legislation on euthanasia as being largely procedural for the reasons Prof. Meijler had explained. In Prof. Meijler's view we should not even try to harmonise laws on decisions on the end of life, but we should try to develop a common framework for embryo research.

Prof. De Beaufort asked Prof. Den Hartogh about the role of public debate. The same issues are being discussed over and over again. Is it because we need these debates to go through them, like we need to go through puberty? Shouldn't we profit much more from what has been said in other countries? And what is the role of mass media, there seems to be a general attitude against technology? According to Prof. Den Hartogh it is not a matter of either/or. We have to go through a learning process in which the people of that particular community are involved. But on the other hand we should take into account, to a far larger extent than we do, the experiences of other countries. Prof. Vincent sees a sort of complicity between some scientists and some mass media in that they are both against technology.

Prof. Seligman stated that ethics and science should go together. According to him it is an oversimplification to consider the status of the embryo the only impor-

tant ethical question concerning the use of embryos. A vast majority of the ethics committee allowed research with spared embryos. There was however only a small majority allowing therapeutic cloning. An important reason against therapeutic cloning was the fear of a commercialisation in order to get the ovaries. Also scientists who expected much from adult stem cells were critical about therapeutic cloning. Prof. Vincent agreed that he had oversimplified the matter and thanked Prof. Seligman for his precision.

Prof. Drenth explained that there are two schools in sociology of law. One is that laws follow the attitudes and opinions of the people. Given the existing differences and the requirement of tolerance that would lead to pluralism. The other school is that laws do not follow but create values. Laws have an educating and transforming function. This view leads to little acceptance of differences in Europe, particularly since the move towards the international civic society. Prof. Drenth proposed some reservation with regard to pluralism. Within one country there is a plurality of opinions as well, but nevertheless we strive for harmonisation based on a democratic majority. Prof. Den Hartogh believed that the educating task of law exists only within limits. Lawmakers can never be too distant from values that live within their society. His own point however was not sociological but normative. Even if the lawmaker was completely free to impose whatever values he wants, he should not do so because of the argument for tolerance. According to Prof. Gevers law cannot only be a reflection of opinion, it should have an important symbolic and educational function. Most international law is meant to be precisely that: a guideline. Prof. Legemaate suggested that it should depend on the issue in question which school we adopt. Prof. Gevers agreed with that. Prof. Den Hartogh added that it should be clear for the European parliament which strategy to adopt on which type of issue.

At the end of the discussion the president of the Netherlands Academy of Arts and Sciences promised to work out a concept for a resolution on the use of stem cells that could be discussed in the afternoon.

Presymptomatic genetic diagnosis

Hans Galjaard

Predictive DNA testing; technology and social acceptance

Introduction

Research and application of (molecular) biology has become subject of a broad public and political debate. The reason is that modern dna technology is of considerable importance in various disciplines and affects different aspects of societies. At the same time there are great concerns about possible negative consequences and ethical aspects especially in case of a combination of gene modification and artificial reproductive methods. Despite the headlines in the newspapers and the mostly negative approach in the media it is fair to say that dna technology has already contributed significantly.

As a member of the International Bioethics Committee of unesco I have experienced that the following five issues are of most concern: human genes, genetically modified plants, transgenic animals, embryonic stem cells and presymtomatic DNA testing. In addition, representatives of the developing countries fear that the already existing gap with the wealthy countries in terms of gross national product, literacy and infant mortality and future prospectives will further increase because of the rapid incorporation of information- and communication technology and biotechnology into Western societies. Up till now medical technology and fundamental research in molecular biology has been mainly a matter of developed countries and the same is true for the development of clinical genetics services. During the past few decades the latter were mainly focused on the early diagnosis

and prevention of congenital malformations and rare monogenic diseases expressed in childhood.

The last few years there is a shift towards the elucidation of the genetic background of frequent multifactorial disorders in adulthood, such as cancer, cardiovascular diseases, diabetes, asthma and neurodegenerative disorders including dementias. Although much has been accomplished in terms of treatment and repair of some of these diseases, the main causes of mortality in the Western countries have not changed significantly during the past decades. The increase in mortality due to cancer is mainly related to the ageing of the population and this factor also results in a worrying increase of patients with (Alzheimer) dementia. For most of the disorders mentioned above the molecular etiology and pathogenesis is still unknown. With the advances in human gene mapping and a better understanding of the function(s) of the encoding proteins it is hoped that in the future new therapies will be designed which are directed specifically to a defective molecular mechanism. Since most of the diseases in adulthood are thought to be the result of complex interactions between dna sequences in several genes and environmental factors it will take quite some time before effective means of treatment and/or prevention will be available. Until that time more and more dna sequences will be found to be associated with an increased risk of a specific disease. This will offer new perspective for 'predictive medicine' but will also raise new psychosocial and ethical queries which have to be addressed.

Prediction of health risks

In the beginning of 2001 a first draft of the complete human genome was published. Contrary to earlier expectations humans 'only' have some 32,000 genes but since many of those show alternative splicing more than 100,000 proteins are awaiting the elucidation of their molecular interactions and intra- or extra cellular functions. In many instances homology studies of lower organisms will be of great help, but about one third of the predicted human proteins have no match in other organisms.

The increasing knowledge about the human genome, the improvement of dna analysis combined with family studies have revealed gene sequences which are associated with an increased (and sometimes a decreased) risk of specific multifactorial disorders. In some instances the risk is only slightly higher than the average population risk, in other cases like in various forms of cancer a specific gene mutation leads to a considerable health risk. In the evaluation of a predictive dna test in clinical practice it is of course also important what the á priori risk for a specific disease is and whether the finding of an increased genetic risk can be followed by preventive measures. In general, clinicians prefer a diagnosis to be made as early as

possible and the same might be true for the establishment of an increased genetic risk. In case of diabetes or cardiovascular diseases early adaptation of one's life style might have a beneficial effect. In other instances like in hypercholesterolemia timely administration of drugs may delay or prevent clinical symptoms. The problem of predictive dna testing is that it only provides a risk and no certainty. There is nothing wrong with adapting a 'healthy life style' even if it turns out to be 'for nothing' but unnecessary medicalization should be avoided. Most of the associations between specific gene sequences and the risk of a particular disease are still in an experimental phase. There are, however, some predictive dna tests which are already used in clinical practice:

a. Colorectal carcinoma

The risk of colorectal cancer for people of > 50 years is 1-3%. The risk becomes considerably higher for people with one or more affected relatives (10-20%). Such at risk people may choose for bi-annual colonoscopy which enables the early detection of a tumor and its timely surgical removal. During the past decade a number of dna mismatch repair defects have been found to be associated with a considerable increase of the risk to develop colorectal cancer (life long risk 75-90% for male carriers and 30-60% for females). On the basis of a family history of colorectal cancer healthy relatives may request dna testing. When a normal result is found they can be reassured; if they carry a mutation in one of the five dna mismatch repair genes associated with colorectal cancer they are at high risk and are likely to chose for regular gastro intestinal follow-up. It has been estimated that such a follow-up and timely surgery extends the average life expectancy with 7 years. A disadvantage of this approach is the psychological burden and the medical risk of regular colonoscopy and the fact that a life long medicalization may turn out to be useless because even with a high risk a person may not develop a tumor.

b. Breast cancer

The cumulative population risk for breast cancer is 1 in 10 for women. In most Western countries regular mammography is offered to all women of > 50 years although its effectivity has recently been questioned. 5-10% of all breast cancers is of a hereditary nature and in the mid nineties mutations in two genes (brca 1 and 2) were found to be associated with a considerably increased risk of breast cancer and/or ovarian cancer (cumulative risk of 60-95%) Such mutations are mainly found among women with a family history of early onset breast and/or ovarian cancer. Because of the hereditary nature of the gene defect healthy female relatives of a patient often in several generations are eligible for a dna test. In our own centre 50-60% of close female relatives of a patient with a hereditary form of breast cancer

request dna testing (3-5 per patient). Sometimes family studies give rise to relational, psychological and ethical problems. Relatives to be tested will usually be informed by the patient who was found to be a carrier. But some people do not want to be informed about a possible risk and others refuse to be tested. Their autonomy should of course be respected but at the same time there is a responsibility towards possible carriers whose health may be at stake.

Women who are a carrier of a brca mutation may opt for regular follow-up by mammography or they may opt for the radical approach of preventive mastectomy and ovariectomy. The latter approach has been heavily criticized by colleagues in France and some other countries because of its irreversible nature and the uncertainty of its effect. Also cultural aspects seem to play a role. In our Rotterdam centre 54% of female carriers undergo preventive bilateral mastectomy and 86% undergo ovariectomy after completing their progeny. A follow-up study during about 4 years among two groups of 100 female carriers indicate that among those who chose for regular follow-up 8 developed breast cancer whereas none of the women who underwent mastectomy/ovariectomy so far developed cancer. The future will reveal whether these differences are consistent and hopefully new ways of treatment prevention will be developed for women at high genetic risk.

Another problem in the search for brca mutations is the fact that the American company Myriad has patented the dna test for brca 1 and 2. In the usa this has been accepted but in Europe it is still a matter of debate. Not only does the patent imply that tens of dollars extra must be paid for each test it also sets demands on referral of patient material when the usual mutations are not found.

