Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé

# Reflections Concerning an Extension of Preimplantation Genetic Diagnosis

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Preimplantation genetic diagnosis (PGD) has been authorised in France since 1994, but is strictly limited to cases in which there is "there is a strong probability that the unborn child will be affected by a particularly severe disorder".

On February 5th and July 18th 2001, the possibility of extending this indication, and of performing HLA typing in the course of that diagnosis, for families affected by FANCONI's anaemia so that a disease-free embryo could be transferred and be a potential donor for an existing sick child, was referred to CCNE.

On April 27th 2001, the question of the legitimacy of using PGD for a couple, in which one member belongs to a family affected by Huntington's disease, wishing to produce a disease-free child, but not to be informed of their own genetic status, was also referred to CCNE.

These two referrals raise the issue of an extension of PGD, no longer in the sole interest of the child, but in the interest of a third party.

## I Introduction

Preimplantation genetic diagnosis, which has been permitted in France since 1994, consists in performing a genetic diagnosis on one or two cells of an embryo at the 6-10 cell stage, before it is transferred in utero. Therefore, PGD can only be performed after in vitro fertilisation. Furthermore, an ICSI (intracytoplasmic spermatozoïd injection) is usually required to avoid contamination by the DNA of another sperm cell. PGD must be repeated with several embryos so as to select one which is certainly unaffected by the condition which it is feared may be present. It can (or could) be used to screen for or prevent 3 categories of diseases :

- sex-linked genetic diseases when there is no possibility of diagnosing the disease directly : the embryo's sex is

diagnosed and an embryo of the sex which is not vulnerable to the disease is implanted ;

- genetic diseases in which it is possible to detect the molecular anomaly with the help of molecular biology technology ;

- chromosomal abnormalities.

These results can also be obtained through prenatal diagnosis (PND) after amniocentesis or trophoblast biopsy, in the case of "spontaneous" pregnancy. In this case, discovering an anomaly may lead the woman concerned to request a termination.

## II Present situation in law and in practice

PGD is allowed by Law n° 94-654, dated July 29, 1994, governing the donation and use of elements and products of the human body, medically assisted reproduction, and prenatal diagnosis.

According to article 14, a new article L.2131-4 of the Code of Public Health, was inserted after article 2131-1, reading :
"Biological diagnosis using cells taken from an in-vitro embryo is only permitted in exceptional circumstances as follows :
"A physician practising in a pluridisciplinary Antenatal Diagnosis Centre as defined by article L.2131-1 must certify that, because of the couple's family circumstances, there is a strong probability that the unborn child will be affected by a particularly severe disorder, known to be incurable at the time of diagnosis.
"Diagnosis may not be performed before prior and precise identification has been made, in one or other parent, of the anomaly or anomalies which are the cause of such a disorder.
"Both members of the couple express in writing that they consent to such diagnosis.
"Diagnosis may have no other purpose than to detect this disorder and the means to prevent and cure it.
"It can only be performed in an institution which has been specially licensed to this effect, with the approval of The National Committee for Reproductive Medicine and Biology and Antenatal Diagnosis, and in conditions as decreed by the Conseil d'Etat."

Lawmakers therefore authorised using PGD only in exceptional circumstances, and solely to avoid giving birth to a seriously sick or disabled child. This authorisation reflects the debate regarding PGD and research on embryos, and the desire not to allow this activity to become commonplace because of the risk of its abuse for eugenic purposes. It may be useful to recall that CCNE has already published several Opinions related to this subject :

- On December 15, 1986, Opinion n° 8 on Research and use of in-vitro human embryos for scientific and medical purposes, in which CCNE recommended that no medical indication for IVF-ET be proposed apart from infertility or proven hypo-fertility,
- On July 18, 1990, Opinion n° 19 on Embryo research aiming to achieve pre-transfer genetic diagnosis for which a moratorium was declared in 1986. At the time, this Opinion had come to a negative conclusion as to even the possibility of performing PGD, and mentioned the risk of abuse of MAR with fertile couples. Uncertainties concerning still hesitant DNA research justified a extension of the moratorium.
- Opinion n° 60 on the Re-examination of the laws on bioethics, published on the occasion of their revision, did not make any specific statement on an extension of PGD.

In France, since July 1999, PGD can be performed in two licensed centres (one in Strasbourg, and one in Paris. A third centre in Montpellier was approved in January 2000.

An article published in 2001 in "Médecine Sciences" reports on the activities of the three centres in the last two months of 1999 and for the whole of 2000.

"In the period considered (November 1999 to December 2000), 260 case files have been opened. Cystic fibrosis represents the bulk of requests (48%) for autosomal recessive diseases, and spinal muscular atrophy comes second (22%). For dominant diseases, there is a prevalence of trinucleotide repeat expansion diseases, such as Steinert myotonic dystrophy, and Huntington's disease. For the latter, half of the requests come from patients who are aware of their genetic status, and the other half from patients refusing pre-symptomatic diagnosis, and for whom PGD is presently legally not authorised. In X-linked diseases, there is a predominance of Duchenne dystrophy, and of the fragile X syndrome. Chromosomal translocation represents a third of applications. A majority of couples (67%) have already experienced one or several prior pregnancies. Forty-four per cent of them had already experienced a pregnancy beyond 28 weeks. Only 22% had had at least one healthy child, 28% at least one affected child, and 40% had undergone at least one elective abortion for medical reasons. This background explains the reasons for requests for PGD; genetic risk and opposition to medical termination of pregnancy represent two thirds of these requests. The other third concerns couples at genetic risk and with low fertility needing medically assisted reproduction (MAR) techniques."

