Opinion on research and use of in-vitro human embryos for scientific and medical purposes. Report.

N°8 - December 15, 1986

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Opinion

The human embryo in the early stages of its development has become accessible to the sight, and more importantly to the power of biologists, doctors and patients as a result of the development of in-vitro fertilisation intended to allowing infertile couples to have children.

- This situation exists de facto in scientific and medical institutions which endeavour to meet the wishes of unhappy couples and resort to experience and knowledge acquired in animal research. The application to human beings of practices for the improvement of scientific and technical control of reproduction, is still in its early stages. Rapid progress is now opening new avenues for research, tests on human embryo or application to humans beings of techniques already applied for reproduction of certain animals (gender determination and selection), etc. for procreative purposes. The human embryo can also be used for fundamental research or experiments not as yet related to a personal procreative project.

- All these procedures which are already feasible today or will become possible in the future, raise serious questions of different kinds (philosophical, ethical, scientific, legal, and even possibly economic). They worry many people, including researchers who, with some justification, question the validity of such advances, assess the risks - for the present and for the future - of medically assisted procreation, and the possibly negative consequences that such developments could bring about in medical or social practices as well as in the psycho-social representation of the human being.

It is now considered that all scientific advance does not necessarily mean progress, as it may have ambiguous or undesirable consequences. These questions have led to many studies, from different viewpoints which provide a better understanding of the purpose of biomedical research applied to human embryos in the early stages of their development. However, the rapidity of scientific developments and practices leaves very little time for ethical reflection and calls for, -in an overall context which is both hazardous and changing - the establishment of standards to regulate these new powers.

- Concerns and hopes arising from the possibility mastering human reproduction generate a need for standards and/or regulations. Many States, or National or International Authorities, when confronted with this problem, became aware of the need not to let such practices become a fait accompli as they are related to the very essence of "human life", or "person", and therefore must be rigorously assessed from ethical and scientific viewpoints, as well as for the benefit they can provide to individuals, families or societies.

- The National Consultative Ethics Committee for Health and Life Sciences, studied existing analyses and opinions, and asked various experts to provide observations and viewpoints. It now publishes an opinion, limited to questions of in-vitro embryo research and practices for medical and scientific purposes.

- The present opinion prolongs and completes former opinions published on 22 May and 23 October 1984 when the Ethics Committee presented certain views and recommendations, some of which could be usefully reproduced here.

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Opinion on research and use of in-vitro human embryos for scientific and medical purposes

"To allow birth by artificial reproductive techniques raises ethical issues". They do not result from an a priori opinion regarding what is artificial. The new fact to which society has no answer yet is that, as they dissociate the different steps of the reproductive process, the new techniques lead to separate consideration of the interests of patients, of potential parents, and of the future child.

Also, the embryo acquires a brief period of existence, for which it has, for the time being, no status (opinion of 23 October 1984).

The Committee notes that the development of procreation by in-vitro fertilisation reinforces the trend which uses the human body as an instrument. Moreover, techniques such as the freezing of embryos increase the artificial nature of reproduction, especially as a result of the dissociation between conception and pregnancy. The de facto situation resulting from

the production of a larger number of embryos than can be medically transferred raises questions that we should try to answer. However, solutions proposed in the present opinion do not legitimate this de facto situation. Such solutions are, therefore not final: one can envisage and hope that, in the future, research will allow fertilisation only of the necessary oocytes for transfer for the birth of a future child. Medical research should endeavour to reduce the number of cases raising ethical issues, rather than accumulate an ever-growing amount of problems of a degree of severity which is disproportionate to the intended objective.

The Committee, in its first opinion of 22 May 1984, stated that human embryos should be recognised as potential persons and that this definition should imply that they merit respect. After a critical review of this statement, that some may prefer to word as "the potentiality of a person", the Committee maintains that this assertion, based on the rule of reason, must be understood as the enunciation of an ethical concept. In fact, indications supplied by science regarding the different steps of embryo development, besides the fact that they are uncertain and are subject to scientific discussion, cannot define per se the threshold or thresholds of emergence of the person and be the basis for the notion of respect due to the embryo. The Committee maintains that the principle of respect due to the future human being starts with conception(1). Without deciding as to the ultimate foundation of the person, but with regard to the diversity of metaphysical or philosophical options, the Committee is of the opinion that the foundation of and due respect for the embryo can be based on the rule of reason. Not only should the anthropological, cultural and ethical meaning of the beginning of life be taken into consideration, but also the consequences or upheavals that certain practices or research could imply for the overall representation of the human person.

Such consideration should take precedence over the advantages that might result from using human beings as though they were objects, even though it represents potential for the improvement of medical knowledge and furtherment of science.

Respect for human dignity must guide both the development of knowledge and the limits or rules to be observed by research (cf. Ethical report).

It is however necessary to materialise this requirement for undefined dignity in its practical consequences, taking into consideration contingencies related to the present state of knowledge, research objectives, and means to achieve them.

Ethical requirements cannot always be formulated in "absolute" dogmatic terms. Elaborating and implementing rules implies compromises made tolerable by the ethical principle of the lesser of two evils. The lesser evil, can be determined by weighing immediate and medium or long term risks and advantages, of a scientific, medical, psychological, social, cultural or philosophical nature. The difficulty of such an evaluation justifies prevailing careful attitudes.

Therefore, logic involving greater efficacy or efficiency, or the temptation of omnipotence of researchers, medical practitioners or patients, must be prevented from prevailing over the ethical or scientific assessment of the use of human embryos. Such limits or conditions that are recommended by the Committee, will have to be reconsidered, taking into account experience resulting from their implementation, from their scientific and social developments, from further ethical reflection, and from the possible adoption of relevant legislation.

- From a scientific viewpoint, research on human embryos is motivated in practice by problems of infertility and by the hope of improving the still rather mediocre efficiency of IVF-ET. In the last few years, progress has been made based on animal research. Such progress is partly due to a greater availability of embryos resulting from multiple ovulation treatment which makes it possible to compensate for the low, though variable, ability of each embryo to develop until delivery by the transfer of multiple embryos.

Such a practice usually leads to the production of excess embryos, which can now be kept in their frozen state. These embryos thus become de facto available for research, not only with a view to improving IVF-ET, but also (although to a limited degree) to extending possible use (in particular, to predict anomalies or genetic diseases carried by the embryo). There seems to be no limit to such developments, if one thinks of animals for which laboratory techniques, now applied to domestic animals result in the creation of chimeras, clones or new lines of animals with a modified genetic inheritance (cf. Scientific report). Present practices reveal that research on human embryos does not always abide by the conditions of the animal "prerequisite". Such conditions should always be applied. Yet, they are not sufficient to justify the application of the results of animal research to human embryos without critical scrutiny.

- in the light of ethical and scientific reports published in an annex to the present opinion, the National Consultative Ethics Committee makes the following recommendations to researchers, medical practitioners and patients and to research institutions and public authorities.

Some members of the National Ethics Committee have expressed dissenting opinions, presented as an annex to the ethical report.

General recommendations

Human fertilisation always leads to the formation of an embryo which, as a result of a parental project, should lead to the birth of a child, although, obviously this cannot be guaranteed. Since, in the case of In Vitro Fertilisation, the creation of human embryos is deliberately intended, respect due to the future person in the form of the embryo is all the greater.

As a result :

- The purpose of In Vitro Fertilisation must be the birth of children. As far as IVF-ET is concerned, (which is a remedy, not a cure for infertility), since it is still experimental and represents a very trying technique for the patients, and remains costly and of limited efficiency, public authorities and research institutes should give priority to work on the treatment of infertility and prevention of its causes.

- Even with the consent of genitors, fertilisation should not be done for research purposes alone. If it were, human embryos would purely and simply be used as tools or objects, and human dignity, which must override scientific research, would not be respected.

- Fertilisation, or other medical or scientific intervention on human embryos must exclude all forms of commercialisation. Human gametes or embryos must not be sold nor submitted to any form of trade; donors must not be compensated and persons or organisations storing human embryos must not derive profit from this activity. Legal provisions should guarantee such principles.

- Fertilisation, or other medical or scientific intervention on human embryos can only be done with the free and informed consent of genitors.

A duty to inform the latter rests with the persons and centres which proceed to fertilisation and store the embryos. Any pressure to obtain patients' consent is illegal. Patients, may, without any prejudice to their right to such treatment, refuse certain modalities of IVF-ET which would be in contradiction with their ethical beliefs.

In the same way, practitioners and researchers may put forward conscience clause should they wish to refuse to perform certain techniques.

- In Vitro Fertilisation and Embryo Transfer, as well as embryo research may only be done by persons or centres specially authorised by public authorities according to an agreement procedure, the conditions of which are defined in paragraph IV of this opinion.

Recommendations regarding IVF-ET as a remedy to infertility

IVF-ET is developing in France as an acceptable reproduction technique, if the indications and conditions of application are properly defined (A). Nevertheless, for the time being, it is not always possible to avoid fertilising an excess of embryos. It is necessary to decide on what should be done with these spare embryos (B).

A. IVF-ET indications and conditions of application

Development of IVF-ET is a palliative to sterility. It seems desirable to try to avoid excessive use of a technique, which is hazardous, cumbersome and costly, and not void of physical, - and even more psychological - , risk for couples.

The Committee also draws the attention of the medical profession and patients to the potential dangers of aggressive obstinacy in attempts to procreate.

Regarding IVF-ET, the Committee makes the following recommendations :

- Medical indications to resort to IVF-ET only concern couples suffering from proven sterility or low fertility, and motivated by a common parenthood project, in a steady relationship between man and woman. No other indication can be made at this date for IVF-ET.

- Free consent must be given individually by the two partners, after they have been objectively informed of the uncertainties, risks and constraints related to IVF-ET.

- Such information must also mention the possibility of obtaining a number of embryos larger than what can be transferred in practical terms, and written consent should be obtained after a period of reflection. Such consent may mention the number of oocytes to be fertilised.

- The couple must be informed of the number of oocytes actually collected and fertilised and the number of embryos obtained.

- The number of embryos transferred must be limited to reduce the risk of multiple pregnancies, which is a danger both for mother and future children.

- When the number of oocytes collected and fertilised is larger than those medically transferable, the excess embryos may be kept for future attempts. Such a procedure which requires freezing the embryos must be submitted to the couple's agreement.

- A compromise between the risks of multiple pregnancy and respect for embryos conceived to produce life, is, for the time being the lesser of two evils. Such a compromise should remain provisional and one can hope that a scientific breakthrough will avoid producing embryos not intended for immediate transfer.

B. The problem of excess embryos

The de facto existence of not immediately transferable embryos requires examination of the issues related to their possible destruction, freezing or donation to other couples.

Destruction

Destruction seems paradoxical in the case of a technique intended to create life.

From an ethical viewpoint, destruction, because it is deliberate, like fertilisation, can only be justified by the argument that, in nature, many embryos fail to nest. The Committee considers that such destruction can only be envisaged as the lesser of two evils and that it is inevitable whenever conservation is not possible. Such destruction shocks those who consider that the life of embryos should be protected as soon as they are conceived.

FREEZING

Freezing, whatever its purpose, creates intemporality in the genesis of life, increases the risk of dissociation between fertilisation and gestation. It can contribute to an accumulation of embryos. For the time being such a technique remains largely experimental and is not completely under control.

As a consequence, the process of freezing must abide by the following recommendations :

- As a consequence of its experimental nature, freezing must follow the above recommendations and be done in certified centres offering required scientific and technical guarantees.

- Although it raises oppositions in principle, freezing can be justified as a means of achieving the parental couple's effective procreative objective at the time. It can be accepted as far as it permits the transfer of embryos in a woman at some point during a future cycle, or later transfers in case of failure, without having to again collect and fertilise oocytes. Also, it avoids having to destroy embryos which cannot be transferred immediately.

- Freezing should be limited in time, taking into consideration a specific procreative project and not an undetermined general parenthood programme.

The medical practitioner should decide on the most appropriate time for transfer after thawing. Such a transfer should not be performed more than six months after freezing. In case of failure of the first transfer, spare embryos may be used for transfer within the same six months. Conservation should not be extended, except for medical reasons, beyond a maximum period of twelve months after fertilisation. The medical reasons for such a possible extension should be examined by a Committee of Ethics.

- After a first child is born, if spare embryos of the same couple still remain, the question arises as to whether it is acceptable to transfer them to obtain a second child. The Committee was unable to reach a unanimous position on this question. For some, the use of frozen embryos with a view to a second child is incompatible with the principle according to which freezing is only justified on a temporary basis in the case a specific procreative project. Moreover, it seems extremely difficult to define non-arbitrary conditions to which parents must comply when they express their intentions.

The idea of a stock of embryos submitted to the omnipotence or the variations of parental aspirations should be dismissed. It would be unwise to let freezing techniques become, little by little, a different and independent way of procreating. More generally it appears that somewhat carelessly, there is progression to an extension of the use of freezing techniques although the risks, difficult to asses but nevertheless real, would justify abstention.

For other Committee members, various reasons (avoiding the need to collect new oocytes and fertilise more excess embryos, freedom for the couple to manage its own reproduction, avoiding destruction, etc.) justify the possibility of preserving the embryo to give birth to a second child, with the condition that the couple should clearly express its intention.

With due consideration to such differences of opinion, the Committee recalls that freezing is still experimental and should therefore be used with care. Nevertheless, and in spite of the

dissenting opinion of some members, the Committee suggest that an extension of another twelve months after the first child is born should be made possible for couples who want another child.

- Whenever the parents renounce their project or the project becomes impossible (for instance, due to separation of the couple), the only solution considered by the Committee, as the lesser of two evils, is destruction of the embryos (with the reservation of possible donations for research).

- The Committee recommends that within three years a review of the preliminary results of the freezing of human embryos should be prepared. This report should be based on a census of frozen embryos; it would make it possible to determine the benefits and drawbacks of various methods used, taking into consideration results as well as perinatal and psychological consequences for the child and for the parents.