Several European centres and countries consider the unnecessary increase of diagnostic costs and limitations of the way of testing unacceptable; they rightly consider a patent of a diagnostic assay without any innovation 'against public order.' More in general the French and German government have asked the United Na-tions and wto to ban patents on dna sequences with unanimous support of the unesco Bioethics Committee.

c. Incurable multifactorial diseases

Gene linkages associated with an increased risk are also found for incurable diseases. Here, the psychosocial and ethical issues are even more pronounced. Which use would it be to find out by dna testing that a person has a 1:50 risk of developing schizophrenia compared to a 1:200 population risk? The same applies for risk factors like Apo E variants for Alzheimer dementia though the á priori risk is much higher among the aged. Yet, a British survey among adult children of Alzheimer patients indicated that three quarter of them would undergo a predictive dna test if this were available. Similar results were obtained more than a decade ago in a

survey among possible carriers of another untreatable neurodegenerative disease, Huntington chorea. However, from the time when the responsible gene mutation for this disease was found (1993) only 10-15% of high risk relatives actually underwent dna testing.

Extensive psychological studies among relatives of Huntington patients revealed that the minority requesting predictive dna testing are people who feel they cannot live with uncertainty. They justify testing by their wish to be informed about a future health risk and to plan their future. The large majority who does not want to know hope they will not develop the disease symptoms; for them hope is a strong motivation to live on despite the 50% chance of developing the same deteriorating disease as their father or mother. These observations show that it is impossible to define one rule that would satisfy all counselees even in the case of incurable diseases. Some people want to know, others do not and both groups have arguments that are related to their background, life situation and future. The main guidelines in bioethics are 'do good', 'do not harm', 'do justice' and 'respect autonomy'. The specific problem in clinical genetics is however that different relatives often in several generations are involved and their interests may be contradicting.

Suppose an adult son of a father with Huntington's disease does not want a predictive dna test. His right not to know should of course be respected. His wife respects her husband's attitude but when she becomes pregnant she does not want their child to have the same fatal disease as the grandparent, so she asks for prenatal dna testing. If the fetus would be affected the couple might decide to interrupt their pregnancy thereby preventing the birth of a child bound to contract an untreatable neurodegenerative disorder. At the same time the mutation found in the fetal cells can only be derived from the father. As a consequence the right not to know of the father is abolished by the right to know of the mother. What is right, what is justice and whose autonomy should be respected? Sometimes new technology raises problems which cannot be solved by the usual ethical guidelines. With further advances in predictive medicine more attention should be given to the psychosocial aspects. How do young adults react to the knowledge of being at risk of a severe disorder many years later? Does early medicalization influence the motivation to study and work and does it affect relationships? Also, the knowledge about increased health risks by third parties may restrict social opportunities. Some countries like The Netherlands have legislation that prevents life insurers (below a limit of about $ 150,000) to ask for results of genetic testing and the same applies to employers. In other countries this is still matter of debate because insurers are afraid of unequal knowledge about health risks. It seems that in these important matters agreement and uniformity in legislation at the European level is desirable.

Future developments

Many of the problems described in the previous section could be avoided if effective means of treatment or prevention would be available. Most researchers are optimistic about future developments and believe that new vaccines against major diseases in the Third World and new medicines against the major diseases in the wealthy countries will become available. Theses new medicines will be targeted to the specific molecular defect that underlies a particular disease. It is also expected that new and harmless viral carriers will be developed which will enable gene replacement therapy.

The main issue is the time schedule for those new developments. The optimists point to the enormous opportunities of micro array technology and bio-informatics. The expression of tens of thousands genes can be simultaneously analysed and the same is true for protein analyses. Also the molecular effects of tens of thousands mutagenic /carcinogenic chemicals can be effectively tested. Epidemiological studies will reveal associations between genetic disposition and environmental factors. Research leaders in pharmaceutical industry expect that major advances will already be made during the next 10-15 years and that pharmacogenetics, where the effectivity and side effects of drugs will be individualized on the basis of prior dna studies, will already become clinical practice within a few years. Others, like myself, believe that it will take considerable more time before effective treatment or prevention of the major multifactorial diseases will be realized. The basis for future therapy is the understanding of the molecular etiology and pathogenesis and the past has shown that this requires a long period of persistence. The elucidation of the molecular defect underlying a variety of monogenic diseases, from lysosomal storage disorders to familial hypercholesterolemia and from cystic fibrosis to frontotemporal dementia has taken several decades of work by many research groups. And the etiology and pathogenesis of multifactorial disorders is much more complex.

Even when the molecular etiology is understood it does not automatically imply that an effective treatment can be developed. The responsible gene defects in Huntington's disease, X-linked mental retardation and Duchenne muscular dystrophy have been resolved more than a decade ago but no treatment is in sight and the same is true for the hemoglobinapathies the molecular pathogenesis of which is already known for several decades. Even when the molecular basis for a new medicine is patented it takes an average of 10-12 years before a medicine will be available on the market. Since only 1 in 10 new medicines are (highly) profitable the average costs of development of a successful medicine are between $ 500 million and $ 1 billion. This raises of course the question of equal accessibility to treatment or prevention in the future both within wealthy countries and at a global level.

In the unesco and the Human Genome Organization the suggestion has been made to create a global fund where the pharmaceutical industry and biotechnology companies would put a percentage of their profits to bridge the gap between the wealthy countries and the Third World. In addition to the continuation of basic research and clinical care maybe one of the main tasks is to support people with severe health risks, to avoid exaggerated expectations of technology and to create at a global level more equity in income, education and health care.

Anne Fagot-Largeault

Presymptomatic genetic diagnosis: ethical aspects

Introduction

In the following I shall rely on a crucial distinction between presymptomatic diagnosis of a muted gene, the mutation of which is known to induce a given disease, and presymptomatic diagnosis of a genetic trait which is known to participate in a predisposition to a disease. I shall choose my examples from psychiatry for two reasons. First: the burden of psychiatric disorders is heavy on health systems, as evidenced by the who 2001 Report on Global Health (recently published), pointing to schizophrenia, depressive episodes and suicide attempts (especially in teenagers) as costly worldwide plagues. Two ethical imperatives are appropriate here: (1) one should aim at better prevention and better treatment of such conditions, and (2) one should resist the temptation to dream of eradicating such conditions (Europe has unfortunately had recurrent experience of discriminating against, and doing away with, populations of mentally handicapped people). Second: in the hospital wards in which I work there is a research unit of genetic psychiatry. A team of researchers has followed for a number of years, and keeps following, a double cohort of schizophrenic patients and their families, and of maniac-depressive patients and their families, for the purpose of genetic research – that is, for the time being, of a type of research that does not yield any direct medical benefit to people included in the protocols.

When a muted gene causes a serious disorder, it makes sense to aim at preventing the disease from appearing or spreading in the population. Some diseases including mental disorders, such as Huntington's disease, are now accessible to genetic diagnosis (including prenatal diagnosis) long before any symptoms become apparent. The diagnosis does not as yet lead to effective (etiological) therapy, only to the knowledge that the origin of the disorder is organic (rather than psychogenetic). The current consensus is that any diagnostic process with a view to detect the muted gene must be accompanied with appropriate psychological help. This was extensively studied in the years 1980 when the test for Huntington disease became available. It is generally accepted that prenatal positive testing may result in a decision to terminate the pregnancy, if the couple wishes so. When the diagnosis is made available to persons who were already born, the rationale is that, should the result of the test be positive, they would not want to pass the muted gene on to the next generation, that is, they claim a right (or duty) to responsible procreation.

The Huntington case is especially clear, because the transmission of the gene is dominant with complete penetrance, which allows sure predictions. Also rather consensual is the case of trisomy, recognized as a handicap making termination of pregnancy permissible if the mother wishes so.

Other more difficult cases offer ethical dilemmas, such as cases of fragile X, or of a 'gene of deafness'. The prenatal detection of a fragile X does not allow a confident prediction of mental retardation, because the degree to which the handicap will be expressed cannot be exactly predicted. A muted gene responsible for impairment of hearing (deafness in the newborn) was recently identified. A prenatal diagnostic test is now available. Can it be used ethically? This has been the object of a controversy in France. Associations of persons with hearing impairment have argued that being deaf does not make you *diseased*, but *different*; that predicting that a baby will be born deaf allows the parents to prepare for educating him/her in the language of signs; that the language of the deaf, like any other language, allows for children to develop normally. They will have to be raised within a different culture, that is all. In that context pnd was offered in France, at the Pasteur Institute, with so much precaution and warning that only very few couples (two in one year) felt allowed to ask for the termination of the pregnancy.

The situation is very different with the possibility, now arising, to detect vulnerability factors to various conditions such as hypertension, obesity, progressive impairment of hearing, and possibly tomorrow schizophrenia. For several psychiatric diseases, such as schizophrenia, infantile autism, obsessive-compulsive disorders, manic-depressive disorders, and some addictive disorders, family studies have evidenced that there exists a familial aggregation of cases. Twin and adoption studies regularly tend to prove that the influence is genetic rather than environmental.

However, current researches also show that factors other than genetic may play a role in the propensity of some patients to develop the disorders. In other words, such disorders are multifactorial disorders, due to a variety of genetic vulnerability factors interacting with environmental factors and with developmental factors. Many positive results of genetic linkage studies for mental conditions have not been replicated, which suggests that the genetics of such conditions is the genetics of 'normal' genes, on which rest interindividual differences and human diversity. Should one anticipate that genetic (prenatal?) testing for vulnerability factors to conditions such as having delusions or a depressive mood will be possible, it is not a straightforward ethical task to envisage in what sense making the test available could best be beneficial for the individuals and families who suffer from schizophrenic or melancholic pathologies.