A recent publication by René Frydman and Coll. at the Académie nationale de médecine, dated May 14, 2002, provides the results of medical teams in Paris in 2002 and 2001.

From January 2000 to July 2001, for 71 cycles, 59 couples were assisted. Out of the 505 embryos produced, 421 were biopsied, and genetic results obtained for 302 of them (74%). A total of 127 embryos were transferred with a total of 58 transfers. The biological pregnancies which ensued numbered 18, and there were 12 clinical pregnancies (7 single, 4 sets of twins, and 1 of triplets). A total of 16 children were born. The breakdown of conditions for which PGD was used shows that 25 couples were at-risk of chromosomal imbalance, and that 34 couples were running the risk of transmitting a single gene disease. These genetic defects were for the major part connected to an autosomal recessive condition (cystic fibrosis) or a dominant disorder (Steinert myopathy). As regards X-linked conditions, Duchenne dystrophy or X-linked mental retardation formed the bulk of indications.

These two studies reveal that limited use is made of PGD and that the success rate is relatively modest.

Although an extension of the genetic indications of PGD for the sake of the child does not raise any legal or ethical problem as such, it does give rise to major legal and ethical problems when it concerns the interest of a third party (cf. Opinion n° 70). Would there not be in this case a contradiction with the principle that a child should be born for his own sake ?

## III Preimplantation genetic diagnosis to detect HLA compatibility in a case of familial Fanconi's anaemia

### III - 1 Addition of a secondary motive for screening

Starting a pregnancy with the single aim of producing an HLA compatible child, whatever might be the indication as justified by the severe impairment of a sibling, appears to be in contradiction with the principle that a child should never be a means to another's ends, not even to save that other. However, in the particular case referred to CCNE, immunological compatibility screening is added to what should remain a priority : give birth to an unaffected child.

The object of this further screening is to help a seriously sick child by a transfusion of stem cells from cord blood [1] once the new brother or sister is born. As noted above, the present state of the law does not allow such screening. The function of PGD, as stated by law, is to choose an embryo unaffected by a severe genetic disease, to the exclusion of any other non pathological characteristic. If PGD were to lead to selecting an embryo out of the unaffected embryos, because its immunological compatibility would be of therapeutic advantage for an existing sick child, then the indications listed by law would be exceeded.

It is of course very understandable that a distressed couple and a medical team, confronted with a severe lethal disease in a child, would wish to do everything in their power to save that child. From a strictly therapeutic view, transplanting stem cells from the umbilical cord of the second child would appear to be the best solution for the time being since immunological compatibility obviously conditions any chances of success.

## III - 2 Medical possibilities

Fanconi's anaemia is a hereditary single-gene autosomal recessive disease which may be the result of mutation involving several genes. Symptoms include bone marrow aplasia which develops progressively, starting around 6 years of age. Death habitually occurs by the age of 15 or 20, through infection or haemorrhage, sometimes acute leukaemia, or later through cancer - more especially of the oropharyngeal area. A study of affected children demonstrated that 40% were likely to develop leukaemia or cancer.

Treatment includes prescribing androgens alone or in combination with steroids. For want of cord blood cells, available therapy is mainly based on bone marrow transplant.

The medical benefit derived from cord blood cell transplant, harvested at the birth of an HLA compatible sibling, appears to be very encouraging for the sick child, as some results of research in France or elsewhere based on existing HLA compatible children have shown. The technique is easy, and is in no way immediately detrimental to the donor child. However, there may be cause at a later date, because of renewed haematological problems, to suggest bone marrow transplants. In this situation, new issues need to be addressed since renewed "donations" by the HLA compatible child is bound to be one of the options. For that matter, the generally spurious nature of a "donation" by a small child, also arises in this context.

Transplanting cord blood cells, taken from a compatible donor born after PGD, is a ray of hope since it means that the haematological aspects of the condition can be treated. However, it is no prevention against other manifestations of the disease (various morphological or visceral anomalies).

## III - 3 Ethical issues

This particular case therefore raises several ethical problems :

- procedural constraints
- differences between PND and PGD
- the question of a modification to the original intentions of MAR
- the need to select, and the criteria for selecting, the embryo for transfer

- the instrumentalisation of the child
- intra-family relational problems

## III - 3.1 Medical constraints of the procedure

For the mother, in vitro fertilisation is mandatory, as it will be necessary in any case to screen for Fanconi's anaemia. Ovarian stimulation will be used to obtain a large number of oocytes. Such stimulation - and all the more so because a normally fertile woman is concerned - represents a risk of over stimulation. Several cycles are generally needed to obtain about 10 embryos. In this connection, it must be noted that although this is a relatively easy procedure before the age of 30, it becomes much more difficult with advancing years. For the embryo, several embryos must be created and analysed. A maximum of two embryos will be transferred, and the probability of achieving pregnancy is about 12 to 15%. Obviously, these techniques are far from absolutely reliable. HLA screening, using one or two cells, may be fraught with methodological problems. For the medical team, awaiting the birth of a child to provide otherwise unavailable therapy, is an uncomfortable and dubious position, where a new life is reduced to the dimension of a therapeutic possibility. The new pregnancy may be experienced as a not altogether acceptable waiting time to save a sick child. Any mishap in this hypermedicalised pregnancy could be cause for particular anxiety or even guilt on the part of the mother and her intimates. Furthermore, the therapeutic aim of saving the sick child may override the specific expectation of the second child. It could well happen that any worsening of the sick child's condition could inspire thoughts of provoking a premature delivery so that cord blood cells would be available when wanted, as has already been found to happen in certain circumstances.