Embryo donation

The donation of embryos from one couple to another through a conservation centre requires special attention in view of conflicting opinions expressed within the Committee.

On the one hand, donation could be considered as a sort of ante-natal adoption with the advantage that it would avoid destruction of excess embryos, if the parental couple decided not to proceed or failed to achieve their project.

On the other, it could represent a first step towards the production of embryos intended for adoption. The resulting "supply" of embryos leads to a serious risk of commercialisation, and might give rise to illicit trading.

Presently, no legislation allows such a donation which combines the problems related to the donation of oocytes to those related to the donation of sperm. Legal questions which would arise (specially in the area of filiation) cannot be answered in the present state of the legislation.

Therefore, the Committee is of the opinion that legal provisions should be devised, before considering the possibility of donating embryos to other couples. The Committee stresses the need for urgent legislation in that domain. Failing that, a real "black market" for embryos could emerge.

The number of practical questions related to In Vitro Fertilisation and Embryo Freezing show how difficult it is to elaborate fully satisfactory solutions. It also demonstrates the sequence of risks which could derive from uncontrolled medically assisted procreation. This is why one should endeavour not to fertilise more oocytes than it seems reasonable and safe to transfer. However, in the present state of knowledge and practice, it is not always possible to fertilise only the necessary oocytes. In vitro embryo research may be justified to reach this goal.

Recommendations regarding in vitro embryo research

Basic principles for research on human embryos

Ethical and scientific justification of human embryo research always leads to major differences of opinion, whether on a question of principle or of modalities.

Some simply reject the very principle of embryo research as a result of the respect they feel for the person they recognise in the embryo. As a consequence, they consider that the embryo cannot be used for research as this would make it into an object.

Others, who do not object to the principle of research, nevertheless diverge on how to analyse its purpose and methods, as well as on whether it is truly useful and on the definition of limits.

However, human embryo research has become a fact that cannot be ignored and must be regulated.

In spite of the opposition of some members, the Committee is of the opinion that it is not possible to exclude *a priori* any form of embryo research nor prohibit the donation of spare embryos for this purpose.

The Committee is also of the opinion that such research, because it deals with human embryos, potential persons, and because of its consequences, must be regulated and controlled in societal terms by bodies composed in such a way as to reflect various schools of thought.

Such rules and controls are necessary to limit the power of science over the genesis of human life and to oblige those who carry out and apply this kind of research to report on how they use the powers put into their hands.

The rules should take into consideration, not only the basic ethical requirement, but also the contradictions, risks and uncertainties regarding research on human embryos, as well as the advantages to be reasonably expected :

- for instance, contradiction between the legitimacy of research aiming at the benefit of the child to be born and the need to make prior experiments on human embryo;

- risks related to the determination or selection of the identity of children to be born, risks of drifting towards eugenics or parental convenience practices;

- uncertainties regarding the actual possibilities of research, taking into account the conditions necessary to obtain human embryos;

- Advantages which could contribute for instance,- as and when the embryo development mechanisms are better understood - , to the improvement of IVF-ET and a reduction of the ethical questions it raises, specially as regards freezing.

As a consequence, the Committee formulates precise recommendations, the restrictive nature of which is based on the need :

- to make sure of the reliability and scientific value of research projects likely to be authorised;

- to have sufficient time to determine the merits of genetic research, in particular :

- to avoid research without any medical utility and with unacceptable ethical or biological risks being undertaken.

Recommendations regarding in vitro human embryo research

Recommendations for research on the conditions under which embryos intended for transfer are obtained and developed.

1) Clinical tests with a potential individual benefit

Are considered as such, all clinical tests which can reasonably increase the couples' potentialities to have a child.

Such tests can only be undertaken if a sufficient number of preliminary data in humans are already available to indicate that there is a reasonable hope that this objective can be reached.

Based on animal studies, the treatment considered should have been proven safe for the continuation of normal development after transfer.

No test is possible without the couple's consent. Such consent should be obtained after giving full information on current practices applied to these tests.

Tests on embryos should be made by authorised biomedical teams under the responsibility of a biologist and a medical practitioner. A Committee of Ethics should be allowed to assess these tests at anytime.

Such tests are intended for couples in the framework of infertility treatment.

Presently authorised for clinical tests: research on ovarian stimulation treatment with a view to produce several oocytes for fertilisation and research to create in-vitro conditions for fertilisation and culture close to those permitting the in-vitro development of the embryo prior to its transfer to the womb.

Not authorised for clinical tests at present: research aiming at predicting certain genetic characteristics of the embryo, specially regarding gender and possible anomalies.

2) Clinical tests without potential individual benefits

We have mentioned under this chapter some types of research for which sufficient information is not yet available to demonstrate that they increase the potentialities of birth ;

- such research should only be considered when scientific data in animal research is convincing enough and that it can be demonstrated that its application to humans is clearly a step forward ;

- after clearly informing the couple of the purpose and stakes involved in such tests, written consent should be obtained :

- tests on embryos can only be achieved by authorised biomedical teams after scrutiny by a Committee of Ethics. When authorisation is granted, the Committee must be informed, if requested, of the tests results ;

- should be considered for the time being as clinical tests without potential individual benefits, all types of research on embryo freezing. Such experiments have been proven to represent potential progress, specially to increase the efficiency of IVF-ET, but they should not be systematically applied as long as the conditions to assess them from an ethical and scientific viewpoint have not been defined ;

- should not be used at this time for clinical tests, any research using embryo invasive(2) techniques and/or aiming at predicting certain genetic characteristics, specially regarding gender or potential anomalies.

Recommendations regarding research on spare embryos no longer suitable for transfer .

The Committee stresses that fertilisation of embryos for the purpose of research is prohibited. It also states the opposition of some of its members to the very principle of

embryo research. However, it is of the opinion that the donation of spare embryos for research is acceptable provided it is strictly regulated.

The investigations taken into account in this opinion are related to the acquisition of data necessary for future clinical applications (increasing the chances of implantation or oocyte fertilisation after freezing, for instance). Such investigations make it possible to extend to humans research already confirmed in animals (cf. Scientific report).

Embryos whose transfer to the womb can no longer be envisaged are called excess embryos.

1) Research is only possible :

- when the genitors' procreative project has been completed and with their free and informed consent ;

- when the animal research results has been reviewed in depth ;

- when its purpose has been properly defined, taking into account how it can improve therapy ;

- when in-vitro embryos are in the very early stages of development. In this respect it does not seem necessary - from an ethical or scientific perspective - to set a general limit to the time during which the embryos can be left to develop in-vitro. The two week duration recommended in some publications corresponds to no scientific indicator and leads to think that under this limit the human embryo is not a potential human being deserving respect, but only research "material" freely available. The Committee considers that human embryos must not be cultured without the legitimacy of a research project. It stresses that embryos deserve respect since fertilisation. However the value and medical interest of a research project must also be taken into consideration to determine the maximum duration of in-vitro development. The conflict of interests must be solved on a case by case basis. However, but this is purely indicative, the Committee recommends not to initiate research projects implying that it would be necessary to keep embryos beyond the time of transfer, that is around seven days.

2) It must be proven that embryo research is the only and exclusive way of acquiring the expected data.

3) Research must be carried out by other teams than those practising IVF-ET to avoid any possible pressure on couples during treatment.

4) First of all, the research project must be presented to the National Consultative Ethics Committee. If the project is agreed, it must be supervised by an authorised Committee of Ethics (or, if there are none, by the National Committee). This Committee shall report to the National Committee.

5) Freezing of embryos can only be authorised for a specific scientific project. Research teams must not make stocks of embryos if they do not have a precise research project. The duration during which frozen embryos can be kept must be fixed on a case by case basis according to each project.

6) Results obtained from the authorised investigations must me published and brought to the National Ethics Committee's knowledge.

7) The results obtained cannot be applied to clinical practice before receiving an opinion by the National Consultative Ethics Committee.

Moratorium on research

The Committee recommends that a moratorium should be established on research related to pre-transfer genetic diagnosis (diagnosis related to chromosomes, genes or gender).

This concerns only investigations associating collection by micro-manipulation (biopsy) of part of the embryo's cells (or nuclei) and analysis of the cells genetic characteristics. Such investigations have been considered by some researchers to improve, in the future, the rate of success of IVF-ET, by sorting the embryos, and, moreover, to remedy serious pathologies without having to resort to ante-natal diagnosis methods in the foetal stage.

Such research would lead de facto to new indications for IVF-ET besides infertility.

Of course, if the above mentioned recommendations were to enter into force, such a moratorium would not be necessary. But many uncertainties remain as to the immediate implementation of such recommendations.

Thus, in spite of the reservations expressed by some members as to the very principle of a moratorium, the Committee considers, after in depth debate, that such a moratorium is indispensable for ethical, medical and scientific reasons.

A risk exists with such practices to develop eugenic practices, which, becoming commonplace, could lead to ethically reprehensible practices of standardising human reproduction for reasons of health or convenience. Nowadays, such prospects rightfully raise concerns and even hostility from a large part of public opinion and a number of researchers and medical practitioners. To be tempted to select a child to be born on the basis of its qualities may seem contrary to human dignity as it jeopardises the respect for difference, singularity and freedom of that child.

In any case, it is indispensable to study in depth ethical consequences of the whole matter before considering a case by case review of the timeliness of such investigations.

Moreover, couples can now resort to reliable methods of ante-natal diagnosis at a foetal stage. Such a diagnosis may lead, in certain cases to therapeutic abortion. Trying to avoid the moral problems related to abortion by resorting to in-vitro embryos genetic diagnosis before implantation, is refusing to admit that, in fact, the difficulty to decide on abortion protects us against the temptation to sort genetically in-vitro embryos.

Present research on animals shows that embryo genetic diagnosis methods before transfer are still rare and not sufficiently tested.

The Committee considers that a three year moratorium would allow, based on animal embryo research, investigators to determine the scientific conditions required to adapt these techniques to human embryos, and ethical groups to better understand the consequences of genetic research.

Investigations to be prohibited

Germ cell gene therapy

Although they do not seem to have been tried yet on humans, but since they might be in the future, the Committee recommends prohibition of any type of research with a view to germ-cell gene therapy, i.e. any modification of the human genome by transgenesis (or production of chimeras) transmissible to offspring.

This prohibition does not concern somatic transgenesis (when it does not imply germ cells) which will be dealt with in a later opinion.

Research without scientific or ethical justification

The Committee also recommends prohibition of any type of research aiming at transplanting embryos from humans to animals, or male gestation.

It considers that there are presently no scientific grounds for research on complete in-vitro gestation (ectogenesis) or implantation of embryos obtained without spermatozoids (parthenogenesis).

Special recommendations for research on so-called excess oocytes

Research on excess oocytes before a possible fertilisation raises two specific problems: one is related to the conditions of collection, the other to the question of what to do with the embryos resulting from their fertilisation.

A) Conditions to obtain oocytes

- Oocytes can be obtained in the case of an IVF-ET. In the present state of knowledge, and taking into account the variability of results, it is not possible to predict the rate of success of fertilisation:

Using oocytes for research reduces the chances of producing a child. Therefore, the couple must give its consent. Such consent must be well informed as regards the achievement of the parental project. No oocyte collected in a IVF-ET procedure can be used for research without the couple's written consent, after having been fully informed, inter alia, of the number of oocytes intended for research.

- Oocytes which could be collected on the occasion of interventions not related to IVF-ET, cannot be collected for research without the written consent of the woman.

- Besides these two cases, it is not legitimate to collect, only for research purposes oocytes after ovarian stimulation, even with the patient's consent.

B) What to do with embryos resulting from fertilisation ?

Fertilisation of oocytes for research is not possible. It would be contrary to the principle described above.

It is, however, possible to envisage that oocytes could be fertilised with the husband's sperm (excluding cross fertilisation test) with a view to establishing a diagnosis. It is up to the couple to decide, with the doctor's approval, whether such embryos should be implanted, destroyed or donated for research purposes, exactly as if they were excess embryos. Such embryos are dealt with according to the rules described above.

C) Investigations on oocytes should be made by authorised biomedical teams under the responsibility of a biologist and a medical practitioner. They must receive prior approval by a Committee of Ethics which should be able to assess these tests at anytime.

Research on oocyte freezing, for which the data resulting from animal research is still inadequate, shows that there is an increased risk of abnormal fertilisation: in the present situation human embryos obtained from thawed oocytes should not be implanted.

The Committee recommends to review, within one or two years the results of investigations on oocyte freezing. Such reviews should lead to defining the conditions for possible clinical tests.

Recommendations regarding animal embryo research

Human embryo research must be conditional on the developments of animal research. But experience shows that the results of the latter can be easily, and sometimes hastily transposed to humans. It seems desirable to implement means allowing for an ethical assessment of developments in sensitive areas, such as genetics and developmental biology.

The Committee wishes to co-ordinate its work with that of research institutions.

Recommendations regarding the certification of in vitro fertilisation centres

Because they bear so many consequences for individuals and for society as a whole, artificial procreation centres cannot be left, as regards their creation or their operation, to the sole initiative of free enterprise.

As a consequence, no artificial procreation centre can be created or operate without the authorisation of Public Authorities. Such authorisation can only be given to those centres where the technical skills of its scientific and medical staff is recognised and which are fully able to receive, inform and assist couples who wish to procreate.

Such centres, which can have no commercial objective, must commit themselves to abide by the ethical principles ruling in-vitro procreation.

The opinion of the National Consultative Ethics Committee, or another national authority created for that purpose must be sought for, before granting such authorisation.

As long as such centres exist, appropriate controls should be made as to the way in which they implement the obligations imposed on them, to prevent violations that could lead to withdrawal of authorisation.

Artificial reproduction centres existing at the date of entry into force of the regulations will only be able to continue operating if they obtain authorisation.

The above conditions apply to research on gametes and embryos according to relevant ethical obligations.