The psychiatric condition for which genetic research looks most encouraging, so far, is infantile autism. Two research consortiums in the 1990's have independently pointed to the same area in the human genome as areas which might be involved in the organic determination of autism. Such preliminary results have so far produced at least one beneficial effect. It silenced those who had favoured an exclusive psychogenetic hypothesis of the causation of autism, and who had recommended (and practised) an exclusive psychotherapeutic approach of treatment – that is, it relieved the burden of guilt that had been put on the parents of autistic children, on account of bad nursing. (However, one may argue that the burden of guilt is no less, if you pass detrimental genetic factors on to your children.). So far, the only perspective that can be offered to families or associations in the case of autism is: *empirical therapy, and more research*. That is more or less the situation with all mental disorders, with the difference that, for autism, no specific therapy has been proved better than another, so that currently empirical mixtures of therapies are recommended. By contrast, we do have effective chemotherapy for schizophrenia, manic-depressive episodes, obsessive-compulsive disorders; some form of psychotherapy have been proved effective on mild depressive disorders, while electroconvulsovotherapy (ect) has been proved effective on severe depressive disorders. In other words, what is offered in those cases is: s*ymptomatic therapy and more research*. Ethical problems involved in recruiting patients for research protocols aiming at the identification of genetic factors of vulnerability to psychiatric conditions are well known:

1. the research is without direct benefit for the patients included;
2. it may be doubted that such patients are able to give competent consent to genetic investigations;
3. discriminating between individuals with and without some genetic defect supposedly involved in the predisposition to (for example, schizophrenia) may be detrimental to the peace of families;

4. strict confidentiality is often difficult to guarantee in epidemiological studies, and one remembers with terror the misconducts that were committed in the 70's when researchers were looking for the so-called 'chromosome of crime', resulting in undue stigmatisation of vulnerable populations.

Let us now envisage the possibility (as yet fictitious) that a presymptomatic diagnosis of *genetic risk factors* for schizophrenia, manic-depressive disorders, or obsessive-compulsive disorders, might be made available. What could we do with it?
It would have to be proved that such a diagnosis is helpful in some sense:

1. it might prove helpful in allowing the bearer of the predisposition (or his family) to be prepared and watch for early signs of a manifestation of the disease (but anticipation could also cause anxiety);
2. it could prove helpful in allowing psychiatrists (or even general practitioners) to better adjust treatments to particular genetic profiles;
3. it would probably teach us a lot on the interaction between genetic and environmental events in the outburst of the episodes (that benefit is primarily for research);
4. eradicating the episodes, or even the disease, does not appear as an acceptable or realistic objective. Thus, what one might hope for is: *better management and no eradication*.

Conclusion

The issue of the 'cure' is controversial among the psychiatric community. The reason is this. When you diagnose schizophrenia, or mdd, or ocd (or a propensity to commit sexual aggressions, a case for which the French law requires compulsory psychiatric treatment), either you consider that the whole person is diseased, dysfunctioning, misconstructed (from bad genetic lottery, or from wrong existential choices), and, assuming that you know the cure, you would want to reconstruct the whole person from the bottom, either genetically or psychologically (educationally). Or you consider that the person is an autonomous subject, afflicted with a disease; in which case, you need the cooperation of the subject to make changes (genetic or cellular therapy, as well as chemotherapy or psychotherapy); and applying a treatment does not spare the person the task of integrating the change into his/her personality. From that point of view, *even gene or cell therapy would be symptomatic*. Most psychiatrists today deem that they are not invested with the mission to cure or re-educate persons; they merely want to treat (and hopefully alleviate) diseases.

References

1. Advisory Committee on Genetic Testing, Report on Genetic Testing for Late Onset Disorders, London: acgt, 1998-06.
2. Boué André, *La médecine du foetus*, Paris: Odile Jacob, 1995.
3. Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé, Génétique et médecine. De la prédiction à la prévention, Avis et rapport n° 46, oct 1995; Consentement éclairé et information des personnes qui se prêtent à des actes de soin ou de recherche, Rapport et recommandations n° 58, 1998. www.ccne-ethique.org
4. Fagot-Largeault A. & Bellivier F., 'Génétique et psychiatrie, questions éthiques', *Psychiatrie française*, sept 2000, xxi (2): 75-82.
5. Grenier-Lépinay Y., *Le diagnostic prénatal – ses implications psycho-sociologiques et éthico-philosophiques*. Une étude comparée France-Québec. Thèse de doctorat de philosophie, Paris: Université de Paris-xii, 1991. Cette thèse a reçu le Prix d'Ethique Maurice Rapin 1991.
6. Klarsfeld A. & Granger B., 'Faut-il dépister les prédispositions aux troubles psychiatriques?', *Médecine/Sciences*, 1991, 7 (1): 58-61.
7. Leboyer M., Bellivier F., Nosten-Bertrand M., Jouvent R., Pauls D., Mallet J. 'Psychiatric genetics: search for phenotypes', *Trends Neurosci* , Mar 1998, 21(3):102-5.
8. Lelord G. et al., *Possible association of C-Harvey-ras (HRAS 1) marker with autism*', Psychiatry Research, *1993*.
9. Nuffield Council of Bioethics, *Mental Disorders and Genetics: the Ethical Context*, London: Nuffield Council, 1998-09. www.nuffield.org/bioethics
10. Oberlé I. & Mandel J.-L., Retard mental avec X fragile: une empreinte génomique très localisée, étroitement liée à l'expression clinique, *Médecine/Sciences*, 1991, 7 (4): 378-379.
11. Philippe A., Martinez M., Guilloud-Bataille M., Gillberg C., Rastam M., Sponheim E., Coleman M., Zappella M., Aschauer H., Van Maldergem L., Penet C., Feingold J., Brice A., Leboyer M., Genome-wide scan for autism susceptibility genes, Paris Autism Research International Sibpair Study, *Hum. Mol. Genet.*, May 1999, 8(5):805-12.
12. World Federation of Neurology: Research Committee, Research Group on Huntington's Chorea, 'Ethical issues policy statement on Huntington's disease molecular genetics predictive test', *Journal of the Neurological Sciences*, 1989, 94: 327-332.

Jean-François Bach

Predictive medicine in the adult

It is well accepted that the earlier in the disease history a treatment is applied, the better its efficacy. It is an unquestioned aim of medicine to attempt preventing diseases rather than treating established diseases. It remains, however, that treatment are often proposed at a late stage of the disease process either because of late diagnosis or fear of drug side effects. This situation is most often damaging for the patient and sometimes fatal, notably in the case of cancers. The solution to this problem is essentially based on the discovery of early diagnostic tests with the hope that precautious diagnosis opens a window of opportunity for more efficacious treatment and drugs with more acceptable side effects than those that would have been necessary at a later stage. Ideally, one would like to detect the disease process before its clinical manifestation (preclinical medicine) or even better before the beginning of the biological process under the form of genetic predisposition (predictive medicine). Although these concepts are widely accepted, they have posed questions of various types either medical, economical or ethical.

At the medical level, the list of diseases where early diagnosis (preclinical or predictive) is possible becomes quite significant. A large number of monogenic diseases are concerned, and even some polygenic diseases for which a major single gene allows good prediction. It should be admitted, however, that genetic prediction is usually impossible in these polygenic diseases because of the complexity of the genetic set up and of the usually low relative risk associated with each predisposing gene. Concerning preclinical medicine, a large number of clinically overt diseases are preceded by the progressive chronic appearance of biological symptoms as

in the case of insulin dependent diabetes mellitus (iddm) (anti-islet cell antibodies). The main problem is the level of reliability of the prediction. In monogenic diseases, the question is that of penetrance of the incriminated gene. For biological assays, the question is that of the specificity of the abnormality detected. A further factor of complication is the uncertainty about the lag between the prediction and the disease onset. Thus, in juvenile glaucoma, identification of a mutation on the tigr gene is associated with a close to 100% risk of developing the disease. However, only 70% of subjects will develop the disease before the age of 30. Similarly, in the case of iddm, presence of auto antibodies against glutamic acid decarboxylase, ia-2 and insulin in the family of a diabetic patient is associated with a close to 100% risk of diabetes. However, the disease may only appear between 5 and 10 years in 20% of patients. In brief, one has to evaluate the risk of error in the prediction (falsely positive prediction) and the risk of very delayed disease appearance. One may hope that further research will generate markers for the rapidity of disease progression.

Economical aspects are important and in fact pose ethical questions. The difficulty relies on the comparative evaluation of the cost of the disease care, and of that of the prediction testing. This is not an easy matter as far as the disease related cost is concerned because of the variety of aspects involved. The evaluation of predictive tests is easier in a first instance but remains imprecise in the mid-term future because of the likelihood of technical improvement. In the end, the ethical question is to determine whether one can restrict the usage of a prediction test because of a superior cost compared to disease care not taking a full account of the patient's suffering. In any case, one should make a clear distinction between the economical aspects and the ethical one that we shall discuss now. In other words, one should not take the excuse of the economical aspects to escape the ethical problems and reciprocally.

At the ethical level, two major problems must be thoroughly discussed: the risk of generating unacceptable anxiety in a patient or his family and that of exposing the subject to a treatment at the origin of side effects potentially more deleterious than the putative disease in question. In fact, the two questions are tightly linked. The risk of generating anxiety can only be justified by the existence of a satisfactory treatment both efficacious and sufficiently safe. A persistent problem is to determine what are the rights of physicians to overcome the potential individual's will of not knowing his medical risks. Of course, a test can only be done after acceptance by the subject. The question is how much should physicians insist to convince subjects of undergoing the test. This is often a very personal problem with many other examples outside medicine. Most of us will agree that speed limits are mandatory to avoid car accidents but many of us do not always respect these limits with the hope of not to be caught. Coming back to medicine, a classical example is that of a person

at risk of aids postponing hiv testing, although early detection of seropositivity is a critical condition for successful antiviral therapy. On the other hand, can we accept because of all the associated costs that diagnosis is made late when it could be made early?