## III - 3.2 Prenatal diagnosis (PND) versus PGD

There is a major difference between prenatal diagnosis and preimplantation diagnosis. PGD is not simply early prenatal diagnosis. Made possible by MAR in a context of particularly severe genetic diseases, it can avoid having to terminate a pregnancy for medical reasons, and is therefore a possibility of choosing a lesser evil. That PND should be used to detect HLA immunological compatibility, is simply not an option, not even a secondary option. To terminate a pregnancy solely for reasons of incompatibility would indeed constitute intolerable injury. Prenatal diagnosis is therefore not the proper vehicle for detecting HLA compatibility.

## III - 3.3 The issue of change in the initial intention of MAR and the possibility of abuse

Initially, the aim of MAR was to counteract infertility. Adding PGD to MAR seeks to avoid the birth of children affected by genetic disorders, and therefore to avoid the consequent suffering. If PGD is not strictly

controlled, there is a risk of extending its applications to diagnosing less severe late-onset disorders, and of its use for restorative purposes. Cord blood, full of stem cells, is in fact one of the simplest ways of obtaining cellular material required for grafting children suffering from leukaemia or haematological genetic diseases, such as in particular hemoglobinopathies. Added possibilities may be obtained by freezing stem cells. In such circumstances, medically assisted reproduction is deviated from its original intention and becomes assistance to therapy for a third party. Furthermore, there would be a risk (already frequent in certain cultures) of choosing gender for convenience and not because of X-linked disorders.

## III -3.4 Selecting an embryo and selection criteria

The aim of PGD is to supply information so that a choice can be made. In the situation which was referred to CCNE, PGD is used to provide assurance that the embryo will be unaffected by a genetic mutation (negative choice), and that furthermore it is compatible for HLA tissue groups with an affected existing recipient (positive choice). Healthy spare embryos which are not transferred into the uterus, are frozen for possible later transfer or donation. In some cases, none of the healthy embryos are compatible, and in others, several are compatible. Should several of the embryos be unaffected by the genetic mutation and yet be compatible, choosing one of them is not a problem. One always aims to keep the number of transferred embryos to a minimum. If on the contrary, all the embryos unaffected by Fanconi's anaemia are incompatible, what will happen to them ? Would not destroying them, or simply freezing them without any future parental project, be evidence of an unacceptable instrumentalisation of embryos ?

Are there any decisive objections to embryo selection guided by the HLA compatibility criterion ? Insofar as embryo selection is inherent to IVF, and assuming the final aim is laudable, does it become reprehensible solely because it is guided by the search for a specific item of information regarding a particular characteristic of embryos ? If no selection is made, then the decision is left to chance. Why should leaving fate to decide represent a higher moral ground than making a deliberate choice ? The criteria used to make the choice are surely more to the point. Are the criteria as such morally unacceptable ? In fact, the choice would be unacceptable if it were guided by racial considerations, or social values. However, in the present case, there is no trace of an effort to "normalise" human reproduction. The choice is based on a very general and relational characteristic (compatibility). For that matter, if compatibility were to be found existing after spontaneous fertilisation, everyone would easily agree on this being the best possible outcome. This demonstrates that the situation one hopes to arrive at (an unaffected compatible embryo) can, without reservation, be viewed as good.

## III - 3.5 The issue of the instrumentalisation of the child

For a child to be born, who will be helping to treat another child subsequent to an appropriate selection, raises the major issue of the risk of instrumentalisation of the unborn child. This fact is worthy of consideration. As in Kant's dictum, "Never use human beings solely as a means, but always treat them as an end".

In this case, is instrumentalisation a fact ? The child will be born to his own fate and life. He will not simply be the means to an end. Although his existence is linked to HLA compatibility, there is more to his existence than HLA compatibility. The selection by immune compatibility could be equated to the solidarity born of brotherhood. The child will still be a singular being in his own right, and it is that singularity which makes him a unique human being ; the biological bond is in no way weakened by its prominence. The gift of cord blood cells is non invasive and therefore a simple procedure. The matter is not so simple in the medium term if other transplants turn out to be necessary, so that the possibility of compulsion, and therefore of submission, in the case of repeated donation, cannot be eluded.

Should one consider that selection of the embryo leads necessarily to a risk of instrumentalisation ? If PGD reveals that one or several embryos are unaffected, but are not HLA compatible, the fact that they were all rejected would indicate that truly the unborn child was not wanted for his own sake, but for the sake of another. How then not conclude that he was above all viewed as the instrument of the therapeutic intervention that was the real object of desire ? Parents must be apprised of this possibility before any action is taken. Healthcarers should be committed to giving priority to the transfer of unaffected immuno-compatible embryos, if there are any. Otherwise, they would offer to transfer available unaffected embryos, even though they were not completely suitable as regards histocompatibility antigens for a possible recipient. However, a woman must clearly not be forced to accept an embryo transfer she rejects. But the medical profession which in these cases is asked to intervene, must anticipate the possible occurrence of such a situation and explain beforehand the moral complexities so as not to be caught when the time comes in a dilemma where the interests of a sick child would prevail over those of an unborn one.

## III -3.6 Intra-family relational problems

One cannot deny that bonds of dependence could develop for a child born as a result of PGD embryo selection, whose immune identity was chosen with a view to saving a brother or sister. Can one ignore the possibility of psychological risks for the unborn child, and of personality construction hazards?
One could also reverse the situation and suppose that such a child might feel highly valued on learning about the vital health problems of his older sibling, and all that entails, and was able to appreciate the efforts made by his parents. Seen from this angle, he could understand that he is the

core of this intra-family solidarity, which would have been in his favour if he had been in the same situation as his older sibling. This direct reciprocity is of course only virtual, but could be potent.