The Committee wishes that, whenever possible teams involved in artificial reproduction should be different from those doing research. Independence should essentially be sought for when research applies to embryos which cannot be transplanted. Such separation aims at avoiding any a priori objective in artificial fertilisation.

The Committee recommends that Public Authorities should abide by the recommendations described in this opinion.

Authorities in charge of artificial fertilisation and research centres must have the possibility of obtaining at any time, all relevant information regarding all the centres where embryos are kept frozen. The purpose of this is to allow authorities, together with the committees of ethics to supervise the transparency of medical and research practices.

The Committee draws the attention of the research institutes' scientific councils to check that the recommendations described above are actually implemented by the research centres and investigators.

It is the responsibility of Public Authorities to draw the consequences of possible violations of ethical and scientific rules in biomedical research on human embryos, and to implement

the instruments to ensure their enforcement (specially regarding the role of Committees of Ethics, and of the National Consultative Ethics Committee.)

These conditions will eventually allow the public Authorities to supervise clinical and scientific practices and to consider adaptations or revisions that these recommendations may require for the future.

Contribution to the present opinion by Jean Gelamur

This opinion deals with a question related to the respect due to the human embryo. It is based on a reality that openly denies fundamental ethical beliefs.

It is legitimate that it should mention the reservations and objections expressed by certain Committee members. Expression of dissent stimulates ethical reflection. This reflection must be raised to the highest level when the progress of science challenges the conscience, as is the case for in-vitro fertilisation and research on human embryos.

I am of the opinion than research leads to considering the embryo as an instrument. Instead of having with the embryo a relation that respects the autonomy of embryonic life(3) , research creates a relation of omnipotence over the embryo.

Whereas in my opinion, the level of respect due to the embryo as soon as it is fertilised, implies that it should be given a chance to be born and that no-one should threaten its life.

Research also carries a serious risk of escalation.

This is why I think that research on human embryos is not acceptable when it leads to its destruction.

Therefore I am opposed to the part of this opinion regarding research that endangers the life of the embryo, and specially on spare embryos and production of embryos from excess oocytes for diagnostic purposes.

However "as human embryo research is a fact", it is necessary to define restrictive ethical rules and a rigorous external supervision, to prevent, as far as possible investigations from going astray. I believe that this concern is represented in this opinion.

As regard IVF-ET, I, personally accept its principle and I recognise the ethical value of many recommendations proposed, namely those relative to the couple's information and consent, and those aiming at not "fertilising more oocytes than it seems reasonable and safe to transfer".

But I have strong ethical reservations regarding the risks resulting from authorised practises: frequent destruction of surplus embryos, creations of stocks of embryos.

For these reasons I shall abstain on this part of the opinion, and I express the hope that all due precautions should be taken by the Centres, at the request of couples, so that procreated embryos can be transferred in satisfactory conditions.

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Scientific report

A coded macromolecule, a gene, a chromosome, an oocyte: all this belongs to the living. But none is fit to be born. If, one day, it were possible to achieve the compete development of a human oocyte or spermatozoid, it could not be called a birth. The "not born yet" only begins with the fertilised egg, made an individual, that is unpredictable although determined, by meiosis and amphimixis. To be born as an individual person, is to be produced, different from all others, not re-produced.

Georges Canguilhem in Biologie et devenir de l'Homme

Proceeding of the World Colloquium, Paris 1976

Introduction

In Vitro Fertilisation and Embryo Transfer (IVF-ET) in humans have become a form of infertility treatment only after many years of research originally made by a small number of teams around the world.

Now this research is developing at great speed and implies the use of human embryos. Should the very principle of this research be rejected, even though it allows major progress for science and medicine? If such investigations are permitted, what are the justifications and limitations to be imposed on their implementation?

This report presents the main scientific data necessary to deepen ethical reflection which is now essential to give an answer to these important questions.

It presents the state-of-the-art of research, which associates clinical tests and collection of fundamental data, and draws on previous animal experimentation.

Future prospects based on the anticipation of the results of investigations presently in progress are examined.

IVF-ET has only been taken in consideration for its consequences in the near future, although the speed at which science develops should lead to suppose that a complete transformation of human reproduction will not be impossible in the future.

What is an in vitro human embryo ?

Definition of the embryo

In general terms, the word embryo is used to describe the developmental stage which begins with a single cell, the ovum and ends with a complex set of cells, the foetus. During this phase, the ovum divides, then the cells differentiate and organise themselves to determine progressively the special characteristics of the foetus (cf. Annex 1).

Usually, scientists use, (in most cases indifferently), the words zygote or divided egg (sometimes even pre-embryo), to describe the stage which corresponds in mammals to the very first cell divisions (4 to 6) before differentiation into two lines of cells giving rise to the embryonic disk, (also called inner cellular mass), or a part of the future placenta (trophectoderm or trophoblast). One also refers frequently to pre and post transfer stages to describe the development phases before or after transfer into the mother's uterus. The word foetus is used to describe development stages when the major organs are organised and when the general shape, which is specific to the species is recognisable (in humans, the end of the eighth week after fertilisation).

- More accurate definitions of the word "embryo" have been proposed, specially to serve as

a reference for decisions regarding the limitations to impose on the use of human embryos in artificial reproduction programs. These definitions have led to the fact that today, the same word describes different situations.

- The human embryo has thus been defined either by developmental stages within the implantation period (sixth day after fertilisation, Walker Commission, Australia, 1983) or by the period of time corresponding to the six to eight weeks after fertilisation (Warnock Commission, 1984, Commission of Law Reform, Ontario, 1984). More recently, it was suggested that the term human embryo should be kept to describe the developmental stages ulterior to the formation of an axis of symmetry (primitive streak), that is around 14 days after fertilisation, which is also the last phase where identical twins can be formed; the word "pre-embryo" then defines all prior stages of development (European Medical Research Council 1986, American Fertility Society, 1986).

- This absence of consensus illustrates the difficulty of establishing a precise framework for a continuous process undergoing major events, such as the activation of the embryo's individual genome, cell differentiation, implant in the mother's uterus or formation of the main organs.

- The will to determine precise limits to define the human embryo, results from a utilitarian approach, which cannot, by itself, represent the idea of the beginning of a human being's life. Moreover the use of a new word (seldom used in scientific publications) "pre-embryo" may create the feeling that, for some time, the embryo could be treated differently, with less respect, namely in research, due to the fact that at this stage, only part of the cells will constitute the foetus, the others forming the placenta.

- It seems therefore preferable to use only a general definition for the human embryo.

Following the suggestion of the Council of Europe (CAHBI, 1986), the word embryo will describe all the developmental stages of the zygote, before the foetal stage which is reached in the eighth week of pregnancy.

In vitro human embryos, "spare" embryos

- In vitro human embryos means embryos resulting from a fertilisation occurring outside the mother's body, and maintained in an artificial environment before it can be transferred to the womb. It is considered as different from an in-vivo embryo, resulting from natural fertilisation or artificial insemination (AI).

- In vitro human embryos are generated in IVF-ET programmes, a well tried solution to infertility.

- In practice, the IVF-ET technology (cf. Annex 2) consists in collecting by laparoscopy mature oocytes directly from the patient's ovary and putting them in contact with the husband's sperm for in-vitro fertilisation. Another similar method is called GIFT (*Gametes intra fallopian transfer*) and consists in reimplanting immediately the oocytes (usually two or three) with the sperm in the oviduct. In this case, fertilisation can be obtained in-vivo but only once the gametes have been exposed to an in-vitro culture medium. On average, 50 to 70% of oocytes are fertilised, but the rates of success vary and depend very much on the quality of the husband's sperm. Embryos, are maintained in a culture medium at 37°C for one to three days before transplantation. During this period of time, they divide to reach the stage of eight to sixteen cells; division of in-vitro embryos is similar although often slower than in-vivo. In both cases there is a high level of loss due to the high failure rate in implantation. The rate is still higher with in-vitro embryos as it is considered that, if transferred one by one they would only lead to birth in 10% of cases whereas this rate is 25 to 30% for in-vivo embryos.

- To improve the chances of success, ovarian stimulation methods have been developed

allowing simultaneous collection of several oocytes. In fact it seems that the number of pregnancies increases as a function of the number of embryos transferred: the number of births is about 20% when three embryos have been transferred (and almost 30% with five embryos). But this increase also leads to a greater number of multiple pregnancies.

After hormone treatment it is possible to collect an average of more than three oocytes (four or five); the individual response varies and on some occasions it occurs that more than ten mature oocytes are available for fertilisation. As in practice, only a maximum of three embryos are now transplanted at the same time (to reduce the risk of multiple pregnancies), there are usually "spare" embryos.

- This had promoted the development of freezing technologies, so as to keep embryos not transferred immediately for future attempts.

Embryo freezing can be achieved with success at any stage of development, starting with one cell (two pronuclei) to the blastocyst (around four days after fertilisation). Only a proportion of these embryos (60 to 80%) survive this procedure: in this case, they maintain their normal development capability, but the rates of success to be expected from routine use of such a technique are not yet known. The freezing of mature oocytes sometimes results in a reduction on the fertilisation rate, and an increased rate of abnormal fertilisation.

- As a consequence, IVF-ET produces regularly "spare" in-vitro human embryos. This definition, commonly used, consists, in fact, of two different situations.

The first one corresponds to embryos that will be transplanted later to achieve the purpose of the couple (or of another couple) to have a child. Such embryos are all frozen and the data available in animals shows that it is very likely that they can be preserved for prolonged periods of time without any prejudice to their viability. The second one corresponds to the embryos which will not be used to achieve the purpose of the (or a) couple; such "spare" embryos are in most cases frozen or directly used for research.

- Last, it should mentioned here that, to be entirely accurate, one should refrain from referring to "excess" oocytes; it is not possible to know in the present state of in-vitro fertilisation to decide, even in the case of a large production of oocytes, as to how many will eventually be fertilised and fulfil the objective of the couple.

State-of-the art of embryo research

The case of in vitro human embryos

- The methods used in the case of IVF-ET are in constant progress. Implementing these methods is an incentive for biomedical teams to develop their research activity to improve their control over existing technologies and to devise new ones and understand the optimal conditions in which they should be implemented.

- In France, such research activities have not yet been listed or assessed for their impact on artificial procreation, or for ethical implications. The only available references are publications in scientific or medical journals, and communications at conventions.

Research can be broken down into three categories :

- The first one deals with the many clinical tests done for routine in-vitro fertilisation and embryo transfer. Such tests are essentially related to the definition of ovarian stimulation, conditions of oocytes and spermatozoid maturation and culture media composition. Their purpose is to confirm observations suggesting that the test will bring immediate advantage to the couple concerned as it will enhance safety and efficiency of IVF-ET, or will allow more comfort for the patients or a decrease of the overall cost of procedures. This research

describes the behaviour of the embryo cells (or gametes) during the in-vitro period. It may be of a fundamental nature, for instance when it deals with biochemical messages exchanged between the embryo (or oocyte) and the medium. Biologists take into account the aspect of embryos after the test to decide whether to proceed to embryo transfer.

- The second type of research concentrates on clinical tests aiming to an improvement of techniques not yet or little used in humans. Contrary to the first category, there is no immediate advantage for the patients and it results in the destruction of some of the embryos concerned: this is the case at the present time with embryo freezing. It must be underlined that only one team has the National Ethics Committee opinion as to this type of intervention.

- Last, a third category of research deals with the acquisition of the knowledge necessary for a possible future clinical application of these technologies: detailed description of the cells structure; definition (aspect, number) of chromosomal anomalies after fertilisation and culture; measurement of certain cellular parameters, such as permeability or electric potential, measurement of the synthesis of proteins to determine the embryo's activity, etc. This type of research is frequently of a fundamental nature. It usually requires the destruction of embryos. It allows generalisation to human embryos of techniques acquired in animals. This is the case, at present for instance, of oocyte freezing or of fertilisation by micro-injection of spermatozoids obtained from apparently non fertilising sperm.

- There is now an increase in the number of infertile couples and also an progressive increase in the medical indications for IVF-ET. IVF-ET was originally used in cases of women's sterility due to tubal obstruction, but other indications(4) were soon accepted, namely in the case of natural (hormonal disequilibrium) or acquired (infection) partial infertility in women. Other indications were given such as men's infertility which represent 20% of the cases of infertility of a couple.

At the same time, there are new avenues for in-vitro research on human embryos. It is proposed, for instance, to use embryonic cells to study certain genetic characteristics, such as those allowing the predict ion of anomalies related to certain diseases. Some researchers even consider that, in a distant future, it might become possible to correct genetic defects carried by the embryo.

Before going into what can be expected from research on human embryos in-vitro, it is best to clarify animal research and what methods are applied.

The case of animal embryos

Objectives

- Basically this research aims at understanding the events that permit a single cell, (the ovum) resulting from the fusion of two gametes to develop into a living being.

The development is obtained by the division and differentiation of cells to acquire the specialised forms and functions of the organism. It is the result of the differentiated action of genes, segments of DNA carried by the chromosomes. This complex process is not completely understood. It is not known yet, for instance, why cells multiply for three or four cycles in mammals and then start differentiating from one another. It is not known either how cells exchange signals with other cells and their environment and how this results in the formation of a foetus. On the other hand, very little is known about the regions of the genome which play a major role during development, and how the genetic programme has been modified with the evolution of species.

- Research on animal embryos is also done to check the "in-vivo" behaviour of some cells used for "in-vitro" cultures. This is typical of research on the evolution of tumoral tissues which reproduce the same type of differentiation as observed during normal embryogenesis.

This is also typical of the observation of the effect of (spontaneous or induced) mutations which interfere with the differentiation process of morphogenesis.

- Last, this research is sometimes done to meet the needs of industrial sectors; the pharmaceutical industry to check the possible teratogenic effects of a new molecule, but, even more, the agricultural and agro-industrial sectors where embryo research has made it possible in the past few years to achieve breakthroughs in the reproduction of domestic species and in the generalisation of genetic progress thanks to the selection of the best genitors.