Preclinical or predictive medicine is only justified when a preventive treatment is available. Here again, one has to weigh the efficacy and the safety of the treatment against the own disease risks. It may be important to stress that is not sufficient that the risks of prevention are lower than those of disease. They must be much lower to be acceptable and this for two reasons: first, because the subject to whom prevention is applied is initially healthy (or at least apparently so) and second, because one has no absolutely precise idea when he would become sick. If one takes the case of measles vaccination in Africa, where the disease associated lethality is more than 5%, one could say in theory that taking serious risk is acceptable for the vaccination inasmuch as the total number of vaccinated subjects suffering from this risk is significantly lower than the number of children dying from the disease. This is obviously not acceptable because there is no evidence that the children that will suffer from the vaccination will be those ultimately showing a severe form of the disease inasmuch as they get it. The more severe the disease, the more acceptable is the risk for the preventive treatment with the constraints that a treatment risk must remain much lower than the disease risk.

When the treatment is essentially safe and easy to administer as in the case of glaucoma with eye drops or even surgery (trabeculectomy), the question must be raised of the obligation for the physician to perform familial detection of the disease predisposition (mutation detection when the disease gene is known or measurement of ocular pressure). This is only very seldom done today. Will there be in the future trials where patients whose disease has been discovered at a stage with late irreversible lesions will sue the ophthalmologist for not having performed the family investigation that would have allowed him to be treated earlier?

Other important ethical problems deal with insurance companies and employers. There is a real risk that insurance companies take advantage of predictive medicine to increase the cost of insurance for subjects at risk of hereditary diseases. This risk is a direct consequence of the insurance company logics that each individual should pay premiums proportionate to his personal risk. This logic is acceptable within certain limits when the risk relies on the person's behaviour as in the case of car accident insurance. It is obviously much less acceptable for health and at a first analysis totally unacceptable for genetic tests. Additionally, the capacity of insurance of modulating the premiums according to genetic tests could have the negative consequence of discouraging people to undergo genetic tests which in many settings would be counterproductive for their medical care. In fact, several major

institutions including unesco, United Nations and European Council have written important texts banning any discrimination based on genetic tests. Some countries have taken laws prohibiting the use of genetic tests for insurance premium evaluation, notably the Netherlands, Austria and Denmark. Germany is about to do it. In the us, federal employers for recruitment and promotion took a law last year against the usage of genetic tests and a text is in preparation for insurance companies. Conversely, Great Britain has authorised to some extent the use of genetic tests by insurance companies. In France, there is no law yet. However, insurance companies have signed a moratorium according to which they will not request genetic tests, they will not use the results of already performed tests or tests to be performed. This moratorium was signed in 1994 for a period of 5 years and has been renewed for another 5-year period in 1999. In fact, the problem is a more general one. Is there any real difference between the detection of a predisposition gene for hypertension and the discovery of hypertension done on the occasion of a medical examination performed at the request of the insurance company. Is there any absolute difference between a reliable positive genetic test for type 2 diabetes and the finding of a transient hyperglycemia? Insurance companies to increase the premium value will use such hyperglycemia and one can certainly argue about this. On the other hand, one cannot readily accept that a given individual aware of a disease process and anxious about its potential progression applies for an insurance in conditions different from those of a healthy individual, notably concerning the insurance level. It is unacceptable that an individual is penalised by his medical condition. An intermediary and interesting solution is that presently existing in France for hiv seropositivity which insurance companies can only get information about when the subjects applies for a life insurance of an amount higher than € 150,000.

To conclude, we have to admit that, in any case, predictive medicine will develop whether or not physicians and ethicists consensually support it. The problem is to avoid any inappropriate behaviours either excessively aggressive or too cautious usage of the predictive test and of therapies. Because of the likely growing importance of the field, laws should be taken in all countries to avoid irresponsible behaviours notably by insurance companies and employers.

Guido de Wert

Comments

Introduction

It is increasingly possible to perform predictive genetic tests. Prof. Bach even predicts that predictive medicine will become a major aspect of modern medicine. In this comment, I will briefly address some of the ethical issues of a) predictive genetic testing of both adults and children and b) prenatal testing, especially for late onset disorders.

Predictive testing in adults

According to Galjaard (first thesis), 'Presymptomatic testing for risks of serious, non treatable disorders should be performed with great reservation and only after consent of professional and patient organizations.' The paradigm case is presymptomatic testing for Huntington disease (h d) (also addressed by professor Fagot-Largeault).

While some critics object that presymptomatic diagnosis of untreatable disorders like h dis at odds with the traditional principle 'first, do no harm', many consider this criticism to be unjustifiably paternalistic. First, this objection neglects that individuals at risk may have good reasons to apply for the test even if therapeutic or prophylactic remedies are not available. Furthermore, the objection neglects that for some persons at risk the uncertainty about their genetic status is unbearable. And third, experience with presymptomatic testing for h d until now suggests that

most clients can integrate the test result in their life. At the same time, caution is necessary: International guidelines for presymptomatic diagnosis of hd rightly stress the importance of, amongst others, adequate pre-test counselling (iha/wfn, 1994).

According to Galjaard (second thesis), the main bio-ethical principles 'do good', 'do no harm', 'justice' and 'autonomy' are of little support in clinical genetics when several relatives and generations are involved. Clearly, these principles do not produce univocal ethical guidance in case of conflicting duties and responsibilities. One of the main tasks of ethics is to provide assistance in the balancing of conflicting principles, acknowledging that in some dilemmatic cases there may not be ideal solutions.

Difficult conflicts can arise when testing the applicant will – or can – provide diagnostic information about another person at risk who has not requested the test. Situations like these mostly involve applicants at 25% prior risk, whose parent at risk (50%) does not want to know his genetic status. Testing the applicant (i.e. respecting his right to know) could conflict with the relatives right not to know. Which (or: whose) right should prevail? Ethical commentaries at this dilemma have, until now, focused mainly on hd. On the one hand, it is argued that giving priority to the relative's right not to know is at odds with the principle of respect for the autonomy of the applicant. Furthermore, would it not constitute an intolerable breach of the principle of equal access to health care if persons presenting themselves for the test are selected according to whether or not their relatives claim the right not to know? On the other hand, proponents of a restrictive policy argue that the principle of non-maleficence should take priority. Testing the applicant may cause the relative immense stress, and has even resulted in suicide. In view of the complexity of these cases, a univocal guideline may not be appropriate. Handling the current type of conflicts is especially difficult when the request concerns a late onset disease for which preventive or therapeutic measures are not (yet) available, like hd. The availability of preventive measures, however, has moral relevance, in that the relative moral weight of the applicant's right to know will increase. As effective preventive methods emerge, e.g. for carriers of brca1/-2 mutations, overruling the applicant's right to know in view of a relative's right not to know will be increasingly difficult to justify (De Wert, 1998).

It is often argued that the international guidelines for presymptomatic diagnosis of hd can be used as *a model* for other applications of predictive testing. The cloning of these guidelines ('normative cloning') may, however, be as dangerous as reproductive cloning; after all, the protocols and ethical guidance need, at least in part, to be disease-specific. Ethically relevant variables include the mode of inheritance of the specific disorder and the availability of preventive and/or therapeutic options.

An interesting case may be susceptibility testing for untreatable disorders, like the common, multifactorial variant of Alzheimer disease. There is a strong consensus not to perform this test because of a combination of factors:) the low predictive value, b) the lack of preventive/therapeutic measures for the carrier of the susceptibility, c) the questionable relevance of this information for reproductive decision-making. An issue that needs further scrutiny (in view of the just allocation of scarce resources for health care) is whether this kind of tests should be collectively financed.

Predictive testing in minors/incompetent children

A major issue is whether (healthy) minors can justifiably be tested for mutations for late(r) onset disorders, and, if yes, on what conditions. At least two questions need to be considered. First: is it appropriate to presymptomatically test incompetent children at the request of their parents? And second: is it appropriate to test minors who ask for such testing themselves? In some situations, predictive testing for childhood disorders allows for effective preventive intervention. Good examples are predictive testing for multiple endocrine neoplasia 2a (men2a) and for retinoblastoma. In these cases, testing is clearly appropriate, as early medical intervention substantially improves the prognosis for the child. A question needing further analysis, is whether parental refusal to give proxy consent for predictive testing could ever constitute medical neglect, warranting societal intervention.

A different picture emerges with regard to untreatable late onset disorders, like hd. There is a strong consensus that predictive testing of minors (at the request of the parents) would be inappropriate, for at least two reasons. First, the children's right not to know, i.e., their right to decide for themselves at some stage whether or not to be presymptomatically tested, should be respected. (This right belongs to the class of 'anticipatory autonomy rights', protecting the child's right to an 'open future'.) Second, such testing could cause serious harms, including damage to the child's self-esteem and distortion of the family's perception of the child. Some critics of this view argue: 'This may be true, but it may not be – we just lack the evidence. There may also be benefits, such as giving more opportunity to prepare for the future. Until we know what the actual, rather than the possible, effects are, we should avoid basing policy on speculation.'(Michie, 1996) In my view, evidence could only be obtained by experiments with *disproportionate* psychosocial risks for the child (De Wert, 2002).

What about predictive testing of minors for susceptibilities to psychiatric disorders, like schizophrenia (still a hypothetical case)? Again, we should give due attention to the potential for harm: Those who are predisposed to such illnesses may be

more vulnerable to emotional stress and being identified as susceptible would then all to easily become a self-fulfilling prophecy. The suggestion that knowledge of susceptibility could be helpful through permitting the vulnerable individual to modify their lifestyle assumes that environmental stresses could be avoided, but ignores the fact that such information could itself be a powerful stressor (Clarke, 1997).

With regard to the second issue (the testing of minors who ask for the test themselves), the international guidelines for hd-testing recommend that 'the test is only available to individuals having reached the age of majority' (iha/wfn, 1994). Many commentators argue that this recommendation be followed in protocols concerning predictive testing for brca1/-2 mutations. An alternative guideline is that the capacity to understand is the appropriate criterion – what matters is not age as such, but the (in)competence of the individual minor applicant. 'Emancipated minors' should not a priori be denied access to the test (De Wert, 1998).