Between two such theoretical possibilities concerning a child born after PGD selection, reason can hardly choose. However, comparison with better known situations, transplantation within a sibship, gives an insight as to the situation of those directly concerned.

What must be considered here are both the fragility of a sick child during the crucial period when efforts are made to save his life, and the later prolonged fragility , possibly throughout his lifetime, uncertain but possible, of a child born to save his older sibling. To quote P. Ricoeur, this is a "confrontation between the situation of a child about to die, and that of a child who may be entering a lifetime of constraint".

Is the recipient's own identity threatened ? The accounts of recipient children and donor children reveal the importance and complexity of the accompanying symbolic phenomena, be they the source of the tightest of bonds or of fierce hatreds within the sibship, which is reason enough for future studies to be undertaken in inevitably difficult conditions of non-discrimination.

Parents may also find it difficult to adapt to this situation, in particular in case of failure. How can feelings of guilt be overcome if helping a sick child becomes an impossibility, or if such fragile pregnancies fail repeatedly (one should not forget that the chances of success are low), or if the transplant is rejected ?

## III - 4 Some landmarks

### III - 4.1 Principles

Technical progress seems to point in the direction of ever increasing control over life. However, perhaps "authentic" control is to know where to stop, and to think about the boundaries of what can be done to treat a sick child.

Some of the principles set out in the reports and opinions of CCNE may be quoted :

- non instrumentalisation of individuals, born or as yet unborn,
- respect for the integrity of a person, - choosing the lesser evil when objections can be found to all proposed solutions.

One must be aware that this latter principle, which is akin to the weighting process which is an integral part of medical decision making, can sometimes be in conflict with principles that are generally accepted and considered seemly.

### III - 4.2 Risks of extension of HLA compatibility research

Solidarity with other human beings is one of the powerful principles of our humanity. A graft taken from a live donor is one of its most perfect illustrations. However, the boundaries of this philosophy are only too visible when we encounter illicit trading in human organs and commoditisation of life itself. Opening up PGD to researching immune compatibility carries the risk of extension to widespread genetic and haematological diseases, affecting possibly millions of individuals, but also to cousins or even parents who might want at some point to benefit from cord blood cell transplant for other reasons in view of restorative therapy. Obviously, no objection to any such extension could be voiced at this point to reject such requests, and the whole situation would become unmanageable. In this way, solidarity as a value is confronted with the utopian nature of such practices.

A real danger of another kind is represented by the probable future simplification of the HLA identification technique; it would become tempting to construct systematically HLA compatible families of siblings so that they could mutually and endlessly repair each other.

Any technique and any instrument, can be made to serve opposite finalities, some good, and some bad. It may seem unjustified to object, because of risks which can never be totally discounted (although their existence may sometimes be totally devoid of empirical foundation), to hopes induced by the use of new techniques, of proven efficacy. However, such promises are confronted by limits which society must never cease to redefine.

## III - 4.3 Limits and precautions

In the presence of such requests, is it possible to prohibit, or accept exceptions, or accept extensions ?

The possibility that an extension of PGD, as it is considered here for Fanconi's anaemia, becomes a matter of routine applicable to a great number of congenital or acquired disorders, is forbidding. Although one may consider that harvesting stem cells from the umbilical cord is such a simple non traumatic procedure that society could hardly see it as a serious problem, there must be no forgetting that an extension of PGD in that situation can lead later to pressure to "give" bone marrow. The possibility of psychological consequences for a child who learns that one of the facts of his existence is that he was chosen so that he could save another child and that he might later be subjected to repeated "donations", remains uncertain. It is essential that parents be alerted to the far-reaching significance because of its potential implications, of this action, so that they are not solely aware of its salvation value. But the family must be allowed to think for itself. One can easily understand that a distressed couple, together with a medical team, confronted with serious and lethal sickness in their child, would want to do everything humanly possible to save that child. Insofar as the graft of stem cells and later of

bone marrow seems to be the only possible therapy for the time being, because of immune compatibility, to simply prohibit seems harsh. Having recourse to the principle of the lesser evil is understandable in such cases, but it does open the door to a new kind of restorative medicine which again raises the issue of the boundary between a reasonable therapeutic effort and excessive obstinacy.

Everything rests on the awareness of the medical team, and above all of the family, to this problem. The first requirement is a true parental project. The first justification for performing PGD is the birth of a child, unaffected by the serious genetic disease which threatens to affect him. Searching for immune compatibility with a sick elder sibling must take second place, otherwise the gift of cord blood is tantamount to life-long subjection. This imperative is the only safeguard for the family, and providing information together with psychological support must be seen to construct a strong family bond, preserving the autonomy and integrity of the child born post PGD. The issue is not just selecting an embryo ; only profound respect for otherness can, in such a situation, justify the choice of a therapeutic objective.

## IV Diagnosis by exclusion for huntington's chorea

On April 27, 2001, a problem concerning PGD for Huntington's Chorea was referred to CCNE. The parents do not wish to know whether they themselves are at risk of being affected by this appalling disease. As of now, the law does not permit this, since PGD must be limited to detecting a genetic mutation known to affect the parents and transmitted to embryos. The person concerned wishes to have a disease-free child but claims the right not to know.