Experimental practice.

The production of embryos is generally obtained by hormonal stimulation of the female. It is remarkable that, in a given species, the number of oocytes obtained after treatment, may vary considerably according to the animal (from zero to dozens). Such a difference is observed including in inbred lines of mice and research aiming at obtaining a limited and constant number of embryos (research on twin pregnancies in cattle) has failed.

In-vitro fertilisation has only been achieved in a limited number of laboratory species (mice, rabbits) and represents a major field for research, especially in most of domestic species where the success rate is still low. This research essentially concerns the recognition mechanisms between the two sexual cells, the modification of the spermatozoid membrane, the penetration of the ovum and the fusion of the two gametes; inter-species fertilisation is little used, except in a specific case: the "hamster test", used in medicine to assess male hypofertility: human spermatozoids are put in contact with hamster oocytes, specially prepared to test their fertilising power. The embryo does not develop beyond the two-cell stage.

Embryo freezing for conservation purposes is well established for various species, but not all (failure with pig embryos for instance). It is now admitted that long exposure (several years) to very low temperatures neither reduces the survival rate of the embryo nor increases the number of abnormalities.

However there is not sufficient experience yet on the freezing of oocytes; the success rate obtained until now (mice and rabbits) are still low and although the morphological aspect is frequently maintained after thawing, there are a large number of abnormal fertilisations and sometimes alterations of the cell structure (mitotic spindle).

In-vitro cultures are frequently used with early embryos as this technique makes it possible to intervene on its development before transfer into a receiving female. Nowadays, chemically defined media are able to sustain an apparently normal continuation of embryo development. But the chances for a given embryo to survive until normal delivery after transfer, decrease rapidly as the duration of in-vitro culture increases. This is true for all species after 48 hours in culture.

The culture of embryos can also be used to create lines of cells which maintain the same differentiation capabilities as an early embryo but which do not organise as they would do in a normal embryogenesis. These lines of cells have similarities with specific cells (teratocarcinoma cells) used as a reference to study the cell differentiation sequence. They represent a precious instrument specially for molecular genetic research. They can now only be obtained from whole embryos (and not from cells isolated by biopsy from these embryos).

Last, these cultures allow for in-vitro observation of a given phase of later embryogenesis and verifying the effects of the environment (drug toxicity, for instance) or the appearance of developmental anomalies. Techniques were devised to follow the morphogenesis, but only over a short period of time (a few days). There are, after the period when the embryo must be transferred, several stages critical for foetal development which, for the time being, makes it impossible to proceed to a complete gestation in-vitro.

- Re-constitution of early embryos by micro-manipulation of whole cells or their nuclei is an experimental approach applied both for fundamental embryological research and profit-oriented research (domestic species).

It is possible to aggregate embryos with different genetic characteristics and to produce chimeras allowing study of the origin of the tissues constituting the organism. It is also possible to cleave an embryo and to obtain identical twins (and exceptionally to repeat the procedure and obtain quadruplets); this technique is used in agriculture.

Transfer of nuclei is used to study functional modifications of the nucleus during cell differentiation. This technique, which has been recently mastered, is used to explore, in mammals, the still very limited cloning possibilities, that is the multiplication of a living being after transfer of the nucleus into a fertilised and enucleated egg. It also makes it possible to elucidate the respective contribution of the male and female originated genome (set of chromosomes) in the development. It was thus shown recently that the production in mammals of an offspring from one single genetic parent (parthenogenesis, androgenesis, single parent embryos obtained by the fusion of two unfertilised ova) had no scientific foundation for the time being.

The induction of modification to the genetic pool of an embryo is an approach used by many laboratories (specially in mice) to understand how the expression of genes (or groups of genes) is controlled. Modifications may result from artificially induced mutation (irradiation, chemical substances,...) or be induced by an injection of genes at the beginning of development (transgenesis), in a pronucleus of the ovum just after fertilisation during the few hours before the fusion of the two male and female genomes): such a method completes the conventional genetic practices of inbreeding selected lines of cells. A large number of genes, cloned and recombined by molecular biological methods are now available. In a small but significant number of cases (around 10%) the gene is integrated before the first division of the ovum and is transmitted like other genes. It is not yet possible to insert the gene at a specific site on the genome (which has tens of thousands of possible sites).

Nevertheless, it is possible to obtain in these transgenic animals the correct expression of the foreign gene (a few percent of the injected ova) and its transmission to the offspring of these animals. The injected gene, can also, as a result of poor insertion destroy one or several genes and promote new mutations that will be used, in turn as models for the co-ordination of gene expression.

Other methods to modify the genome are considered as the embryo infection with recombined viruses, or creation of chimeras by injection of specific cells (EK cells) into the blastocyst.

This approach can be completed by the direct analysis of the embryo genome to detect early anomalies or the presence of genes expressed in the first cycles of differentiation (implication of cellular oncogenes, for instance). In that case, conventional histological methods (karyotyping) are used as well as labelled genes (gene probes) hybridised on cell genes.

This approach is now used in agriculture to predict the sex of embryo prior to their transfer to the womb.

Human embryo in vitro research perspectives

IVF-ET and fertility control

Research on human embryos aiming at improving IVF-ET techniques should be considered to be a priority over other types of embryo research.

IVF-ET remains a not very efficient way to procreate, as it requires an average of eight to ten attempts to collect oocytes to obtain one birth. This success rate is about half of the estimated rate of natural fertilisation. Some couples undergoing IVF-ET obtain a positive result at their first attempt whereas others seem not to be able to succeed in spite of numerous attempts. The majority must accept the various constraints necessary to implement the IVF-ET protocol(5) and also the uncertainties as to the results of each attempt. This explains in part the high cost of this method of medically assisted reproduction: the cost of IVF-ET was estimated in 1985 around 15 000 French Francs(6) and the cost of birth of a child over 150 000 FF. (70 000 to 300 000 according to the teams).

To improve IVF-ET the biological events starting with ovarian stimulation and ending with pregnancy must be better understood and controlled . As a matter of fact, a halt in the development is observed at the time of implantation (between day six and fifteen) :

implantation is complete in only 15 to 30 % of cases. This hight failure rate results from several causes such as the transfer of the embryo to the uterus at a stage where it should normally still be in the tubes (desynchronisation), or the hormonal changes in the environment in utero as a result of the ovarian stimulation treatment, or the large difference in embryo quality : it is assumed that around 25 % of embryos have chromosomal anomalies incompatible with full development.

Research should thereforee concentrate on all the phases of in-vitro development, before and after fertilisation. Most of it can be achieved without a direct intervention on the embryo, by investigations on the medium or media in which they are placed prior to their transfer. Such investigation would, for instance, allow analysis of the signals exchanged between the in-vitro embryo and its environment. It could also be completed by investigations excluding the transfer of embryos to analyse the various aspects of cellular activity (metabolism, genome synthesis...) or intented to check whether the treatment has altered the functions which are essential to continue a normal development (to appreciate the " toxicity" of a medium compound, or to assess the efficiency of a low temperature conservation protocol).

This type of research can be extended to fertility regulation, and help to define new contraceptive methods modifying the gametes or embryos physiology. In such a case, the use of spare embryos is necessary to verify in-vitro the effect of these methods on early development. The implementation of this type of research raises several questions of interest beyond the scientific and medical context.

Regarding the conditions of use of spare embryos, and oocytes, not used in the framework of the couple's parental project.

- Under what conditions such embryos, or oocytes are available for research ?

What form of consent should be asked of the parents ?

- Regarding the availability of embryos and oocytes.

This is a small number : according to our estimates, the spare embryos not used in the framework of the couple's parental project but available for research represent only 10 % of spare embryos, which are more and more frequently frozen for conservation. Certain types

of research require at least a few dozen embryos to allow an accurate analysis of the resultss obtained. Several teams have large stocks of frozen spare embryos (three to six hundreds, that is thirty to sixty spare embryos available for research if our figure of 10 % is adopted) while others still do not freeze embryos.

Is it necessary to register (frozen) spare embryos which are not used for the couple's project and to suggest that several IVF-ET teams should work together on a research project ? To increase the number of available embryos should the creation of human embryos for research be authorised ?

- Regarding the duration of embryo culture.

The critical phase for transfer occurs between the sixth and fifteenth day after fertilisation. It has not been studied in depth as today it is not feasible to develop an embryo in-vitro for such a long time : today, only 20 % can reach the blastocyst stage after six or seven days in culture and only a few present the characteristic aspect of an embryo in the implantation phase. The complete gestation of an in-vitro embryo is far from being a concern for the near future.

Should this make it unnecessary to set a deadline for in-vitro culture of embryos ?

Should a limit be fixed arbitrarily or decided on a case basis, according to research objectives ?

All these important questions must be related to that of future alternative measures to IVF-ET, such as tube graft or transplant.

Genetic diagnosis of the embryo prior to transfer

The analysis of the embryo's genome is considered for a very early diagnosis of genetic diseases, to avoid later therapeutical abortion.

We have seen that in animals it was possible to separate from the embryo a few cells without any prejudice to its development ; we also know that an embryo can be frozen after a biopsy. If these two technologies are associated its is possible to consider transferring the embryo into the mother's womb only after genetic examination of the cells.

The development of the analysis of the genetic characteristics of isolated cells is spectacular. Methods in molecular biology become more sensitive and simple and allow genetic diagnosis with only a few cells (less than ten, and maybe soon only one).

But such methods have not been tested in depht in animal embryos: in fact, the research objectives in animals do not require an early diagnosis. There is a recent exception, the sex determination in cattle embryos, but the efficiency of this method as a routine procedure has not yet been demonstrated.

Moreover, the reliability of such methods is not yet known. In practice, there is no secure way to culture or multiply isolated embryonic cells to obtain a sufficient number of cells for the tests.

One could consider cloning the embryo by nucleus transfer to reproduce identically a given embryo but the success rate of this method is still very limited ; several copies could be used for genetic diagnosis purposes, either directly of after some time in culture.

It seems, therefore, necessary to define first in animals the real possibilities offered for genetic diagnosis on the in-vitro embryo before considering applying these techniques to human embryos. However, if a practical and reliable solution could be found in the near future, it would still be necessary to consider the medical consequences of its application

which requires, at least : in-vitro fertilisation, freezing of the embryo while the diagnostic analysis is made, and transfer. The genetic diagnosis of the embryo could be used for couples who apparently do not succeed in procreating and have had several spontaneous abortions. It would then be possible to transfer only embryos apparently free of (chromosomal) defects. But couples who run the risck of conceiving children with a genetic anomaly are usually fertile. With the antenatal in utero diagnosis, as it exists today, if the foetus has an anomaly, there can be an abortion ; in the far most frequent case, that of autosomal recessive diseases linked to the X chromosome, 75 % of pregnancies reach their term and the child is normal, if the transmission is dominant, 50 % will end with the birth of a normal child.

In the case of a diagnosis made in-vitro on the ovum, an in-vitro fertilisation would be necessary, and the rate of birth is only 10 to 15 % even if the implanted egg is normal.

This would replace the physical and psychological traumas resulting from abortion by the physical and psychological traumas resulting from in-vitro fertilisation in a fertile couple.

Anyway, it seems necessary to proceed to antenatal diagnosis to verify the first diagnosis and to solve the problem, if necessary, of anomalies resulting from normal conception ;

The decision to use in-vitro human embryos for research aiming at allowing genetic diagnosis of the embryo must take into account the existence of methods of prenatal diagnosis in utero. Such a diagnosis is obtained from embryonic cells collected by chorionic villi sampling, amniocentesis or umbilical blood sampling. These methods present various possibilities of chromosomal analysis or gene analysis, either by expression of the gene (haemoglobin or enzymes, for instance) or by research on the DNA by direct methods (revealing the mutation) or more frequently by indirect methods (genetic link with DNA polymorphism). These methods can be extremely reliable when used routinely in specialised centres.

Modification of the embryo's genetic pool

Transfer of genes into the embryo's cells could be considered treatment by " gene therapy" of anomalies of the embryo, i.e. to replace one (or several) defective genes by one (or several) undamaged genes.

To do so it would be necessary to transfer the new gene exactly to the very site from which the defective gene has been removed. This has not yet been done successfully in animals (see above) and has only been observed on rare occasions in culrured cells. In practice, the transferred gene is inserted in an in an uncontrolled way and, in a number of cases, may alter another gene and induce mutations (in 10% of insertions).

Although it is possible that this difficulty may be solved in the future, the transfer of genes to the embryo in-vitro at the beginning of its development could alter the genetic pool of the somatic cells of the future foetus, but also that of its germ cells as they are derived from the primitive ectoderm and differentiate only in the third week after fertilisation. The new genetic character could therefore be transmitted to the offspring. This probability is high if the integration of the foreign gene is done at the single cell stage. "Gene therapy" by transfer of foreign genes to the embryo in-vitro leads, de facto, to a modification of its hereditary genetic pool, transmissible to future generations; it is "germ cell gene therapy".

Medical applications of this practice must take into account their low efficiency, as the probability for a proper insertion of the injected gene is now only of a few per cent. It requires in-vitro fertilisation, in-vitro analysis of the embryo to detect the anomaly and embryo treatment before transplantation. Last, one should keep in mind the fact that in Mendelian transmission, there are always at least 50% (dominant character) and most frequently 75% of conceptions that result in a normal child. Therefore, there will be,

amongst the embryos obtained from couples at risk, normal embryos, (except in the extremely rare cases where the two parents are homozygous for the anomaly).

Not to mention the cost of such a practice, is it reasonable to propose the reimplantation of an abnormal embryo after gene therapy while normal embryos are available (and would therefore become spare embryos!)? Such a programme seems absurd from a medical point of view.