Prenatal testing for late(r) onset disorders

Galjaard and Fagot-Largeault argue that prenatal testing for *late onset* disorders is especially controversial. Can this type of testing be morally justified, and if so, on what conditions? The paradigm case concerns, again, hd – even though only a small minority of person at risk opt for prenatal testing. While prenatal testing for hd is controversial, one may well argue that this is to some extent the simple case of prenatal testing for late onset disease, as hd is both autosomal dominant and lethal, and has mid-life onset.

Let us take a closer look at some moral issues that concern the conditions for prenatal testing for hd (De Wert, 2002). First, what about the ethics of prenatal *exclusion* testing? This method offers the chance to ensure that children are free of hd, while at the same time protecting individuals at-risk from learning potentially traumatic information about their own carrier status. From a *fetalist* perspective, focussing on the moral value of the fetus, it is objected that the traditional justification of selective abortion is being stretched in this situation. If one knowingly refrains from differentiating between fetuses that carry the hd mutation and fetuses that do not carry the mutation, abortion no longer is a *last resort* to prevent the birth of a child with a handicap or defect. The question arises whether aborting a fetus at 50% risk instead of trying to preserve the fetus without the hd mutation is not too a high a price for protecting the at-risk person's right not to know. The answer depends on one's view on the moral status of the fetus. Those convinced of a very high moral status of the fetus may regard this practice as an example of trivialising abortion, whereas those who think differently most likely will consider this practice to be justifiable.

Second, the international guidelines state that 'it is essential that antenatal testing for the hd mutation should only be performed if the parent has already been tested' (iha/wfn, 1994). (The guidelines add that prenatal exclusion testing may be a possible exception to this guideline). In other words, it is recommended that centres should abstain from direct mutation analysis of the fetus without prior knowledge of the genetic status of the at-risk parent. I assume that this guideline aims at protecting the at-risk person from psychological harms resulting from a 'double positive' test result that simultaneously reveals that the fetus as well as the at-risk person himself carry the mutation. Should counsellors really (categorically) refuse to give access to direct prenatal mutation analysis for *paternalistic* reasons, i.e. on the basis of the 'best interest' of the client? While prenatal mutation testing without prior knowledge of the at-risk parent's genetic status is not ideal, the *alternative* options (including: 1) no test, just carry the pregnancy to term; 2) no test, just terminate pregnancy; 3) 'sequential' testing. i.e. first, presymptomatic testing of the at-risk person; should he/she prove to be a carrier, then prenatal testing can be performed; 4) prenatal exclusion testing) carry their own psychological risks and ethical problems, and do not necessarily bring about a 'net benefit' for clients. Therefore, the iha/wfn guideline is too restrictive and should be reconsidered.

Third, while, generally, access to prenatal diagnosis should not be restricted to those women who intend to terminate affected pregnancies, the question arises whether this principle of 'unconditional' access also applies to prenatal testing for hd. It is important to see that there are morally relevant differences between the traditional applications of prenatal diagnosis on the one hand and prenatal diagnosis for hd. Should a fetus prove to be a carrier and should the pregnancy be completed, then there is a risk that the presymptomatic child will be harmed by being confronted with very burdensome information. Furthermore, the child's right not to know may be violated. Of course, one cannot enforce women to abort a fetal carrier – but to conclude that, for this reason, access to prenatal testing for hd should be unconditional, simply is a non sequitur.

Can the ethics of prenatal testing for hd be used for constructing a model for the ethics of prenatal testing for other late onset genetic diseases? The principles of justice and consistency require us to treat identical or similar cases in the same way. Therefore, guidelines regarding prenatal testing for hd can, and even *should*, guide the evaluation and regulation of prenatal testing for other adult onset disorders which are similar in relevant aspects: *untreatable, lethal, manifesting itself in midlife, and dominant*. Relevant examples include some of the other neurodegenerative disorders, like early onset Alzheimer disease, hereditary Pick's disease, and various autosomal dominant types of amyotrophic lateral sclerosis. However, the guidelines regarding prenatal testing for hd *do not necessarily apply* to late onset disorders

that differ from hd in morally relevant aspects, like disorders that are, at least partly, *treatable and/or preventable*, multifactorial, and/or manifest themselves later in life. The ethics of these cases needs separate attention, and cannot be simply deduced from the ethics of prenatal testing for hd. Needless to say, that it is important to place this debate in the proper perspective: prenatal testing will be even more rarely requested in these cases.

References

1. Clarke A.J. The genetic dissection of multifactorial disease. In: Harper P., Clarke A. *Genetics, Society, and Clinical Practice*. Oxford: bios Scientific Publishers, 1997, 93-106.s.
2. De Wert G. Ethics of predictive dna-testing for hereditary breast and ovarian cancer. *Patient Education and Counselling* 1998;35:43-52.
3. De Wert G. Ethical aspects of prenatal testing and preimplantation genetic diagnosis for late-onset neurogenetic disease: the case of Huntington's disease 2002. In: Evers-Kiebooms G., Zoeteweij M.W., Harper P.S., eds., *Prenatal testing for late-onset neurogenetic disease*. Oxford: bios Scientific Publishers, 129-157.
4. International Huntington Association/World Federation of Neurology. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* 1994;44:1533-1536.
5. Michie, S. Predictive testing in children: paternalism or empiricism? In: Marteau Th., Richards M., eds. *The troubled helix*. Cambridge: Cambridge University Press, 1996, 177-183.

Jean Frézal

Comments

The astonishing achievements of genetics and genomics raise expectations and hopes. At the same time, they arouse great fears, related to the past history of eugenics and the dark perspectives of categorisation, discrimination, and instrumentalization as well as the prospect of genetic engineering and cloning that they are supposed to open. Both expectations and fears stem from the awareness that these prodigious advances pave the way for a comprehensive knowledge of the genetic characteristics of individuals and populations and for genetic engineering, for the better or the worse. However, both may appear somewhat excessive or even unwarranted, although perfectly understandable considering the obtrusive mediatization of genetic information, and its oversimplified presentation which is not exclusively of the responsibility of the media. It is difficult to ignore that the results of the research of susceptibility genes are over interpreted and the publications biased in favour of apparently positive results. Although resting on insignificant or spurious association studies, the so-called discovery of a candidate gene for a complex disease or character, for instance the gene of homosexuality or of the gene of obesity often makes the headlines of the press. Consequences of this misinformation may be good for cleaver gamblers at the Stock market. Incidentally, we have to stress that besides the mediatization, the entrance of biotechnologies and especially of genomics in the Stock Exchange and the resulting pressure is a major event, the consequences of which being not fully appreciated. Whatsoever, unwise mediatization associated with overconfidence in the power of technology, may unfortunately lead to delusive hopes for patients and families. As a fact, besides the old data on h l a-

association with diseases, there is, currently, hardly more than an handful of positive results such as apoe-epsilon 4 allele and Alzheimer's disease, the coagulation factor V-Leiden and the risk of deep venous thrombosis, the caspase activator nod2 and the inflammatory process of Crohn disease, the peroxisome proliferative activated receptor, gamma and a putative reduced risk for non immune diabetes mellitus. As stated recently by Dunning and al., among 46 published case-control studies that have examined the effect of common allele of 18 genes on breast cancer risk, twelve report statistically significant associations, none of which were reported by more than one study.

Considering the results of genetic scans in 31 different human complex diseases, Altmüller et al. note that more than 66% show insignificant results and that the results of studies of the same disease were often inconsistent. They conclude that positional cloning based on whole-genome screens in complex human disease has proved more difficult than generally envisioned; detection of linkage and positional cloning of specific disease susceptibility loci remains elusive. One can take the full measure of the challenge, if we consider malformation syndromes such as Beck-with-Wiedemann, Prader-Willi, Smith-Magenis or Williams-Beuren, sometimes coined as contiguous gene syndromes and which are associated to a specific and well characterized chromosome rearrangement. Although the region affected by the rearrangement has been entirely cloned and sequenced, the genes identified, their eventual imprinted status determined and so on, in no case it is currently possible to definitely designate the unique or the multiple culprits. It is also worth to note that in all these cases as well as in many other diseases or malformation syndromes, the disorder is linked to a singularity of the chromosome structure such as a repeat or a duplication, a feature which may be common to everybody or constitute a variant in some individuals. These peculiarities are likely more important in the causation of malformation syndromes than most of the exogenous factors commonly referred to.

Coming back to the susceptibility for common diseases, we also should like to stress that the inconsistency of association studies do not necessarily disqualify all of them. It may suggest, as do the extraordinary heterogeneity of many mendelian disorders, that the same phenotype, the same susceptibility, let us say for hypertension or for schizophrenia, may be due to different combination of genes, each set acting independently from each other or in interaction with the others. Their incidence is unlikely to be the same in different populations and their frequency may also vary among populations. Their impact on the phenotype may be equal but some are likely to be 'more equal than others'! Finally, either the sets or the combinations of susceptibility genes will increase the risk of certain diseases only in the presence of specific environmental and behavioural factors.