This raises several problems :

1. - ignorance of parental status claimed as the right not to know
2. - the issue of an exclusion diagnosis as regards collective health care choices,
3. - disparity of situations depending on parent gender,
4. - the status of the healthy future child,
5. - possible extension to other genetic situations,
6. - children's rights and the right to bear children.

### IV - 1 Ignorance of parental status claimed as the right not to know

The right not to know is an established right. Huntington's disease is in fact one of its most significant examples insofar as its full penetrance leads to a binary conclusion : the risk is either zero or one hundred per cent, with neurological and psychiatric disorders at an age, which cannot be foreseen, of between 30 and 60 years. There is no warning sign of

future disease so that individuals concerned cannot decide whether they can safely have children unless this test is used. The issue arose therefore since the 70s of whether such patients should be told, if they so request, that the mutation is present or not. Since that time, multidisciplinary teams composed of neurologists, psychiatrists, and psychologists, have made it possible for that information to be given in a reassuring environment to those who wished to know. But this information, however reassuring, is still an immense shock. Even though persons concerned may not wish to know, there is nothing to prevent them having children, since the onset of the disease is often fairly advanced compared to the reproductive period in a life.

To have a child without transmitting the disease, there are several possibilities :

- The simplest course is to diagnose for the mutation, but that implies that those concerned are aware of, or discover their status. If the mutation is absent, it is perfectly safe to have children. If the mutation is present, a direct prenatal diagnosis can be requested.
- If the foetus bears the anomaly, elective abortion can be offered. For persons born of an affected parent, and therefore at risk, and who do not wish to be informed of their own status, an indirect prenatal exclusion test* can be provided. This is a verification that the foetus has or has not inherited a chromosome 4 from the affected grand-parent. If that chromosome is present, the risk is identical to that of the parent (50%). That leaves two possibilities : either abort this "50% risk" foetus, with as a consequence the elimination of an unaffected foetus half of the time, or continuing pregnancy if the foetus has inherited a chromosome 4 from the unaffected grandparent, i.e. is in a very low risk situation. The guidelines which govern the protocols for presymptomatic diagnoses of this disease accept de facto that the prenatal exclusion test □ can be a possible exception to the general rule which stipulates that prenatal diagnosis is only performed if at-risk individuals are ready to accept disclosure of their own status. This exclusion test is, however, sometimes rejected because it results in the elimination of all 50% risk foetuses, whereas in theory half of them are unaffected. Studies have revealed, for that matter, that a significant number of parents who had asked for this test to be performed and who had initially intended to abort at 50% risk, finally changed their minds and continued the pregnancy.

It is clear however that the prenatal diagnosis hurts the mother who is faced with the possibility of termination, and the wish to turn to preimplantation diagnosis instead is understandable. Here again, two

possibilities are available when the at-risk parent does not wish to discover his/her own status as regards the disease :

- The first possibility is direct diagnosis which makes it possible to select an embryo which is unquestionably unaffected by the disease. The results concerning the at-risk parent are not disclosed to the couple, at their request, but the medical staff may be extremely burdened by this secret. If all the embryos are affected, the absence of transfer would suggest that the parent is also affected, and the notion that a physician would play a role in simulated transfer or prevaricate about the embryo's non-transferable status, to preserve the couple's wish not to know, is unacceptable. If all the embryos are unaffected, this could be interpreted - wrongly - as a sign that the at-risk parent is not a carrier, which could turn out to be erroneous.
- Another possibility reverts to the indirect exclusion test. This is the same method as the prenatal exclusion diagnosis. Only the embryos which have not inherited the chromosome 4 of the affected grandparent are retained. There again, there is acceptance of the principle of destroying embryos of which half are, in fact, unaffected. Furthermore, this method reduces by half the chances of success of IVF, which are low to start with.

As it turns out, in such a situation, the wish not to know is not as easy to respect as one might suppose. The direct diagnosis provides a boomerang diagnosis for the parent, but excludes elimination of an unaffected embryo ; the indirect diagnosis protects the wishes of the at-risk parent, but in one case out of every two, eliminates a healthy foetus.

Furthermore, PGD is only justified in this situation by the parent's wish to ignore his/her status. In fact, if that parent is not a carrier for the mutation, PGD is not necessary at all. If that parent is a carrier of the mutation, only the direct elimination diagnosis of an affected embryo would make any sense. The indirect diagnosis is superfluous.

There is finally the question of the resources made available with the single aim of protecting someone from anguish. And yet, the right not to know is in no way blameworthy and must be respected in the name of solidarity with the most vulnerable of our kind.

## IV - 2 The status of the healthy future child

Members of a family afflicted by Huntington's disease live in a very special climate of uncertainty and anxiety. There is a good chance, if the father is affected, that the child becomes sooner or later the mainstay of a parent in the throes of this fearsome neuro-degenerative disorder. The situation will be better or worse according to the quality of the family and social

support network. Onset of the parent's disease will generally surface during the adolescence of the child who will suffer everafter from a pathological parental image. But is it the task of the medical profession to consider itself the moral judge of such family situations which are perhaps the sole prerogative of those families ? Nor can the issue of the responsibility of the medical profession in a procedure which could have grave consequences for the future child be eluded. It is important that the fullest information should be given to the family concerned. In any event, there must be awareness of the truly dramatic situation of the parents, and every attempt must be made to help them without making them feel guilty.

### IV - 3 Possible extension

The risk of arriving at an extension of preimplantation diagnosis to most late-appearing diseases is considerable. There is no reason why Huntington's disease should be singled out to the detriment of genetic forms of Alzheimer's disease, possibly genetically induced tumorous diseases, etc...