Other types of research

As to the view regarding the possibilities of an entirely artificial pregnancy (ectogenesis) or a male pregnancy, or the possibility to produce children from a single genetic parent by parthenogenesis or fusion of two oocytes, they have no sound scientific foundation as regards animals (mammals) and cannot be considered as avenues for research on human embryos in-vitro.

However, the very existence of this viewpoint makes it clear that there should be periodic reviews of animal research to assess scientific progress and determine possible consequences for applications to in vitro human embryos.

Annex 1 : The human embryo development

Fertilisation - i.e. the meeting of the ovule and the spermatozoid - occurs within a few hours after ovulation. This encounter takes place in the Fallopian tubes (oviducts). The resulting ovum is a single cell which defines the beginning of embryonic life. It is approximately a tenth of a millimetre in diameter.

During approximately twenty hours, the nuclei of the two parent cells remain at a distance within the cytoplasm (two pronuclei stage). Then, they move closer and fuse.

Then the ovum divides into two and then into four cells; approximately four days after fertilisation, the divisions have led to a embryo composed of sixteen cells arranged in a specific configuration, the morula stage, which is formed in-vivo around the time when the embryo reaches the uterine cavity.

Differentiation then begins between cells which form a hollow fluid filled sphere; this characterises a new stage, the blastocyst: the wall cells will eventually form the placenta and the foetal membranes; in the blastocyst, a more dense part of the cell wall forms a inner cell mass, part of which will differentiate to develop into a foetus.

At this stage of development, reached around five days after fertilisation, the embryo is not yet attached to the mother's uterus. The attachment begins on the sixth day and characterises the implantation stage. The embryo implantation is completed at the end of the second week. During all this phase, the blastocyst continues to develop.

A second fluid filled cavity, the amnion, develops within the inner cell mass. Around the fourteenth day, the primitive streak marks an axis of symmetry around which new sheets of cells will align. What is called the embryonic disk is then visible, well delineated and differentiated from the embryonic envelopes and annexes. This stage in development is theoretically the last one in which twins can be formed.

Then there is a series of quick modifications of the embryo. Around the eleventh day, the neural furrow is formed and transformed into neural folds which, in turn, fuse around the twenty-third day to form what will become the spinal cord. At the beginning of the fourth week, the embryo is 3.5 millimetres long. It has the arched shape typical of all animal embryos, with a large bulge at the front which will develop into a head. The primitive heart tube is formed and operational; parts of blood vessels are visible.

In the second week, the embryo has grow much as it is around two centimetres long. The eyes are present and limb buds appear. They start elongating in the seventh week. Although still immature the nervous system and muscles are organised and the embryo can make movements which are detected by ultrasonography.

The eighth week closes on the end of the embryonic phase and the beginning of the foetal phase. By then, the embryo has acquired a general aspect characteristic of a baby. All the principal organs are formed and ready to continue growth and development.

Annex 2 : IVF-ET in short

In-vitro fertilisation requires a series of steps :

- first: collection of mature and fertilisable oocytes ;
- second: collection of fertilising spermatozoids ;
- third: culture proper ;
- fourth: embryo transfer.

Each of this steps is necessary but not sufficient to guarantee the establishment of pregnancy.

In-vitro fertilisation can be considered after ascertaining sperm quality, ovaries accessibility and uterus condition.

First step : collection of mature and fertilisable oocytes.

The preovulatory oocyte is collected after ovulation stimulation, i.e. after intake of tablets or intra-muscular injections stimulating the growth of intra-ovarian follicles. During the few days before ovulation, ultrasonographic examination and blood sampling are performed until the oocyte maturation is deemed sufficient. Then, ovulation is triggered by the injection of HCG.

Oocyte collection is done by coeloscopy (under general anaesthesia) or ultrasonography (local anaesthesia).

Failure may take place already in this phase, as some women have no reaction to treatment, and their ovulation is considered insufficient. Sometimes the intervention takes place but no oocyte can be collected (10% of all cases)

Second step : collection of fertile spermatozoids .

After sperm has been obtained (by masturbation), it is treated by centrifuge diffusion with a view to collecting mobile and morphologically well formed spermatozoids. A quality threshold must be applied to increase the chances of fertilisation, which eliminates a number of male pathological problems.

Third step : in-vitro culture of the ovum

Several culture media are available to proceed to the fertilisation of human oocytes following the physical and chemical requirements necessary for such a culture. The culture is maintained for forty-eight hours during which an embryo of four or eight cells is obtained. 80% of the oocytes reach the embryonic stage : the fact that these are morphologically normal does not preclude chromosomal or other anomalies which could appear at a later stage.

Fourth step : implantation of the embryo .

It is done without a general anaesthesia, by introducing a thin catheter through the cervix and the deposition of the fertilised ovum close to the cervix. The patient is then asked to rest.

The percentage of success is around 15% per attempt. This means 15% of chances of giving birth to a live child, nine month after the intervention.

In fact, it is important to understand how figures are quoted, and what results are compared. Pregnancy does not necessarily mean development of pregnancy as there are losses between the monitoring of ovulation, the operation proper and the embryo transfer, which will eventually only be done in a percentage of patients. It is obvious that the percentage of success by transfer will be higher than the percentage of success for women entering the protocol.

It must also be underlined that the number of embryos produced varies enormously as it already varies between the number of oocytes collected and the number of embryos produced. It is a sort of lottery. In the present state of knowledge, we are not able to distinguish those which are fit for fertilisation. When there are more than three embryos, the so-called "spare" embryos are frozen to be transferred in a later cycle in case of failure of the first transfer, to avoid renewed surgical intervention.

A couple on average makes three attempts a year. The surgical procedure always entails physical sequellae (although extremely limited), but the psychological sequellae of disappointment are worth mentioning.

Ethical report

Contrary to what some would have us think, it is not biology that dictates a certain concept of humanity; it is through a concept of humanity that biology can be used in the service of mankind. (F.Gros, F. Jacob, P. Royer, in Sciences de la Vie et Société, La Documentation Française, p. 288, Paris, 1979).

"A fashion of being both paradoxical and flawless, the relationship of the being to the self, a self which is neither angel nor beast, nor pure spirit, nor simple nature, but all and each and must survive or fail in an impossible synthesis" (Y. Bonnefoy, in Le nuage rouge, Essai sur la poétique, Mercure de France, p. 35, 1977).

We have just opened a scope of possibilities to knowledge and intervention... We have just touched upon the potential, the virtual as a possibility... The master no longer strives to threaten the body of a slave or to better confront death, through audacity or bravado. The aim is to control nature, what shall be born, what is fated or willed to birth, the unborn potential. He controls the straits, the narrows, the restricted portal where possibles claim their chance to exist. He can eradicate them without a struggle. It is there that a fragile ethic appears". (M. Serres, in Génétique, procréation et droit, Actes Sud, p. 28, 1985).

Introduction

1 - The fact that in-vitro embryos are available outside of the maternal body, raises in a new way, the essential ethical question of human responsibility confronted to the genesis of life. Because fertilisation is the result of human decision (couples, doctors, biologists), because the fate of embryos is largely dependant on new decisions, because the future and the destiny of such embryos do not depend any longer on nature only, ethical questions become more difficult than in the times when one could simply discourse in an abstract way on the nature of the being in gestation, on the time when it becomes animate or emerges as a person or subject, although ancient dissertations have not always been devoid of

social, legal or religious consequences nor have entirely lost their relevance to solve problems raised in our times by medicine and scientific research applied to the beginning of human life.

Since Greek and Latin antiquity, and up to the present day, the cultural, philosophical and ethical heritage has painstakingly contributed to a building up a representation and significance for the human being, and establishing respect for the human being's dignity. This is in no way denied. Such a heritage is, quite obviously, plagued with conflicts, doubts, and philosophical or religious disputes. Moreover, scientific and technical development, control of nature and secularisation of our societies have led to desacralise life, and as a consequence, to extend the power of man over it. However, it does not follow that power and freedom have no boundaries, even though the enunciation of limitations does not result from certainties that can be demonstrated. With the help of our cultural achievements, it should be possible to reflect on what can be done today to an embryo, keeping in mind references which give meaning and not just utilitarian efficacy to technical and scientific means of human reproduction and the resulting research. It is also necessary to admit that we are in the presence of new problems, for which solutions cannot be found in traditional cultural references, which in part do not exist. We must also recognise that it is extremely difficult to reflect upon the problems themselves, and also on their medium and long term consequences. Yet, in this vast, hazardous, conflicting and shifting context, we are forced by circumstances to adopt positions, however relative and provisional and tentative, and justify them.

The basic requirement on which the respect for human dignity is based is the highest of all values, and must be translated into the actual de facto situations. It should constitute the criterion allowing a choice between conflicting values or interests derived from the possible use of human embryos.

The respect for human dignity that some scientific or medical practices could jeopardise by considering subjectively only their own aims cannot be separated from the respect for science itself and its own methodological requirements. To seek in human dignity ethical grounds for science itself requires that the intellectual ethics of science should be respected. If scientific knowledge per se is indicative and not prescriptive, if its true grandeur resides in the humility and rigour of research, then science has nothing to fear from rules not secreted by itself which guarantee the respect of science because it is not used incautiously, for scientifically or ethically unfounded objectives and desires.

Trying to define ethical principles respecting human dignity (as regards the potentiality of a person represented by the embryo as soon as fertilisation occurs and the consequences that its use may have for the representation of the person in general) and the dignity of science for the benefit of knowledge and protection of life requires confronting this dual requirement with the power that we have acquired of what amounts to using human life for various purposes. On the other hand, in-vitro fertilisation and the resulting availability of in-vitro human embryos require justifications and limitations that only external opinion of critical judgement can endeavour to formulate, so that deeds, already done, or likely to be done in the future should not be considered only in the light of efficiency but also taking into account the often uncertain and contradictory values which found medical or scientific action, especially when the intervention takes place on the very threshold of life and where several possible futures are at stake and must be chosen from.

2 - In-vitro fertilisation development and the dissociation it creates between sexuality and conception, between conception and gestation, the existence and development of cryopreservation and the resulting time separation between fertilisation and gestation, and, lastly, the production of embryos in numbers larger than medically necessary, or desired by parents, for transfer with a view to the birth of a child, and the availability of embryos intended for destruction, donation to other couples or research are facts that require serious examination. The legitimacy and consequences of these facts must be thoroughly assessed, as they could serve as a foundation for the principle and measure of human responsibility

and therefore of the rules or guidelines applicable to the use of human embryos, to be ethically acceptable, if not always justified.

3 - In some cases, to reduce responsibility, it is argued that in-vitro fertilisation is not artificial as the purpose of medical intervention is to reproduce natural conditions, or that the destruction or wasting of untransferred embryos reproduces nature: some 50 to 70% of fertilised ova are eliminated before uterine implantation.

Although it is true that the artificiality may be more or less pronounced in different cases, and that nature is not always betrayed in medically assisted reproduction, reference to nature is not per se a sufficient justification of human actions. It ceases being a justification when, not any longer content with curing, science and medicine far from correcting a natural order disturbed by specific diseases remedy and modify that natural order and act at the very source of life. The fundamental ethical question, from which all specific ethical questions derive is less the result of artefacts introduced by reproductive medicine than of the very principle of human voluntary and deliberate intervention to induce fertilisation, organise human embryos, decide their fate and, in particular, transform them into material for fundamental or applied research with what may appear to be now, or in the future, unlimited consequences.

4 - From an ethical viewpoint, it would not be satisfactory either to follow only commonly approved customs of our society. On one hand, principles may differ and are based on diverging opinions; on the other, and more importantly, customs are not the law, although they represent a useful indication on which to establish rules. Regarding the status of the human embryo, the increasing use of contraception, and the depenalisation of abortion suggest that, in a legally defined time frame, a human embryo is purely an object in its mother's power; this leads certain medical practitioners or researchers to think that the existing power to destroy (even though the law allows abortion only in cases of distress, which is the legal equivalent of the lesser evil) entitles them to use the human embryo as they see fit and in particular for research. The contradictions of a society, which for the sake of individual preferences, allows quantities of potential children to be destroyed, whilst at the same time endeavouring to produce children by means which are not normal human reproductive procedures and at a high cost, may be considered regrettable. It is also possible to stress the contradiction embedded in in-vitro fertilisation which, acting to create life, is compelled at the same time to destroy life.

To legitimise *a priori* the possibility of using human embryos by an *a contrario* reasoning based on the neutrality of the law or common usage regarding abortion, is not entirely justified. This reasoning ignores the fact that the law not only is concerned with implanted embryos, but also, and essentially the fact that, for social more that moral reasons, it has moved ethical questions out of the domain of law to that of individual consciences. The ethical issue remains intact and continues to divide public opinion.

To refer to principles alone would lead ethical reflection onto the path of moral relativism, although our society, in spite of its contradictions or conflicts is in search of ethics unencumbered by pure dogmatism or relativism.

5 - The present and future power of science, acting as third party in the genesis of life and able to modify a subject's identity, requires a difficult ethical reflection on the meaning, purpose, means and consequences for man of such new powers, as well as the elaboration of ethical, deontological or legal standards combined with the establishment of pluralistic control authorities, to orient the exercise of such a power in the direction of the common good.

6 - Ethical reflection and the elaboration of standards are ab initio confronted with serious theoretical and practical difficulties that we should try to overcome, if only on a temporary basis. Such difficulties are related to the very principle and scope of a normative intervention, the basis and contents of standards, guidelines or recommendations to be devised, the methodology for their preparation and enforcement procedures. Last, and more

importantly, taking into account a changing, fluctuating and uncertain social and scientific environment, as well as unpredictability of medium and long term risks and advantages resulting from medically assisted procreation and embryo research, the major difficulty lies in the necessary arbitration between mandatory universal ethical requirements and contingencies related to practical situations and the plurality of philosophical opinions which may justify or demand mitigating the possible ethical dogmatism and absolutism.