On the best hypothesis, only a limited proportion of cases may be attributed to a well-defined susceptibility genotype and it could be possible to state that the risk to be affected by a common disease is not really increased after a positive test, nor is it significantly decreased when the test results are negative. In such a situation, one can estimate with Neil A. Holtzman and Theresa M. Marteau that (quotation) 'the complexity of the genetic of common diseases casts doubt on whether accurate prediction will ever be possible'. Even in the cases where the responsibility of a gene has been accurately ascertained, the relative risk remains low, as it is the case for brca1 and brca2 in breast cancer, where the relative risk for carriers of the susceptibility conferring genotype is about 5. In most instances, this relative risk does not exceed 2, a figure which, however could, not be insignificant in highly prevalent diseases with susceptibility conferring genotypes displaying polymorphic frequencies. In any case, the probability that the disease will develop in a person with a positive test result is usually very low, leading the Advisory Committee in uk to conclude that 'there is not significant predictive ability of genetic tests at the moment to allow accurate risk assessment' (quoted by J. Feingold). The situation is different in targeted populations, for instance in familial cancers, even if, in each case, the genotype accounts for no more than a few per cent of all cases. In our opinion, the problem of testing people in the work place might be considered from that operational point of view rather than at the level of general principles. That is to say, we have to consider that the workers must benefit of the more recent resources of the art, including genetic testing, to appreciate their ability or their risk to occupy a work post, in keeping with the usual legislation. Could not a disabled worker to whom the test would have been prohibited, be entitled to engage a lawsuit against his employer or the State? The current trend goes undoubtedly in that direction.

Another debatable issue is related to the presymptomatic diagnostic of late-onset diseases for which Huntington disease may be considered as the paradigm. The ethical bases of the testing are firmly assessed and it is generally agreed that psychological and social benefits expected from testing can justify the risks of definitely knowing to be affected. What is remarkable is how the predictive test has become rapidly incorporated into health programs in almost all industrial societies after international guidelines have been developed, in a very close relation between professionals, patients and lay groups. What is no less remarkable is that while more than 70 percent of people at risk claimed that they wanted to be tested as soon as the test become possible, according to a survey by Peter Harper in uk, confirmed in other countries. Less than 25 percent of people at risk, in France hardly more than 10 percent, have chosen to receive predictions of their risk of the disease, after testing became available. Furthermore, among tested people, a few proportion requested a prenatal diagnosis, suggesting the ethical reluctance of most people to

accept pregnancy termination for a disease with a disastrous course and outcome but compatible for decades with a normal life. At 55 years of age, 25p100 of the persons at risk will still be unaffected. Let us recall that Mozart died at 35, Vermeer at 42 years, Descartes and Spinoza in their fifties. Another debatable issue regarding Huntington's disease concerns the testing of children. Harms or benefits are sensitive to many factors such as individual resources, family support, supportive social services, insurance company policies and so on. Giving the complexity and diversity of the social attitudes and systems, the effects of genetic testing remain largely conjectural. Therefore one can rightfully wonder if testing in children should be under the power of the Law without due consideration for the parental rights or, conversely, should testing remain of the parents legal responsibility, after adequate information has been provided and, hopefully, understood.

Finally, I am afraid that my comments be more oriented through technical than ethical considerations. As we are in the city of Spinoza, I asked my great daughter, who is a better philosopher than I am, what was Ethics for Spinoza. Her answer will serve me as a conclusion. For the great philosopher, Ethics was not only a philosophy of knowledge and more than a moral doctrine; ethics was essentially a philosophy for conducting his life.

Summary of the discussion on presymptomatic genetic diagnosis

Chairman Prof. Francois Gros opened the discussion by pointing to the relationship between scientists, clinicians and patients. The implications of technologies should be considered. They might influence existing (role-) responsibilities and the way patients and illnesses are understood and treated. Furthermore, the new genetic technologies raise questions about patentability, the protection from misuse of genetic information and the dangers and promises of population genetics.

Prof. Vandenbroucke had two remarks. One was that the discussion jumped constantly between the ideology of public health and evidence based medicine and the ideology of genetic counselling in clinical genetics. In public health and evidence based medicine a screening test will only be offered when it has been proven by randomised controlled trials and cost-benefit analysis that it is not only a 'good test', but also beneficial for people. In that case society will (try to) enforce the screening test, such as happened in the case of tuberculoses screening in the past. In clinical genetics, such as prenatal screening for trisomy clinical geneticists will refuse to do cost-benefit calculations to decide whether this screening is worthwhile because this raises the spectre of eugenics. These differences in ideology should be explored. Prof. Vandenbroucke's second remark was that existing data should be used in research by linking several sources of information. Many problems in the application of genetic information can be solved by existing data. However, autonomy, confidentiality and privacy issues have to be faced, because this very necessary research cannot be done anonymously, and some identifiable linking of information is necessary at the earliest stage of data collection.

Prof. Ten Kate realised that there was consensus among the speakers. For multifactorial diseases it is not very good to have presymptomatic diagnosis. In the world outside, however, there is not only big science, but there are also big profits. How do we handle the commercial interest in offering prosymptomatic testing for all kinds of diseases? That is more urgent than to worry about what doctors offer. Prof. Galjaard agreed that this issue was not discussed. He explained that in the Netherlands this problem is dealt with by having a limited number of genetic centres. In order to get money from the health insurance they have to fulfil criteria set by government. The scientist in the us who had discovered the breast cancer gene number 1 and patented it expects his colleagues to pay quite a bit of extra money for every test. Diagnostics may be exempted from patenting in Europe, especially since the patent also involves the compulsory referral of patient material to a commercial laboratory for the tes-ting of as yet unidentified mutations. Prof. Galjaard said he hopes that The Netherlands, France, and other countries consider this against public order; it would also increase the costs of healthcare unacceptably. Prof. Gros states that in France there is a comparable situation. Prof. Bach explained that patients get money from the insurance, but the payment for tests on family members is still problematic. Prof. Bach clarified that there are reasons to expect possibilities for the future to prevent disease onset even for polygenic diseases, which are difficult to predict.

Prof. Tubiana referred to the preventive aspect of mastectomy in women with familial and genetic predisposition, mentioned by Prof. Galjaard. When a physician prescribes a test he should provide information about the consequences for the particular patient. He asked Prof. Galjaard whether he thinks that before a genetic testing the physician should ask the woman whether she would accept a mastectomy if the test were positive. Prof. Galjaard explained that he would not ask that. He would inform women. Most women that come for testing have a family experience, so they are generally motivated and reasonably well informed. During the counselling the uncertainties of the test and the limited options the women have will be explained. The options are (1) to do nothing, (2) to chose for a regular follow-up and (3) to chose for mastectomy. In our country is a public acceptance and in general the media do a good job in telling the people what is happening. The professionals in clinical genetics have always had a good relation with the media. People are not asked before the operation what they will do with the results, because they must be free to change their mind.

Prof. Vincent asked whether physicians follow up the mastectomy with cosmetic surgery. Prof. Wladimiroff stated that they do. Prof. Vandenbroucke said that the very effective prediction (80-85% life time risk) for breast cancer works for selected families where there are multiple cases. In the general population the prediction on the basis of the same b r ca1 and 2 mutations lead to a much lower risk, at maximum

about 50% . In families there are multiple factors that cause the several cases within the family, and therefore the predictions remain correct for the families with multiple cases. But there are problems with simple extrapolation to the general population. Prof. Gros agreed to a large extent with these comments. But in studies about diabetes it has been shown that there is no visible genetic difference between cases, which were studied in consecutive sets of patients, and patients selected from families with two or three cases of diabetes. There was no difference in the studied polymorphism. With additional markers using both genetics and biology one hopes to be able to extrapolate to the general population. In the case of diabetes only 15% of the patients have a history of diabetes in the family. Prof. Gros added that in the case of Alzheimer the known genes predict only 14% of the cases.

Dr. De Wert returned to the remark of Prof. Vandenbroucke about the philosophies in the field of clinical genetics on one hand and in the field of public health screening on the other hand. In the field of clinical genetics, which was traditionally about reproductive genetic counselling, respect of autonomy has been seen to be of paramount importance. Traditionally in the field of public health, prevention is the aim. Dr. De Wert pointed to the concern that when genetic screening programmes will be introduced, the philosophy of the traditional public health programmes might be introduced in the field of public health genetics. Prof. Vandenbroucke remarked that this could be considered a benefit, as well. That, according to Dr. De Wert, is part of the debate. There is a difference in semantics between the us and most European countries. In the Netherlands the term 'community genetics' is used, while some people are using the term 'public health genetics'. Semantics here point to different philosophies. The last group favours a prevention approach in the field of genetics. This will be a dangerous move for the area of reproductive genetic screening. In the case of screening for multifactorial disorders, which might be treatable, a mix of the two approaches might be considered. The idea of being non-directive might not be of paramount importance in the field of susceptibility screening, on the condition that you have something to offer to the person at risk.

Prof. Galjaard referred to Prof. Fagot-Largeault's explication that there is no link between the severity of mental retardation and the fragile X gene defect. Prof. Fagot-Largeault also mentioned that deaf people and their family experience deafness not always as an illness, but rather as 'difference'. Prenatal diagnosis for late onset diseases is not often required. The tests were originally administered for severe diseases in childhood, such as Down syndrome. If we do not talk about a diagnosis but about a risk prediction this demand will be even lower. Since we have different perceptions of disease and different perceptions of risks, we should leave the decision to people who usually decide on the basis of their experiences and who are motivated, even if the risk to get breast cancer is 'only' 40%. Prof. Fagot-Largeault

agreed completely. When she became a public servant in France she was required to take an x-ray for tuberculosis. There might be genetic tests that might become compulsory. The public service in France makes efforts not to recruit people for education with manic-depressive disorders, because they are not reliable. Prof. Ten Kate pointed out that genetic diseases are not contagious, in contrast to tuberculosis from which you have to protect other people. Prof. Fagot-Largeault remarked that you also have to protect other people from a teacher that is manic-depressive. Prof. Bach agreed with Prof. Ten Kate's remark about whether a disease is infectious. However, when he became a civil servant, he was tested for mental disease and cancer. There are situations in which this problem might be discussed. For instance a plane pilot should cause as little risk as possible. Genetic tests in this case are not much different from biological parameters, such as hypercholesterolimia linked to heart attack. It is a more general point to discuss the limits in this area.