## V - CONCLUSION / OPINION

Careful examination of the two cases in question leads CCNE to express the wish that the fundamental principle underlying the law should not be questioned : any action or medical process affecting an embryo, which is to be reimplanted, must have as its primary aim the welfare of the embryo itself and be of direct benefit to the future child. For that matter, the law as it now stands does not offer any solution to the two problems raised.

The Committee finds that although the two questions put to it are connected, since both suppose that account be taken when a PGD is performed of the interest of a third party, they are nevertheless significantly different because that interest in the two cases varies in degree. This difference implies particular ethical values and therefore leads to distinct positions being adopted.

Working on the hypothesis of an HLA compatibility test in familial Fanconi's anaemia, the essential problem is the authenticity of the parental project and therefore of the risk of a child becoming a commodity.

The legitimate wish to bear a child does not equate the right to a child-object. Just as embryos must not be manufactured specifically for use in research and healthcare, a pregnancy must not be entered into for any other purpose than what is right for the child. Very probably, there have always been "remedial" children, but in this case the medical profession

plays a decisive role. A fortiori, selecting an embryo and producing a baby designed purely a potential donor, and not for the sake of the child itself, is unthinkable in the light of the moral values that CCNE has always defended. However, making it possible for a baby the family wishes to have anyway, to represent - also - a ray of hope of a cure for the older sibling, is an acceptable objective, albeit not the prime objective.

These matters are momentous. Contemporary medical science offers new and untried choices for the birth of a child. But extending this possibility to various predictive situations represents a risk of turning child-bearing and children into commodities.

Defending this principle, however, does not rule out that possible secondary benefits affecting others and connected to an extension of PGD, could be considered and found to be legitimate, as long as there is no breach of the principle that the child's best interests remains paramount.

The fact is that although the wish to have a child must prevail, one can hardly pretend to ignore the gravity of the situation. The major risk however is in a pregnancy for purposes which are more therapeutic than centred on the future child. And for that matter one could be doubtful of the true benefit when therapeutic benefits are over estimated to the detriment of fundamental principles which protect the future child.

As long as the interests of the future child are protected, absolutely and as a priority, the medical knowledge of the potential interest that the child also represents for a known third party, is a possibility of confronting particularly harrowing situations in a spirit of generosity.

In the specific case of Fanconi's anaemia, in any event, the practitioners treating the sick child must - in each case, from the outset, and throughout treatment - provide clear and precise information to parents regarding the benefits and drawbacks of such compatibility screening. This information must lead parents to be fully aware, long in advance of the situations of anguish and distress inevitably generated by the disease's progression, of the fact that if they were to want to have another child at some future time, PGD could provide them with the certain knowledge that their child would be free of the disease they are battling against. As a secondary consequence, serene consideration could be given to the possibility of that child being a privileged donor, thus contributing to the treatment of the sibling.

Parents must also be clearly informed that there is a possibility that HLA compatible embryos may not be available. This medical information should anticipate a possible decision to reject the transfer of healthy, but non compatible, embryos. This would provide parents with time to reflect on what they would decide in such a situation. Should the medical profession consent to give priority to selecting a child for its remedial potential and not for its own sake, it would forfeit a major ethical reference.

The Committee would see as unacceptable, for example, that a child who is not being screened for a particularly serious genetic disorder, be chosen solely on the basis of HLA type which could help the older sibling.

So as to encourage parents not to give up completely healthy embryos simply because they are not HLA compatible, their doctor must try and help them understand that giving birth to a child cannot be restricted to the sole purpose of producing a "remedy", albeit to save their existing sick child.

In spite of the compassion and solidarity one would wish to express to a family tormented by the sickness of a loved one, it does not seem acceptable to instrumentalise a child. This is the majority position of the members of the plenary Committee, which took the view that the secondary nature of the screening process must not, for any reason whatsoever, be allowed primacy of place. An otherwise healthy, but HLA incompatible, embryo, cannot be rejected for that reason alone. A child is not born solely for the sake of compatibility.

Certain members of CCNE, however, in a spirit of solidarity, consider that the parents' wish to repeat the PGD procedure in the hope of obtaining embryos that are both healthy and compatible, cannot be opposed.

In the case of Huntington's disease, embryos are chosen because they have not inherited the chromosome which could be carrying the mutation. There is no doubt that the parents actually want a child and that this is their main concern. So the interest of the future child is protected, but there are some ethical issues nevertheless.

- Unaffected embryos are eliminated in the interest of a parent who does not wish to know whether he or she has inherited a serious genetic disease. However, although the elimination of embryos is naturally inherent to PGD and to IVF, and for that matter to any human reproduction process, the deliberate nature of that elimination raises issues and must be appreciated in the light of aims pursued.

- The accountability to future children in a family threatened by the risk of an appalling genetic disease, cannot be eluded.

- Total protection of an individual's right not to know is not without consequences as regards collective healthcare decisions in a context where resources are necessarily finite. CCNE considers however that cost must remain a secondary preoccupation behind the duty of solidarity, particular as regards the more vulnerable members of society. CCNE emphasises the need to fully explain in the course of genetic information given to parents, the constraints and repercussions of using the PGD procedure.

However, there is still the fear of opening the door to uncharted contingencies. Humanity could go in the direction of seeing itself as means

rather than an end. Or prediction mania for late-onset diseases may become irresistible. To shift from the possible efficacy of a medical technique to an obligation imposed on medical science can lead to some major paradoxical ethical problems.