Actually, differences of opinion bear not only on the modalities of regulation, which is considered necessary in essence by most parties. They also apply to the substance of rules or guidelines, because the threshold between what is acceptable and unacceptable is different for everyone, and any argument can be opposed. Finally, they also bear on fundamental principles and in particular the issue of whether and for what purpose or subject to what conditions and limitations, human embryos may be used for research.

The research for, if not an ethical consensus, but at least an agreement as to the deontology of in-vitro fertilisation and embryo research, led the Committee to adopt a position on various issues (with the reservation of expressly dissenting opinions). The main orientations to interpret or clarify this opinion are detailed below.

Problems related to the principle and scope of a normative regulation, the ethical foundations of the substance of principal recommendations, the spirit in which the Committee had to arbitrate on conflicting values to define a research deontology are detailed below.

Legitimacy, scope and modalities of normative regulations

7 - In-vitro fertilisation developed in France without the benefit of any specific regulations in the framework of public or private centres where medical practitioners and biologists cooperate. A number of studies have evidenced a proliferation of centres and medical indications for IVF-ET(7) as a remedy to infertility in a couple.

Obtaining human embryos likely to be used for research raises the question of assessing the present situation, a reality that cannot be ignored even though some may disapprove of it, before actually legitimising such a research.

Whether it is done for reproductive or research purposes the subordination of such techniques to standards or controls must be justified. It is thought in some quarters that an across the board, normative and even possibly mandatory regulation is in conflict with the principles of freedom :

- freedom of physicians to prescribe ;
- freedom of scientific research ;
- freedom of patients, when they resort to IVF-ET techniques.

It is thought by some that any regulation would run counter to the respect for individual convictions and raises the question of *a posteriori* liability in the case of injury or malpractice.

Society should limit itself to verifying that patients have given informed and free consent and that the quality offered by reproductive medicine is technically satisfactory. Whereas it is clear that such conditions are necessary, are they ipso facto sufficient ? Obviously not, as the fact that standards are asked for in this area demonstrate that the sole reference to individual conscience is not sufficient to reflect ethics. On the contrary, once one enters the domain of on-demand medicine, and in particular the domain of the on-demand child, the need for standards defined by others than those directly concerned (patients, doctors, researchers) becomes essential. It is particularly important as a consequence of the limitless nature of expectation and of power whereas the situation tends to eliminate critical

judgement and engages into an ever expanding system which leads public opinion to ask "but where will all this end" ?

8 - By definition, scientific research does not impose limits on its scope and its purpose is to overcome any hurdle it encounters. However, in the case of human reproduction, it remains true that many things are still not known about the genesis of fertilisation, embryonic development, reasons for failure of implantation. It is also true that research on the embryo permits, or will permit in the future, genetic diagnosis, interventions defining human beings, which awaken or reawaken the spectre of eugenics, a potential tool in the hands of science, as is already the case with industrialised reproduction of certain animals. The need to orient research towards ethically acceptable objectives and to limit the way in which embryos are reduced to the status of mere objects, justifies the establishment of rules and controls.

The limitations or difficulties that might arise for certain types of research do not jeopardise research itself, which can move in other less hazardous, albeit less spectacular, directions.

Thus, the Committee is led to suggest that medical research should look for genuine remedies to sterility and to prevention of its causes. Normative regulations applied to fundamental research may seem questionable to those who think that only applied research can be controlled. Yet, in the biomedical field, such a distinction is more questionable with every day that passes. For that matter, it is broadly ineffective for in-vitro fertilisation which, in terms of therapy, remains "experimental" whereas it produces human embryos which in turn enable further research to improve or generalise IVF-ET.

It seemed necessary to decide at the same time on the legitimacy and conditions to be applied to fundamental research for the sake of knowledge, on the advisability of a dual control system - the authorisation to embark on research followed by authorisation to apply the results of research - and, as far as possible, on the separation between research personnel on the one hand, and IVF-ET personnel on the other.

These recommendations are intended to avoid allowing absolute power to enter the human equation, by reference to scientific "progress", the reality of which is not always demonstrated nor the consequences always fully assessed.

9 - Absolute power can also be the result of a human being's yearning to have a child, whatever the cost, as some examples have demonstrated. In certain cases, there is even an expectation that science will produce the perfect child. Desire per se is infinite, and contrary to the moral approach whereby an action depends on prior assessment of its merits, the logic of desire is such that the right to act depends on the power to act.

This combination of desire and power tends to eliminate moral judgement which should be reintroduced by external standards proposing references which cannot be rejected, at least for the time being, despite individual moral standards of a more liberal character than those upon which such references are based.

10 - On the contrary, one could recognise and accept that doctors, researchers or patients entertain more stringent moral principles, and that these should be respected as should the possibility of invoking conscientious objections. This is specially true for in-vitro fertilisation, for instance, to make sure that only oocytes to be transferred are fertilised.

It is also essential that patients are fully informed so that they can freely give or refuse consent regarding the use made of embryos.

11 - One concern of a large section of public opinion is whether ethical principles or deontological rules required to regulate artificial reproduction and biomedical research on human gametes or embryos can be made effective.

In the absence of specific legislation, recommendations or opinions of committees of ethics are not legally enforceable and consequently, there can be no guarantee that centres will

observe deontology. There are risks of slippage or drifting towards uncontrolled practices that could then acquire the authority of the fait accompli. This is why it is important, and on this opinion is unanimous, that Public Authorities should adopt appropriate legislation for controlling practices, ensuring transparency and meeting the real needs of society. It is only through official approval of centres that the scientific and ethical qualities of personnel could be ensured and commercial practices avoided, which in fact corresponds to an attitude which has prevailed in France for many years.

Moreover, it will be necessary for Ethics Committees to be fully independent and pluralistic so as to avoid irremediably conflicting opinions pronounced by a multiplicity of bodies. However, such committees seem necessary to implement and adjust to specific situations the general recommendations elaborated by the National Ethics Committee. It is considered by some that a law regulating conditions and effects of artificial reproduction or the limitations imposed on embryo research, is the only way for society to make sure that ethical requirements and social justice are respected.

Only a law can pronounce sanctions for violations of its rules. As the Committee is not competent to give opinions on social and legal matters related to artificial reproduction and legal protection (civil and penal) of the human embryo or of the foetus, unless it were specifically requested to do so, it has only given an opinion on the official approval of centres.

Nevertheless to be able to discuss within the boundaries of its competence, IVF-ET and human embryo research deontology, the National Committee had to analyse the ethical foundations of proposed recommendations.

Ethical foundations of interventions and research of in vitro embryo

12 - The practice of in-vitro fertilisation as a remedy to infertility is not questionable as to its objectives. When a couple is willing to have a child and is physiologically unable to do so, giving them a chance to procreate appears to be a legitimate goal. However some think that these methods are lacking in humanity since they reduce human bodies to the status of objects. This tendency towards instrumentalisation affects above all the ovum fertilised in-vitro, i.e. the embryo. For the embryo, the issue of whether medical or scientific procedures to which it is subject are legitimate or otherwise, is not simply in terms of how they are performed, but why. This is so whenever embryos are not or no longer to be transferred and it becomes unlikely that they will come into the world. The solution of ethical problems requires prior reflection as to what should or could be defined as a "human embryo" distinguishing clearly between persons who must be treated with respect and inanimate objects which can be used.

During the development of human embryos, the indivisible individual person reaches integrity and autonomy, in a progression through evolutionary thresholds and multiple dependencies where the request for respect appears under different forms. This is the specific difficulty of ethical problems in the field of human embryos: In this borderline case, the common understanding of a personality yields to the necessary accurate definition of its scope, failing that, it could not suffice to base a consensus on the extent of our duties in successive situations leading to the creation of a human being.

The complexity and novelty of questions raised by artificial reproduction require, from a moral viewpoint, an in depth, and partly innovative theoretical reflection.

After explaining the methodological approach followed by the Committee to conduct this reflection we shall ask whether the qualification of the embryo as a "potential person" is based on reason, and what general ethical consequences should be derived. This analysis makes it possible to justify certain recommendations as to the principles enunciated in the

opinion.

Defining the methodology of the problem

13 - A possible approach is to derive from well established definitions of the human person positions to be adopted for each of the issues arising. In spite of its theoretical interest, this approach is not appropriate for an organisation representing the existing plurality of philosophies that disagree as to the ultimate foundations of the person or the necessity of giving fully human status to human embryos whereas such foundations should represent the starting point of such an approach.

Inversely, a pragmatic approach could be to leave aside doctrinal differences and assess empirically, on a case by case basis the advantages and risks of each research program for individuals and for society. Although it can usefully cast a light on the practical consequences of the choices to be made, this approach falls short of really ethical questions which arise inevitably whenever it needs to determine the scale of values according to which risks and advantages are assessed.

Taking due note of these two impossibilities, the approach adopted by the Committee is that of a non-dogmatic exploration of attitudes of principle likely to obtain unanimous, or at least broad consensus and mention specifically categorically dissenting opinions. This approach implies :

- an effort to base as far as possible on the rule of reason an ethical argumentation neither infringing on, nor refuting metaphysical or other choices and which explains the reasons for adopting certain options and makes them consistent;

- a concern for the ever-changing complexity of questions so as to avoid both aspirations to perfection and concessions to relativity and formulate in the present scientific and medical context circumstantial rules not excluding, if needs be, a solution on a case by case basis;

- awareness that in spite of the rapid progress of medical knowledge and know-how, many processes remain obscure and hazardous. They imply immediate risks for the individual in gestation, longer term risks for the attitudes and representations on which the very idea of a person rests. Such risks cannot be assessed at this stage but there are reasons to believe that they are real and possibly prohibitive. This leads to proposing, by default, as long as the necessary conditions for better ethical evaluation are unfulfilled, simple rules of caution that may go as far as a recommendation to establish a moratorium for certain types of research, or even prohibit them.

Is the notion of potential human person based on the rule of reason ?

14 - From what stage of development should the human embryo be considered to be a person? It is in this form that the essential question is raised. Ethical reflection is confronted with this question of respect for the human embryo. There is no easy answer.

Asked factually and without any clarification what is meant by "human person", it does not seem possible to arrive at a scientifically binding and universally convincing answer, as the variety of opinions expressed by researchers or the public at large seem to indicate.

Of course, one could answer negatively, that from a purely biological point of view, the threshold cannot be before fertilisation of the ovum, because, although the separate gametes can be considered to be alive, only their fusion results in a new individual.

Nevertheless the problem remains. Some think that the person is present in the embryo since conception; others believe that it is only possible to speak of a person at a later stage, but opinions differ as to what stage: implantation after the sixth day, appearance of the

primitive streak at the end of the second week, viability around the twenty-fourth week, or birth itself.

The hope of solving this problem on purely biological grounds is illusory if only because these differences of opinions, independently of any metaphysical belief, are based on differences that cannot be arbitrated by science according to a definition of the properties that characterise the human person. Description and prescription should not be confused. For instance, whatever the scientific merits of the novel but controversial notion of pre-embryo that is sometimes used to describe the zygote until the second week, it should not embody per se any decision as to what respect it commands.

Aware of such a difficulty, the Committee did not deem it insuperable. Considering that many biophysical properties of the human person appear progressively during the development of the embryo but that progression towards personal being starts at conception, the Committee defined, in its first opinion, the principle that "the embryo or the foetus must be recognised as a potential human person".

15 - As could be expected, the notion of potential human person gave rise to discussion and even in some cases to opposition based on principles. Taking into account the debate and collective reflection which it led to, it would seem possible and necessary to examine this issue in more depth.

Disputing the notion of the existence of a potential human person is based on the following argument. To identify an embryo as a human person, is, according to the conventional scientific use of this adjective, to accept that the characteristic properties of the person are already present in a latent state within the embryo so that their later expression would be based on the passage of their latent stage to their patent stage. In fact, properties, like conscience, do not belong to one cell or to a group of cells but require the existence of a much later stage of biological development before which considering them as virtually present is futile.

It was opposed to this argument that at least the necessary although not sufficient, conditions for the development of complex levels of biological organisation are present since conception in the genome of the individual. The processes which allow the emergence of the properties of the person are now known and will be better known in the future, and therefore the potentiality of these properties reside in the embryo.

Without attempting here to arbitrate this debate, it should be recognised that, from a biological point of view, it is only possible to refer to the embryo as a potentiality of human being, which is not quite the same thing as a potential human being. In other words - and this is a major conclusion- "potential human person" cannot be understood as a purely biological concept.

16 - So, notwithstanding ethical considerations, the question of the status of human embryos refers, quite clearly, to anthropological and cultural references which extend well beyond the field of biological science.

The embryo is not only a human being because it has a specific genome. It is a human being, also, by virtue of parental intention to procreate and the meaning of this project in the family historybecause of the fact, that even before it is conceived, it has acquired an existence in its parents' imagination, a legal recognition as a subject of law since conception if a viable birth ensues. The early interactions between the foetal development and the physical life of the uterine mother, and other processes of the same order are nowadays better understood. The embryo not only belongs to our species but has to be accounted for at least as a virtual participant of the human species.

It is reasonable to consider that the major dimensions of the biological, relational, and social person exist in a latent state, as virtualities awaiting substance.

To consider, from the beginning, the human embryo as a potential human being, is to be constantly aware of the biological potentiality of a human person residing in that individual being in gestation and of the consequences of our actions on its biomedical future. It also means accepting it as an anticipation of a psycho-social being whose construction is under way, and considering the consequences of our choices for its destiny as a human subject - for instance regarding its future search of identity. It also means trying to assess the possible impact of such choices on the relations, institutions, representations and values which constitute, objectively and subjectively, a person.

Ultimately, it is to feel responsible for the effects on civilisation that our decisions bear in essence. This is what makes research on artificial reproduction so important and why public opinion shows continuing concern albeit for sometimes unfounded reasons. From the time it has been conceived the human embryo is a being and not a possession, a person, not a thing nor an animal. It should be considered as a would be subject, as an "other" of which we cannot dispose and whose dignity defines limitations for the power or control of others.