Prof. Vincent asked why the genotype has to be more protected than the phenotype. Prof. Gros agreed that in the long term the genotype should not be more protected than the phenotype. Genetics often is predictive for the future, so we have become aware of the need to protect genetic information and ensure that it does not hinder the accessibility of employment and private insurance. Prof. Gevers affirmed this need in general, not only concerning genetics. Prof. Gros closed the discussion.

Henk Visser

Concluding remarks

I will make a few concluding remarks, with a personal note. I will limit myself mainly to the subject of bioethics in international context, after all this is the subject of this meeting.

We live in a time of internationalisation, even globalisation. In Europe we see that there is increasing economic, scientific and political cooperation between countries. For science there are no boundaries and certainly not for the biological and medical sciences and their application: health care. As a result there is a need for common policy in the area of bioethics and health law. The registration of new drugs in the treatment of cancer, heart disease, diabetes etc. requires large international, multicenter clinical trials. Obviously there is a need for common ethical guidelines to protect the interests of the patients in such type of medical research. In 1997 the International Conference on Harmonization (ich) of technical requirements for registration of pharmaceuticals for human use published its gcp guidelines to unify standards for the European Union, Japan and the usa. Recently the eu published a new Directive on clinical investigation of medicinal products. There seems to be consensus that the new developments in the fields of gene therapy and xenotransplantation require international safety and quality standards and regulations. But how about controversial subjects as embryo research, the use of fetal tissue, presymptomatic genetic diagnosis etc. Should we strive for a harmonization of bioethical opinions and health law regulations in Europe? Or is it – as Professor Legemaate asked in his introduction – desirable or even necessary to leave room for different approaches and legal systems, based on national tradiotions and consider-

ations? Prof. Den Harthogh answered this question with a clear yes in praise of pluralism: 'on the whole we should allow for, and even welcome, a plurality of legal systems'. Indeed, it was an excellent idea of the Dutch and French Academies of Sciences to address these questions in this symposium.

It is clear that in Europe there are common problems and concerns in the area of bioethics and there is a need for common policy. But will it always be possible to reach such a common policy? It seems to me that here the lawyers are more optimistic than the medical doctors. Medical doctors are well aware that cultural and religious differences have an important effect on the doctor-patient relationship, on ethical norms and local regulations. Although the regional South North differences in Europe are nowadays less pronounced than 10-20 years ago, they are still present. The people of Southern Europe are accustomed to more paternalistic behaviour by their doctors than the people of Northern Europe. I have to be careful and more research is needed, but I think that ethics committees in some countries are not that strict about patient information, informed consent, insurance of the research subject etc. as in other countries. And what is regulated by law in the Netherlands: euthanasia, abortion and embryo research, is unacceptable in other European countries. About ten years ago mr. Wijnberg of the Netherlands Ministry of Health made an analysis of the diversity of legislation covering human experimentation in the eec countries. There were considerable differences, also in such issues as informed consent, norms, liability, insurance, ethics review. I would not be surprised if some of these differences are still here today.

In the Netherlands there is a substantial minority who for religious reasons do not accept euthanasia, abortion and embryo research: they belong to the Roman Catholic and conservative Protestant churches. The Dutch law does not force people to accept euthanasia and abortion. Obviously this is a personal decision. Why should those people who do not accept euthanasia and abortion forbid others to do so? We understand that there are basic ethical and moral norms that should be at the basis of every one's daily life and this is true for the Netherlands. But the majority in the Netherlands has the opinion that euthanasia, abortion, late termination of pregnancy in special situations are personal decisions and they accept embryo research in embryo's left over from in vitro fertilization.

It is clear that international, European regulation of bio-ethical issues as euthanasia and abortion is at this moment impossible. But what about embryo research and non-therapeutic research in those individuals incapable of giving consent, such as children and adults with dementia? Recently the Dutch Parliament accepted by large majority an embryo-law that will make therapeutic cloning possible, when scientific developments in stemcell research indicate that it is feasible and may be of therapeutic value for patients with diseases as Parkinson's disease, diabetes and

others. Such a law I think will not be acceptable by many other European countries. Just some weeks ago the final report of the influential Committee on Human Genetics of the European Parliament proposed to follow a very restrictive policy in most fields of advances in human genetics, including a complete ban on therapeutic cloning and prohibition of prenatal screening aiming at reimplantation of those embryo's with the best chance of survival. Personally I am pleased that this proposal was rejected yesterday in the European Parliament by a large majority.

Professor Gevers and others have mentioned the controversies concerning the recent eu regulation on clinical investigations of medicinal products (Good Clinical Practice, gcp). The Dutch law on medical research involving human subjects accepts non-therapeutic research in those individuals incapable of giving consent (such as children and adults with dementia) with the following limitations: such research can only be done in these groups (and not with legally competent persons) and the risks and burden should be minimal.

Non-therapeutic research on individuals incapable of giving consent is also accepted – but with the same limitations – in the ich-gcp Guidelines for drug research that we have since 1997 in Europe, Japan and the usa. It is also accepted in the World Medical Association Declaration of Helsinki, and by the Convention of human rights and biomedicine of the European Council. The new eu gcpP regulation on drug research has now probably put a halt to this practise. I say probably because there are differences in opinion how to interpret the new regulations. But in my opinion, when I read the eu-Directive correctly, non-therapeutic research in adults incapable of giving consent will be very difficult, if not impossible in the European nations in the future. eu Directives overrule national legislation and have to be implemented within two years into the national legislation of the eu countries. We have to wait how eu member states will implement the new eu Directive and how the ethics review committees will interpret the new regulations of the individual member states.

As Professor Gevers mentioned, a few months ago the Human Rights Committee of the United Nations has criticized the Dutch law on Medical Research involving human subjects. The Committee is not only concerned about non-therapeutic research in children and adults who are incapable of giving consent, but finds it unacceptable and invites the Dutch Government to change the law accordingly. I think the Dutch Government will not do so. I am informed that all the members of the Human Rights Committee of the United Nations are lawyers, not a single medical doctor seems to be a member. As I have stated in a recent commentary in the *Lancet*: it is unethical to stop non-therapeutic research in people incapable of giving consent, because it means denying them the advantages of medical progress. (*Lancet* 337: 818-810,2001).

Professor Legemaate, Professor Gevers and others have asked the question whether there is a limit to the process of international standard setting in the field of bio-ethics. It seems to me that the answer is yes. I think that we have reached consensus on the basic human rights, the fundamental values, in bio-medical research and health care.

The Declaration of Helsinki and the Convention on human rights and biomedicine of the European Council are good examples. But at the same time we should leave room for differences based on national traditions and considerations. A more directive approach by for instance the eu in Brussels should be limited to safety and quality standards, which are essential for the free trade in the common market, but this should not be mixed with ethical directives such as limiting non-therapeutic research in individuals who are incapable of giving consent.

In the coming years we will watch important developments in the field of presymptomatic genetic diagnosis, as has been discussed so well by Professor Galjaard and our French colleagues, Professor Fagot-Largeault and Professor Bach. Particularly in this area we will face new ethical, social and judicial dilemma's. I am convinced that these problems will be solved in different ways, dependent on the social and cultural traditions of the different nations. Professor Galjaard rightly emphasized that in this area not only the index-patient, but also several relatives and generations are involved. The right to know and not to know, the health risk of offspring and relatives and major legal problems should be taken into consideration. A special problem here was well discussed by Professor Fagot-Largeault: many diseases which may be identified by genetic tests in the future are multifactorial disorders and – apart from the problems with genetic linkage studies – environmental factors may vary in time and between individuals. Many committees – national and international – will study these problems in the future and propose answers. I hope that such committees will have members from many disciplines, including medical doctors, and that they will be consulted by the politicians before they decide on regulatory laws.

Let me conclude by repeating what the President of the Netherlands Academy said in his opening speech. As scientists we have the responsibility of discussing together the new scientific developments and its ethical implications. Moreover we have to inform the politicians and try to influence their decisions. Let us agree on basic general standards of ethics and health care, but let us also accept pluralism, differences based on social and cultural variety. Let us learn from each other, also from our differences. This will stimulate new scientific developments.

Appendix i

Resolution on the use of embryonic and adult stem cells

The Académie des Sciences de l'Institut de France and the Royal Netherlands Academy of Arts and Sciences, in a joint Symposium on Bioethics and Health in International Context on November 30 in Amsterdam, have formulated a Resolution on the use of embryonic and adult stem cells which reads as follows: 'Both the Académie des Sciences de l'Institut de France and the Royal Netherlands Academy of Arts and Sciences acknowledge the potential benefit of stem cells in therapy. They realise that more knowledge on embryonic stem cells and adult stem cells is needed. Provided measures are taken to avoid reproductive cloning and to protect female oocyte-donors, both academies support therapeutic cloning.'

The joint Symposium on Bioethics and Health was announced during the official state visit of the French President Jacques Chirac to the Netherlands in February 2000. In a special meeting of the Royal Netherlands Academy of Arts and Sciences President Chirac emphasized the importance of a dialogue between France and the Netherlands on the ethical consequences of modern developments in the biomedical sciences. The ethical issues, which concern the protection of human rights and dignity of the human being, have a universal appeal. But legislation is local, and even in Europe the discussion on common principles has only just begun.

The symposium, recently held in the Trippenhuis in Amsterdam, was organised by the Académie des Sciences and the the Royal Netherlands Academy of Arts and Sciences. The symposium was concentrated on ethical and legal aspects of scientific developments in the field of modern medicine, including the consequences of Brief

knowledge of individual genes. The central issue of the morning session was internationalisation, while the afternoon session was devoted to various aspects of pre-symptomatic genetic screening.