CCNE has no intention of postulating in this respect any censorious or permissive doctrine which could anyway be contradicted by new scientific breakthroughs. It seeks rather to draw attention to the serious and major issues that a decision of this kind concerning a child cannot fail to generate. A child's own interest must never be obscured by the interest of another.

**Preimplantation genetic diagnosis (PGD) - European regulations**
Gwen Terrenoire, CNRS

In the absence of any global European regulation on PGD □, authorisation concerning its practice is the responsibility of each state. Some authorise or forbid it by a specific law, and in some cases a law is in the process of discussion. In other countries, the practice is indirectly authorised by an agency regulating MAR, or research on the embryo, or by a law governing medical research.
A negative opinion on PGD was recently expressed at the European level by the temporary committee on human genetics and other new technologies of modern medicine in the report it presented on November 8, 2001 to the European Parliament □. The Committee feared that excessive use of genetic testing, PGD and prenatal diagnosis in particular, could lead to eugenic practices. However, this report was totally rejected by the European Parliament.

**States with a specific law authorising PGD**

**Denmark**
**Law N° 460, dated June 10, 1997, concerning artificial fertilisation in relation to medical treatment, diagnosis, and research, and Order N° 758, dated September 30, 1997, concerning a report on treatment as regards in vitro fertilisation, etc., and**

**preimplantation genetic diagnosis**

PGD is permitted, but its application is limited to cases where the child runs the risk of being affected by a severe hereditary disease or a significant chromosomal abnormality.

*Chapter 2. Prohibition to treat*

Article 7. 1. *Genetic testing of a fertilised oocyte can only be performed in*

*cases where there is a serious and known risk that the child could be affected by a severe hereditary disorder*.

Article 7.2. Genetic testing can also be performed in connection with artificial fertilisation external to the body of the woman concerned for reason of infertility, when such a test can *confirm or exclude the presence of a severe chromosomal aberration.*

Article 8. Artificial fertilisation involving a selection of sperm cells or of fertilised oocytes before implantation into a woman's uterus with the aim of *selecting the sex of the future child is prohibited, unless the object is to prevent a serious hereditary sex-linked disorder affecting the future child.*

**Spain**
**Law n° 35 dated November 22 1988, as regard medically assisted reproduction techniques**

PGD is permitted, but its field of application is limited. Articles 12 and 13 deal with diagnosis and treatment for prenatal and preimplantation diagnosis.
12.1. *No intervention on a live preembryo, in vitro, with a view to diagnosis, may have any other aim than evaluating its capacity to survive or detecting hereditary diseases to treat them if possible, or to advise against transfer for reproduction.*

13.1. *No intervention on a live preembryo, in utero, for therapeutic reasons, may have any other aim than treating a disease, or preventing its transmission, with reasonable and controlled assurances.*

13.3. *Treatment may be provided for preembryos in vitro or preembryos… only if the following conditions are satisfied : …*

d) *Treatment does not effect non pathological hereditary characteristics and does not seek to improve (seleccion) individuals or the race…*

**France**
**Article L. 2131-4 (CSP) of law 94-654 dated July 29, 1994, et Decree n° 98-216 of March 24, 1998**

*Biological diagnosis based on cells sampled from an embryo in vitro is only permitted in exceptional circumstances, in the following conditions : A physician practising in a pluridisciplinary prenatal diagnosis centre as defined by article L.2131-1, must certify that the couple, because of their family background, has a strong possibility of giving birth to a child affected by a particularly severe genetic disorder, recognised as incurable at the time of diagnosis.*

*Diagnosis can only be made if the anomaly or anomalies causing such a disorder have been previously and specifically identified in one of the parents.*

*Both members of the couple must express in writing their consent to the diagnostic procedure.*

*The diagnosis can have no other purpose but to detect this disorder and seek the means of preventing or treating it.*

*The diagnosis may only be performed under certain conditions, in an institution specifically licensed to do so with the approval of the National Committee for Reproductive and Prenatal Diagnosis Medicine and Biology.*

**Norway**
**Law N° 56 August 5, 1994 regarding medical utilisation of biotechnology**
The law contains a chapter 4. *Preimplantation genetic diagnosis.* 4.1. Preimplantation genetic diagnosis signifies *genetic testing of a fertilised oocyte before implantation into the uterus.* 4.2. *A fertilised oocyte can only be submitted to genetic testing in special cases involving a serious untreatable hereditary disease, such as designated in article 2-10, 2nd paragraph : According to more detailed specifications by the Ministry of Health and Social Affairs, extracorporeal fertilisation may also be performed in the case of a serious hereditary disorder, such as outlined in article 4-2. Royal authorities may decree detailed conditions regarding access to preimplantation diagnosis.* 4.3. *Testing the fertilised oocyte for the purpose of selecting the sex of the child is prohibited, except in special cases involving a serious sex-linked hereditary disease.*

**Sweden**
**Law N° 115 of March 14, 1991, and Instructions by the Ministry of Health and for Social Affairs, on prenatal and preimplantation genetic diagnosis.**

**1995**
PGD may only be performed in order to diagnose *severe and progressive hereditary diseases leading to premature death and for which there is neither treatment nor any possibility of cure.*

**<u>States with a specific law prohibiting PGD</u>**

**Germany**
**Law on the protection of embryos, 1990**

Two articles are of interest. Article 2-1 punishes anyone *using a human embryo for any other reason than ensuring its survival.* Article 8-1 defines the embryo *as a fertilised human ovum capable of development as soon as fusion of the nuclei has taken place.* According to this article, every totipotent cell harvested from an embryo is also an embryo which must be protected.
There is ongoing discussion regarding the possible acceptability of PGD using non totipotent cells.