Such an analysis can be considered as a mere postulate, a fiction that history and science would prove inane. But the essence of culture and recognition is to construct reality by the acceptance of meaningful concepts and not demonstrative realities. Such constructs do not only depend on individual subjectivities as they express a "must be" and base collective responsibilities the scope of which remains to be defined.

Consequences of human embryo research on ethical principles

17 -Taking into consideration the above clarifications, we consider that the notion of potential human being is founded as an ethical construct.

This implies that, as we wrote in our first opinion, the respect for the human embryo "is everyone's duty".

To have respect for the human person - whether in others or in oneself - is, according to a generally accepted principle, to treat it as an end in itself and never as an instrument. As a consequence, the human person must never be treated in a way he would not freely accept for himself. It means recognising the dignity of the human person and therefore considering it to be of incommensurate value. It means granting universal value to this respect and consider any action in the light of results if everyone followed suit.

The field of application of this respect covers the same scope as the person - potential or real - as defined above. However embryonic the person may be in the first stages of the human being, our relationship to the embryo is a true reflection of the morality of our relationship to the person as such, to the social community as a whole and even to humanity itself. Biomedical research, because it improves human well-being in the field of reproduction, but also because it proposes simplified and reified images of human bodies, and because it may make err, exposes the global image of the ethical answers it offers day after day to the complex problems deriving from the conflict between a need for knowledge and a duty to the human species.

18 - Still, respect for the person does not necessarily coincide with respect for the natural and social conditions in which it develops today, if modified conditions appear to be more satisfactory in ethical terms.

- We are far from understanding or controlling all aspects of the natural conditions of human reproduction; and any modification should only be attempted with great care. To know and understand fully what one does and what are the possible consequences is a rule which bears no exception; if it is not scientific, it is not ethical. Yet, ethics do not require that a natural order - in which, for instance, 50 to 70% of all human fertilised ova are spontaneously eliminated before implantation - should be considered inviolable or that it

should oppose the principle of research in the field of artificial procedures likely to correct or improve it. What is ethically acceptable cannot only be derived from what exists.

- In the present state of our institutions and of our representation of kinship, our representation of the person, which are the result of a long history and part and parcel of our cultural identity, we should be extremely careful to avoid any irresponsible action with possible long term consequences even though it may appear at some time to be favoured by some smaller or larger sections of public opinion. Although imprudence is unethical, prudence is not ethics, and customs are not the law. The fact that foetuses resulting from miscarriages or abortions are commonly treated as simple waste, a fact which does not seem to arouse public opinion, does not ethically exempt us from defining rules regarding the collection of tissues from dead embryos for therapeutic or research purposes, as the Committee attempted to do in its first opinion.

- The fact that one or several persons or couples ask biomedical research to perform a certain action must be seen as an expression of freedom requesting assistance from another expression of freedom. However, it does not create per se, irrespective of circumstances, an obligation on research to meet that request. The ethical value of the request still requires assessment before a decision to oblige or not is taken. This observation also applies to human aspirations to knowledge.

19 - What does the construct of potential human person add to the necessary respect for the person in general. The following views would appear to be justified :

- The fact that the human embryo is recognised only as a potential human person does not make the obligation of respect for that embryo optional. Therefore, potential or not, the human person has a dignity and not a price. This leads to consider absolutely unethical any commercial practice in relation with the human embryo. In the same way, in-vitro fertilisation producing embryos solely for research purposes would definitely amount to considering the human person - potential in that case- contained in them as a means, although at the service of the best of ends. This does not seem to be ethically justifiable.

- Although not optional, respect for the person necessarily takes different forms at different stages of development of the human embryo. For instance, the fact that essential properties of the human person are not effectively present in the embryo, such as conscience and freedom, generally demands of biomedical research that due regard should be given to the person in gestation's future freedom and should give all relevant information to the persons on whom the ultimate choice depends. More generally, the merely potential nature of the human person expressed in the embryo means that deontology of research on the embryo has to be circumscribed in the construct of general respect for the real person it could become and of the nature of the person which is the source of its dignity. This is the basis of the possibly ethical value of embryo research to promote its human development.

20 - The possibility of intervention in the embryo at ever earlier stages for predictive, preventive or therapeutic purposes, although it may be for the purpose of giving it greater freedom in its future as a person, increases the risk of developing reproductive methods which eliminate chance for the benefit of ideals of health, family or society. This means a shift towards eugenics, the greatest negation of freedom. Confronted with this risk, it is necessary to stress that what morally justifies present or future biomedical interventions in human reproduction is the hope to cure or prevent a disease. The random element that participates in the conception or development of a human being cannot be made to equate disease. On the contrary, it belongs to the "genetic lottery" which constitutes the basis of individual specificity. At the same time it represents everything that is of a higher order than programming by others, and separates irrevocably the production of a personal being whose destiny is freedom from the production of an object in conformity with a standard and intended for possession. Wisdom and responsibility used to trace the fine and ever fluctuating dividing line between preventive medicine and excessive instrumentalisation is one of the main tasks for biomedical ethics.

What is potentially at stake in the human embryo, at the stage now attained by biomedical knowledge and capacity is inseparably the fate of an individual being and a part of the future of mankind. This is why it is essential to stress that the respect due to the person within the embryo should include the most careful and responsible consideration for collective psycho-social consequences, now and in the future, which could follow from the attitude of biomedical approach to even a single embryo. Ethics would be wide of the mark if it meant assessing the fait accompli or deploring irreversible mistakes. It is upstream of research, on its meaning, purpose, and risks that we must all reflect.

Justification of the principles adopted in this opinion

21 - In the light of the above views, the Committee was able to reach a conclusion as to certain questions related to in-vitro fertilisation and embryo research.

The Committee states inter alia that the purpose of human fertilisation is first and foremost procreative and cannot ignore the benefit for a child to be born, nor its right to be born to a united couple. The use of so-called spare embryos for research purposes can only be secondary when it has become patently impossible to transfer all the embryos.

The Committee wishes that the fertilisation of spare embryos should only be a transition phase, soon to be abandoned, as it means either the destruction or the storing of embryos, which implies in practice and ideologically a certain materialisation of the potential human being.

It is also with a view to facilitating pregnancy, but also to preventing risks for the future child that the Committee authorises embryo freezing, strictly limited in time, and prohibits the conservation of embryos, frozen or not, for research when no effective research project is under way.

22 - Moreover, the deficiencies of ethical research, the serious risks of a shift towards eugenic practices, for convenience or otherwise, or of extending the use of IVF-ET which should not become a common practice because of the reservations it generates, explain the decision to impose a moratorium on certain types of genetic investigations, whether in fundamental research or clinical tests.

Even though researchers may deplore these temporary limitations, they must understand that it is necessary for the sake of caution and above all to prevent the kind of genetic folly that genetic sorting might instil in the minds of those who feel tempted by a programmed child, made to measure like an object, with no regard for respect owed to its individuality and liberty.(8)

On this question, since there is no medical urgency, research should wait until the ethical questions we are dealing with have been elucidated. It is necessary to recall, on this occasion, that no thoroughly elaborated ethics can be formulated to control technical developments, as long as moralists, or society as a whole, are constantly pushed into accepting faits accomplis. The will to progress quickly, more quickly than others, is not an ethical value per se, but only a striving for efficiency which, in this area is not medically or socially essential. Sometimes it is necessary to be able to pause and take time to think.

This is why the Committee did not deem it necessary to apply to genetically oriented investigation or tests the case by case authorisation method applicable to other types of research.

23 - There is no need to dwell on the ethical justification for prohibiting research or so-called research which has no therapeutic interest but is likely to completely upset thinking related to the essential structures of anthropology and personal identity which lie within the concepts of maternal gestation, distinction between human beings and animals, differences

between sexes, the transgression of which, albeit limited to research, borders on foolishness, whereas so many genuine ailments would usefully benefit from research.

The Committee has attempted to take a more detached view in order to set out some ethical rules on a higher plane so as to justify deontology for the present time.

However this is not sufficient and these rules cannot solve all the practical problems or arbitrate all existing conflicts.

Therefore, the Committee had to consider the contingencies resulting from de facto situations or from the diversity of opposing opinions.

An attempt to arbitrate conflicts of values or of interests

24 - The existence of de facto situations shows that there are difficult cases for which there is no obvious answer. This is true for many issues, not all equally important, regarding IVF-ET.

Moreover, in the case of research, it is essential to be realistic and recognise its existence and its possible developments. It is not stated that any type of research can be deemed illegitimate because of its objectives. It remains clear, however, that research aiming at something else than the welfare of the future child leads, if it is accepted, to treating embryos as though they were objects, and for that very reason can be considered as unethical a priori.

On the contrary, those who consider that therapeutic experiments for the welfare of the future child are acceptable must admit that one cannot take a risk for these children without prior testing on embryos not intended for transfer.

Lastly, regarding the definition of thresholds such as the duration of cryopreservation, or the duration allowed for the keeping of embryos (possibly donated for research), there is no non-arbitrary rule which can be used to define the acceptable limit. However it is not possible to do without a rule or leave everything to be decided on a case by case basis.

25 - Confronted with these difficulties, the Committee elaborated a deontology based on several attitudes:

The first one consists of trying to find the lesser evil: in this way, destruction of spare embryos can be accepted. Such destruction, however, seems inevitable and yet unjustifiable, as it could not be justified by the arguments of natural attrition or the existence of legal abortion. Such arguments are illusory. In this case, the only ethical course is to choose the lesser of two evils.

This is also true of embryo freezing. If it is strictly limited in time, the inevitable resulting instrumentalisation of the embryo is a lesser evil, as long as the rate of failure of in-vitro fertilisation remains as high as it is now. Freezing protects the interest of the mother, and also the chances of the unborn child.

26 - The second attitude is dictated by prudence: very little is known of the medium-term physical or psychological, individual or familial side-effects of IVF-ET development, which is still in an obviously experimental phase.

Apart from being cautious as regards medical indications, caution is also required for cryopreservation, which should be limited in time and not give rise to stockpiling of embryos.

Lastly caution may be a reason for abstaining from certain practices in case of doubt or dissent. In this respect, the Committee was not able to reach a consensus as to the

preservation of embryos for a second pregnancy or the legitimacy of donation of embryos to other couples. Although the question of considering a second pregnancy was left open, it seemed necessary to call for legislation on embryo donation.

In substance, differences of opinion show how complex this problem is. For some, embryo donation is comparable to a sort of antenatal adoption; it would have the merit of avoiding destruction of spare embryos not used by the genitors; it could also avoid creating large stocks of human embryos the fate of which is uncertain. Embryo donation would make it possible to help sterile couples.

For others, embryo donation is incompatible with the principle according to which the embryo, as a potential person, cannot be disposed of, even without financial compensation. Moreover it is emphasised that embryo donation combines the problems related to the donation of oocytes to those related to the donation of sperm whereas there is no rule for implementation nor to control the effects of such practices, particularly regarding filiation. Legal trends in recent times are moving in the direction of biological preference. In the circumstance, such practices could give rise to major conflict.

Last but not least, embryo donation could represent a first step towards the production of embryos intended for adoption which would be a major change in the spirit of this institution. This already existing trend, personified by surrogate mothers, was rejected by the Committee in 1984. The Committee members think that it is not up to the in-vitro fertilisation centres to promote, on their own initiative, a practice leading to the disposal of human embryos, leaving society and Parliament with a fait accompli.

Finally, embryo donation could lead to illegal practices or uncontrolled trading.

It is obviously very urgent to adopt legislation on this subject.

27 - The third attitude is dictated by the determination to reconcile realism and the ethical and social need for control over human embryo research.

Many objections are voiced, for questions of principle, to any type of embryo research, except if it has a direct advantage for the future child.

On the contrary, it is also felt that respect for the human embryo does not justify prohibition of research, even when there is no direct potential benefit for the person. The conflict between the human desire (and need) for knowledge about the beginning of life and the respect for a life whose individual nature is still only potential, is resolved differently. Expressed in these terms, the conflict admits no solution. Each argument can be opposed by other valid arguments.

Confronted with this dilemma, the Committee considered that the highest priority of ethical rules required that research, and in particular research not resulting in a direct potential benefit should be submitted to strict regulations and controls ensuring on a case by case basis that ethical and scientific deontologies are not neglected and that the project is of sufficiently obvious interest to be referred to the National Committee itself.

This subordination of research is necessary for ethical and political reasons - human embryos must not be used a priori and without supervision by researchers. Transparency of scientific power is a condition without which there is no technical democracy.

The specific rules defined by the Committee seek to restrict the opening of a door that, according to ethical principles, should only be left ajar. This is all the more justified because it can be hoped that such controls will make it possible for reproductive medicine to use less controversial methods than those presently used.

However, this debate should be continued and recommendations, justified at the moment, should be revised, adapted or modified, taking into consideration progress of ethical

reflection, of science, and the way in which the recommendations of this opinion are enforced.

Conclusion

By way of conclusion, it should be stated that the limitations, prohibitions or conditions imposed by this opinion are as important for what it is forbidden to do as for what it is permitted to believe. Although it cannot be demonstrated, the belief that a human life cannot be entirely controlled because it is not a manufactured product is a guarantee of our liberty and dignity.

Paying too much attention to what divides us, may lead us to forget what unites us:

First of all awareness of our failures which is the foundation of humility essential for ethical research.

- failures related to our ability to invent in ontological terms the being striving to exist, and the extent of our duty of humanisation.

- failures related to our ability to invent cultural fictions which reinstate the "untouchable" or, if preferred, the "sacred" without which society would only be defined in terms of absolute power and action.

- failures related to our ability to forecast, predict or assess the results of our actions regarding production of life and the risks we take for the human person whereas we shall be dead when the "children of science" will come and ask us to answer for what we are now initiating.

Confronted with these shortcomings, and we could quote many more, we should be modest enough to return to the original purpose of medicine which is to cure and prevent ailments and not to produce or generate life in reference to an "ideal" we are unable to define.