Since a single one-day symposium cannot cover sufficient ground, a second symposium will be organised in Paris in 2002. The proceedings of each symposium will be published in order to make the results and considerations available to a wider public.

Programme 30 November 2001

Time	*Activity*	*Speakers*
09.00 - 10.00	Registration	
10.00 - 10.05	Welcome by the President of the Royal Netherlands Academy of Arts and Sciences	Robert Reneman
10.05 - 10.10	Address by the President of the Académie des Sciences	Hubert Curien
10.10 - 10.20	Introduction into the background of the symposium	Herman Berendsen

Internationalisation of norms and regulations in health care

Chairman: Johan Legemaate

10.20 - 10.40	New therapies and their ethical implications in an international context	Jean-Didier Vincent
10.40 - 11.00	International standard setting in the field of bioethics	Sjef Gevers
11.00 - 11.20	In praise of pluralism	Govert den Hartogh
11.20 - 11.45	Coffee break	
11.45 - 12.45	Discussion	
12.45 - 14.00	Lunch	

Presymptomatic genetic diagnosis

Chairman: François Gros

14.00 - 14.20	Presymptomatic genetic diagnosis and social acceptance	Hans Galjaard
14.20 - 14.40	Presymptomatic genetic diagnosis: ethical aspects	Anne Fagot-Largeault
14.40 - 15.00	Predictive medicine in the adult	Jean-François Bach
15.00 - 15.10	Comments	Guido de Wert
15.10 - 15.20	Comments	Jean Frézal
15.20 - 15.45	Tea break	
15.45 - 16.45	Discussion	
16.45 - 17.00	Concluding remarks	Henk Visser
17.00 - 18.00	Drinks, refreshments	

Appendix iii

Organising committee

Prof. Herman Berendsen (Chairman)
Emeritus Professor in Biophysical Chemistry, University of Groningen, Member of the board of Royal Netherlands Academy of Arts and Sciences.

Prof. Inez de Beaufort
Professor in Medical Sciences, Erasmus Medical Centre Rotterdam, the Netherlands

Prof. Piet Borst
Professor in Medical Sciences, former director of Netherlands Cancer Institute (nki), Amsterdam, the Netherlands

Prof. Hans Galjaard
Emeritus Professor in Medical Sciences, Erasmus Medical Centre Rotterdam, the Netherlands, Member of the Science and Ethics Committee of the Royal Netherlands Academy of Arts and Sciences

Prof. Johan Legemaate
Professor in Medical Health Law, Erasmus Medical Centre Rotterdam, the Netherlands, Chairman Bioethics Committee, Royal Netherlands Academy of Arts and Sciences

Dr. Marij Stukart
Executive Secretary, Council for Medical Sciences Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands

Congress coordination

Dr. Michel Cohen-Solal,
Coordinator Académie des Sciences, Paris, France, delegate of the Department of International Relations, Académie des Sciences

Ms. Merel van den Hooff / Maarten Langemeijer, M.A.
Coordinators Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands.

Brief information about the speakers

Jean-François Bach, received his medical Degree in 1966, and his D.Sc. Degree, 1969. Some major earlier and present positions: Head of the Clinical Immunology Unit at Necker Hospital, Head of Immunology Research Laboratories sponsored by the Institut National de la Santé et de la Recherche Médicale (inserm) at Necker Hospital, Professor of Immunology at Necker Faculty, Chairman of the Scientific Council of the French National Cancer League, Member of the Council of the Centre National de la Recherche Scientifique (cnrs), Vice President of the Fondation pour la Recherche Médicale, Editor in Chief of the Journal of Auto-immunity (Academic Press)

Herman Berendsen is emeritus professor of physical chemistry at the University of Groningen. He obtained his Master's Degree in Physics at the University of Utrecht in1957, and his Ph.D. at the University of Groningen in 1962, following a research fellowship at the Massachusetts Institute of Technology. Since 1963 he has been lecturer and since 1968 professor of physical chemistry at the University of Groningen. His main field of interest concerns computer simulations of biological systems and processes. He is (co)author of about 350 scientific papers.

Prof. Berendsen has – among other functions - been President of the iupab (International Union of Pure and Applied Biophysics) from 1993 to 1996, and presently he is Secretary of the icsu/unesco-supported Inter-Union Bioinformatics Group. He was elected member of the Royal Netherlands Academy of Arts and Sciences in 1979 and became a member of the board of the Division of Natural Sciences in 1999,

presently as vice chairman. In this capacity he is the chairman of the organising committee of this Symposium.

Anne Fagot-Largeault, PhD (Stanford University 1971), md (University of Paris-xii 1978), Docteur des lettres et sciences humaines (University of Paris-x 1986). Currently: Professor at the College de France (Chair of philosophy of biomedical sciences),and part time consultant at the Henri Mondor Hospital (Assistance publique de Paris, psychiatry).

Jean Frézal, Emeritus Professor of medical genetics at the Necker Medical School Emeritus Director of the inserm u12 Research Unit of medical genetics. Head of the genetic clinic and of the paediatrics department at the sick children hospital.

Past President of the French Association for screening and prevention of children handicaps, (Organiser of neonatal screening and prenatal diagnosis in France). Creator and Editor of the genatlas database on mapped genes.

Hans Galjaard, received his md and PhD at Leiden University in 1962. After training in radiobiology in England and at the Medical Biology Laboratory tno, Rijswijk, he was appointed as professor and in 1968 chairman of Cell Biology at the Erasmus University Rotterdam. His main research interests were the elucidation of the molecular aetiology of genetic diseases associated with mental retardation and the development of methods for (prenatal) biochemical diagnosis. From 1980 he became director of a newly formed department of Clinical Genetics of the University Hospital Rotterdam. He has fulfilled many advisory functions, most recently in the International Bioethics Committee of unesco and a national committee on genetic modification of food. He received numerous honours in a dozen countries.

Sjef Gevers is professor of Health Law at the Universiteit van Amsterdam. He teaches both at the Faculty of Law and at the Faculty of Medicine (Academic Medical Center). He has published widely in the field of medical law and ethics, including such issues as patients' rights, medical examinations, genetic testing and the legal aspects of new medical technologies.

François Gros, 'Attaché', 'Chargé', 'Maître' then 'Directeur de Recherche' at the cnrs (1945-1972). Professor of Molecular Biology at the Faculty of Sciences (1968-1972). Professor at the Pasteur Institute (Head of the Biochemistry Unit (1972-1995). Professor of Cellular Biochemistry at the Collège de France (1973-1996).General Director of the Pasteur Institute (1976-1981). Counsellor to the Prime Minsiter (Science and Technology (1981-1985). Special advisor to the Commissioner of Science and Technology (eec) (1993-1995). Permanent Secretary of the French Academy of Sciences (1991-2001)

The scientific work of François Gros had dealt with the molecular biology of the genes and has led to the co-discovery (1961) of the messenger ribonucleic acids (mrna), work initiated with J. Monod and F. Jacob. Since 1970, the research work carried out in his laboratory concerns the study of developmental biology.

Govert den Hartogh, a former professor of legal philosophy in the Faculty of law, and of medical ethics in the Faculty of Medicine, is now professor of Ethics in the Faculty of Humanities, Department of Philosophy, in the University of Amsterdam. He is a member of one of the regional committees for assessing euthanasia and assisted suicide. His research interests include theories of justice, in particular justice in health care allocation, and medical decisions at the end of life.

Johan Legemaate; Utrecht University Law School (1977-1982), PhD University of Amsterdam, 1991.

Legal counsel, National Foundation of Patient Advocates in Mental Healthcare (1982B1991); Legal counsel, Royal Dutch Medical Association (1991-2001); Professor of health law, Erasmus University Rotterdam (1993-). Other present positions: Member of the Dutch Health Council, Member of the Committee on Medicine of the Royal Dutch Academy of Arts and Sciences, Chairperson of the Subcommittee on Legal and Ethical Aspects of Medical Research of the Royal Dutch Academy of Arts and Sciences, Member of the organising committee of the 14th World Congress on Medical Law in Maastricht 2002.

Jean-Didier Vincent, Professor University of Bordeaux ii (1973), Professor Chair of Physiology University of Bordeaux ii - Faculty of Medicine (1979) and University Paris xi Kremlin-Bicêtre (1992); Professor *Classe exceptionnelle* Paris (1993); Professor *Institut Universitaire de France* (1994). Several positions Hôpitaux de Bordeaux (1956-1976); Chef de Service du Laboratoire d'Exploration Fonctionnelle du Système Nerveux Central et des Troubles du Sommeil du chu de Bordeaux(1977); Praticien Hospitalier Kremlin-Bicêtre (1992). Research Positions: Director research team asociated with cnrs-era 493 (1973); Director of greco 85 cnrs; Director of Unité inserm (U176); Neurobiologie des Comportements (1978-1990); Director of gdr cnrs go 1410 (1988); Director of 'Unité inserm (U176) Neurobiologie Intégrative (1991); Director of the Institute Alfred Fessard cnrs (upr 2212) (1992); Director of the Institute of Neurobiology Alfred Fessard-ifr 2118 *(2000)*

Henk Visser studied medicine at the University of Groningen. After training in pediatrics (PhD in 1958) in Groningen, he was Fulbright Fellow at the Children's Hospital, Harvard Medical School, Boston, usa (1960-61). He was Professor of Paediatrics at the Erasmus University and chairman of the Department of Paediat-

rics at the University Hospital/ Sophia Children's Hospital, Rotterdam from 1967-1995. His research interests were endocrinology, growth and nutrition. He has been on the board of many national and international organisations. At the moment he is chairman of the Dutch Central Committee for Research on Human Beings and chairman of the Scientific Advisory Board of the Dutch National Institutes of Health and Environment. He is a member of the Royal Netherlands Academy of Arts and Sciences since 1980.

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Appendix v

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