Is it not paradoxical, at a time when medicine is at last in a position to pay tribute to the Hippocratic oath, that it betrays its mission and renders artificial human reproduction techniques commonplace instead of contributing to cure what prevents human beings from freely procreating through the alliance and mutual recognition of man and woman ?

Although this opinion is limited, for the time being, to defining a modest though essential deontology for medical research in its application to human embryos in-vitro, scientific ethics, over and beyond scientific deontology, still need to be devised.

What unites us, is the obstinate though fragile hope that the plurality of our philosophies and beliefs, the diversity and richness of our cultures which must be allowed to flourish, help us to preserve the values which establish meaning and otherness as opposed to the anonymous and reductive universality of technologies.

Therefore we may be able to invent and sustain the "Culturein the plural" that Michel de Certeau(9) compared to "art, conditioned by places, rules and data" that he defined as a proliferation of inventions in a restricted space.

France Quéré : ethical questions and observations on artificial procreation

Until a few decades ago, medicine was confined to its therapeutic objectives: cure man from diseases or at least alleviate suffering. But nowadays, we are confronted with a surprising development of its scope and its powers. Without abandoning its purpose to cure, it also embarks on a new path leading it to control major natural phenomena without necessarily

having medical reason to do so. This extension concerns three domains: procreation, inheritance, the nervous system, although for the last two, it has only just begun.

Because it is now able to take over from nature for normally spontaneous operations, medicine has progressively changed its objectives. It no longer corrects a disturbed order, it modifies a natural order.

We are only at the dawn of times when maniac disorders, dementia or brain deterioration will have become obsolete. In the case of inheritance, it is not yet possible to cure, in-vitro, disorders observed in the first few embryonic cells, but it is possible to detect more and more diseases in utero although we cannot as yet cure them. At best (if the word can be used in that setting) we may give parents the possibility of choosing abortion. Perhaps in the future it will become possible to cure certain foetal diseases and to offer a less painful solution than a so-called therapeutic abortion (which should not be so described since it must be resorted to only because there is no therapy.

These are no more than hopes, but in the field of procreation, the future is already on the march; it is now possible to remedy all forms of infertility whether by advanced technological methods or simple social compensations.

Who would not be glad to see that so many disasters are or will be overcome? But what of ethics?

When the biologist controls what used to be nature's domain, roles are modified. In earlier times, nothing could be opposed to the fatalism of nature (except prayer); but in the presence of human power, claims can be made: "You can, and I want". Where patience prevailed, demand and even a proclamation of rights, takes over. It is true that it raises a number of issues: why say no to someone whose urge is so great? Are we not responsible for that desire which has been nurtured by biological progress and which otherwise would only be regret?

Medicine has reluctantly become accessible to individual demands and the nature of its mission has changed. An alleged or imposed obligation to perform develops between patient and physician, and what is "duty" for one is called "right" by the other.

At the same time as the objectives of medicine change, the demand of patients shifts. There is an enormous proliferation and diversification of demand. The too simple question of cure is no longer topical. It is demanded of medicine that it frees patients from whatever hurts and grants whatever is coveted. There is no limit to the distortion of desire. Any power gained, generates new desires. Exactly in the same way as the improved standard of living, which has in fact eliminated most extreme poverty, leaves the concept of poverty untouched, and the same distress remaining, since poverty is now defined in a comparison with higher standards. In a rich country, frustration remains as a result of comparison with others. In the same way, to protect people against disease and death does not make them feel healthy. The very power which was used to eradicate disease and fatality leaves room for new "affliction" felt to be equivalent. Medicine is, and will continue being contaminated by what is usually called personal convenience (which arouses strong feelings in those concerned). Such changes had not escaped the notice of Michel de Foucault when he explained that the traditional opening line "where does it hurt?" was being replaced by "what is your desire ?"

One should not think that only power or cleverness are dynamic and that human desires remain static, i.e. that human demands would remain identical to those of the century when tuberculosis was omnipresent and be limited to physical health. Power stimulates desire and passes on to it its ambition and unlimited extension. This truth is being discovered with amazement by biology. Economics discovered it and took advantage of it a long time ago; for thirty years, moralists have been claiming that undefined needs are boosted by the production boosted by these needs.

The same desires emerge, distorted and multiple in this new domain: children with no visible father or with no father at all; insemination of women in borderline situations, living on their own or with a companion, storage for a very long time of embryos to be transferred, dream of a perfect child, gender selection, and why not one day establishment of a prior genetic map. Already such fancies are emerging with the Nobel sperm banks, shift in the direction of selection (cf. statements by the Nobel Prize winner Francis Crick), eugenics, super reproduction drifting disastrously towards aberrant materialism.

Although it is a fact that everybody dreams of having the most beautiful child in the world, the means to attain that goal are the subject of grave misconception. They totally underestimate the power of maternal imagination which is such that to every mother nature grants the most beautiful child in the world (except in cases where nature makes a major error) and this constantly fulfilled dream dissolves very slowly over the years and never completely vanishes. Ambitions such as having a "super-child" by a "super-father" co-existing with the number of children born damaged by alcohol and tobacco which their parents consumed in excess, is worth noting and reflects a strange social inconsistency.

It is therefore legitimate to speak of distortions which are already present in some minds and may well imperceptibly turn into reality, and not be content with rejoicing that what some seek others can provide. This is a dangerous and doubtful alliance per se, since the desire-equals-power equation excludes critical judgement, scrutiny of its effects, any suspicion regarding the origins of desire made absolute and the method of satisfying that desire. Scientific research does not impose limits on its scope, on the contrary its purpose is to overcome any hurdle it encounters and human desire always expands. Two aspirations converge, united by their common thirst for infinity that is commonly expressed by "but where will all this end?"

This conjunction of science and liberty is thought by some to mean that any desire is legitimate. For a long time they have advocated a laxist regime (now disputed for education but not yet as regards acceptable behaviour) in which the inclinations of individuals must be satisfied. Others, placing their trust in scientific "progress" continue to cherish the ancient notion that science enlightens the spirit and thereby the heart. This school of thought also believes that if science generates problems, more science will solve them. Yet another view combines in a positive appreciation human satisfaction and a continuation of science. This configuration is thought to be most excellent; how fortunate that what is desirable is also possible! Full steam ahead! Desire is a good thing, fulfilment is a good thing, it is a good thing to desire and to be able to fulfil that desire.

Defining as moral what is acquired thanks to man's intelligence and as legitimate the temptations he encounters leads to a confusion between the possible and the permissible, as though the sole criterion of morality was the creative capacity of man or the needs of his imagination, or a combination of both.

Where does this lead to? To the fantasies mentioned previously which would be the death of a society (for how could it survive solely by imposing a form of contradiction to individuals?) in a frenzied downfall where desire triggers power and power triggers desire, but where there is no conscience capable of control or evaluation. Such a society would be defined only by action and no longer by reflection.

This is why many moralists are concerned that this couple (desire and power) might become dangerous. Preferably to attempting to separate the pair, a third element would be inserted, i.e. the irritation of criticism sufficient to introduce some of the sobriety which is lacking in many minds today. Ethics could be the third element intervening between desire and power to attenuate foolish haste and would have a slowing effect. This, of course, is the usual perception: moral values prevent things from happening. So the perception is a negative one... This is hardly new. The Ten Commandments are expressed in the form of negative injunctions: do not kill, do not steal. The first effect of morality is to prohibit. This could be considered as an unacceptable limitation of freedom (remember May 1968: "It is forbidden

to forbid," said the writing on the wall) and Committees of Ethics have the reputation of being repressive.

All the same, ethics is not pure negation. First of all because negation, as such, produces assertion: when I say "don't" I leave more room for freedom than when I say "do". As the field of assertion is not limited, I remain free to unfold initiatives. The reputation for narrow-mindedness attributed to Ethics and its Committees is unfounded. In fact, to prohibit here is to allow elsewhere. Much more is given than refused. When morality uses negative injunctions, a vast space is left to freedom.

Also, negative reasons lead to positive reasons: just like the Decalogue, it is because one believes in good that evil is prohibited. I quote two examples: the first is related to procreation. The opinion on surrogate mothers published by the National Consultative Ethics Committee is the most restrictive of all. It feared complications amongst adults but was essentially motivated by the most uncertain and unverifiable of reasons, the welfare of the child. It was thought that passing from gestating mother to loving mother would suffice to ensure the child's welfare. It was supposed that the gestating mother's forced lack of interest would jeopardise the relationship between mother and foetus. There is no proof of any of this, but ancient wisdom dictates: "when in doubt, don't" So what stayed our hand? Kant's second categorical imperative "don't treat others as means, but as an end". It was thought that when a human being is entirely dependent (in its foetal stage) no other interest but its own must be served for fear of alienating its freedom. It was considered that there lay treason of the species by the species and more specifically of children by parents, since the role of parents is not to make children the slaves of their father's freedom. Kinship is different from any other type of inequitable relationships because the inequality between father and child is fated to dwindle and end in equality, In certain cases, it is acceptable that inequality be reversed. Paternity and paternalism are not identical.

A genetic example is more revealing. Excellent antenatal diagnosis exempts families who feel unable to bear them, the burden of anomalies and attendant suffering. This is in fact, more frequently than otherwise, facilitates serene pregnancies and encourages those which might otherwise have never taken place or been interrupted through fear. However antenatal diagnosis could modify our representation of the child. The child might then be considered as an object before gaining esteem as a human being. Its quality as a being will depend on its quality as an object: if a part is faulty, send it back to the manufacturer. The right to be a child will depend on a subjective assessment, in the same way as one chooses an object. Where should the threshold of acceptability be situated regarding malformation? An assessment in terms of quality co-exists with an assessment in terms of quantity. what reaction can be expected when malformation is predicted in the form of greater or lesser probability?

The development of genetic engineering will reinforce this tendency to consider human beings as objects. The main danger is a confusion between production and reproduction in a world where a profusion of technicalities distance us from pure fate. Human procreation would therefore be reduced to one particular kind of production offering similar protections and guarantees as any other kind. There would be between us and the child the same relationship as already exists between us and things, i.e. our desire to be in sole charge. We are the masters of objects because we designed and manufactured them. They are at our mercy, once and for all. They were made for us to use and only exist because they are useful and we use them. We want to conform fully to our expectations, more beautiful if beauty is what they are made for, more functional if they are made to serve.

We are acquiring over man the same mastery as we have had for a long time over objects. It may be feared (and this is already happening) that confronted with this human being who is now accessible to our decisions and to our making, we might develop the same attitude of mind and treat a child like an object since, like an object, we consciously make, or eliminate, or alter it. Vocabulary already reflects this, and there are trendy expressions to express the need to have children. This is a demonstration of the fact that procreation mimics production. Desire is the supreme judge: all depends on it: the birth of a child, even

though apparently impossible, the elimination of the child if it is on its way and is dismissed as would be a tradesman knocking at the wrong door. The supremacy of desire is not the only sign that objects are replacing humanity.

Another sign is the power we are acquiring of custom-making a child. Object of the desire it inspires, object for the extent of that desire, the child becomes desire itself.

In this new relationship with the child, the benefit of awaiting the Other is lost. A human being is always Other empowered by individual conscience and freedom, a wonderful unknown. An object does not belong to the realm of otherness because it is devoid of conscience and cannot speak in its own name or to another.

If a child is conceived as an object, love ceases to be where two freedoms meet, and becomes the possession of what is made by its makers and this is of very serious consequences for the product's existentiality. What right do we have to transform beings into things?

What justification is there for modifying, on our own initiative, the psychological and social future of a child? Why should the calculations or views of parents take precedence over the random virtualities of nature? Eliminating in the conception of a child all forms of "lottery", including the possible drawbacks that go with it, is a breach of the child's liberty (except in the case where nature itself would make such liberty impossible). The unmanipulated child, left to the free choice of nature (except in cases where such a choice would eliminate all forms of liberty) is born, satisfies or dissatisfies me, but is Other. He is fully an opposite because his Indetermination which is an essential component of his identity, is out of my control. Imagine a situation which is so far an impossibility and I hope will remain so for ever, where we could ourselves determine the physical and social personality of a child who would therefore live its life in bondage in an invisible and hopeless prison forged by its parents, which would render its "ego" pure illusion.

The child is the fruit of our flesh, not of our calculations nor of our hands. It is generated, not manufactured. Freedom is the fruit of contingency, which is not of the parents' making. The miracle of parenthood resides in respect for the child's alienness, which are the result of nature's play, which education protects, and gives way to a progressive dwindling of authority. Of this individuality is born the transcendence of a being entitled to an inviolable sphere, the "naos" of its conscience and the absolutely individual awareness of its own specificity.

In our conception of the child, as we hesitate between being and object, the religious dimension of our society is at stake. Deprived of transcendence, it negates man as a transcendence and reduces him, for lack of significance, to an object whose only ambition is to be there. If our society can maintain a spirit of religion, (I do not mean an organised religion with pantheons and clergies) simply opening out to others, faith in a possible destiny for mankind, if it keeps a capacity for belief, then mankind may be able to preserve the sense of nobility which halts science and leads it to humility.

Notes

1.Human embryo, therefore designates all the stages of development of the zygote before the foetal stage. "In vitro embryo" means the embryo resulting from a fertilisation obtained outside of the material body.

2. "Invasive techniques" means techniques implying micro-manipulation of embryonic cells

3. The embryo, a potential human person, represents in fact the emergence of a new human life, genetically organised as a separate entity, intended for a future development and to become an individualised member of the human species.

4. Artificial procreation: Rapport préliminaire à Monsieur le Premier Ministre (preliminary report to Mr. Prime Minister) - La Documentation Française, 1986

5. See Annex

6. Nicole Athéa: La Fécondation in vitro, February 1985.

7. In-vitro fertilisation and embryo transfer.

8. see report by France Quéré below

9. La culture au pluriel, Christian Bourgois, Paris 1980.