Professional organisations (Deutsche Forschungsgemeinschaft, Gesellschaft fur Humangenetik, Bundesarztekammer) (The German Medical Association) and other associations are in favour of a modification of the law whereby it would be possible to practise PGD under very severely controlled conditions. The German Medical Association presented draft directives in 2000 following a symposium on reproductive medicine organised by the German Ministry of Health. The Ministry made its opposition very clear, but conceded that it could accept a law permitting the use of such techniques subject to very restrictive conditions being defined. The Conference of German Bishops published a statement expressing its opposition to PGD on the basis of two arguments - the right of the embryo to protection and the risk of encouraging eugenic tendencies.
On May 14, 2002, the parliamentary commission on "Law and Ethics in Modern Medicine" published the conclusions of its medical enquiry. By a vote of 16 to 3, it rejected reversing the prohibition of PGD [6]. The principal argument bears on the impossibility of assuring the protection of the embryo required by the Law, since the technique aims to select certain embryos. Those in favour of reversing the law had proposed decriminalisation of PGD in certain exceptional circumstances, evaluated on a case by case basis.

**Austria**
**Law N° 275 on reproductive medicine, 1992**
Article 9(1) : *cells capable of development may not be used for any other purpose than for MAR. They may only be tested and treated insofar as that is necessary, taking into account the progress of science and medical practices, to obtain a pregnancy.*

**Ireland**
**Constitutional Law**
8th amendment (1983) : *The State acknowledges the right to life of the unborn and, with due regard to the right to life of the mother, guarantees in its laws to respect, and as far as practicable, by its laws to defend and vindicate that right (of the embryo).*

A committee of the Department of Health is currently studying the possibility of establishing instructions for the practice of MAR, which could include PGD.

**Switzerland**
**Federal Law on medically assisted reproduction, December 18, 1998**
Article 5-3 : *Sampling one or several cells from an vitro embryo and their analysis are prohibited.*
In 2001, The Commission on Science, Education, and Culture of the National Council, proposed a review of this prohibition, recalling that it had only been secured because of the President's casting vote.

## States where PGD is permitted in the absence of any specific law.

**Belgium**
A preliminary draft bill "concerning the protection of in vitro embryos" dated December 1998, considers legislation on embryo research, including PGD, considered as a scientific research activity and not for clinical application. : *pre-implantation genetic diagnosis (…) can be used to detect painful incurable diseases afflicting children who die at an early age. It prevents the need for therapeutic abortions which occur when such diseases are only discovered by prenatal diagnosis.*

In the meantime, PGD is regulated by regulations concerning human genetics. A royal decree of December 14 1987, stipulates the standards with which must comply the centres for human heredity so that they may be authorised to perform diagnostic tests and provide genetic counselling. Licensed centres are publicly financed and their services are accessible to anyone having need of them. Two royal decrees dated February 15, 1999, set criteria applicable to healthcare programmes in reproductive medicine and regulate the IVF centres. In a centre authorised for the practice of IVF, approval of the bioethics committee in the institution concerned must be obtained.

**Finland**
**Medical Research Act, Statute No. 488/1999**

This law defines medical research as follows : *intervention touching on the integrity of a human person, embryo, or fœtus with the aim of improving knowledge of the causes, symptoms, diagnosis, treatment, and prevention of diseases or of the nature of the disease in the broadest terms*.

Chapter 3 deals with research concerning embryos and foetuses. It specifically forbids certain interventions : research on an embryo more than 14 days old and without the mother's consent, the production of embryos for research, research aiming to modify hereditary characteristics, cloning of a human being… MAR and PGD techniques are not mentioned as such, but since they are not forbidden, they are deemed to be permitted, provided certain conditions are respected (approval by an Ethics Committee, consent, approval by the national authority for medical and legal affairs…). Early in 2002, a law on MAR was being prepared. It is likely to authorise PGD in a clinical framework.

**Greece**
Before 2000, there were no regulations as regards embryo research. The subject was covered by a statement from the General Council for Health in 1988. Research must be approved by a competent Ethics Committee. In 2000, a presidential decree prohibited embryo research.

**Italy**
For quite a long time, there was no law regulating medically assisted reproduction. A draft bill, on which the Chamber of Deputies voted in June 2002, is being reviewed by the Senate. Article 3, although it does not mention PGD specifically, seems to forbid it when "using MAR for eugenic purposes or for selection to predetermine the characteristics of a future child" are proscribed.

**Netherlands** 7
PGD is viewed as a research procedure and must conform to the law on medical research on human subjects, which entered into force at the end of 1999. Protocols must be approved by the Central Committee for Research which was created in connection with this law. PGD is approved because its aim is to prevent the sufferings of future children and of their parents. Centres must be licensed. A draft bill currently being discussed offers rules for the use of gametes and embryos, in particular for research, but does not specifically mention PGD.

**United Kingdom**

PGD is implicitly accepted by the 1990 Human fertilisation and Embryology Act [8] which regulates medically assisted reproduction and defines the conditions in which research on the embryo is allowed. The development of methods of detecting genetic or chromosomal abnormalities in an embryo before implantation are among the objectives justifying embryo research.

In 1999-2000, the Human Genetics Commission and HFEA wished to discover the opinion of the public on a possible extension of criteria for application of PGD. Following this public consultation, a working group prepared recommendations, including the following : *PGD should only be available when there is a significant risk of a serious genetic condition being present in the embryo* [9].

HFEA's Ethics Committee published a favourable opinion in December 2001 concerning a request for associating HLA typing and PGD to help a seriously ill child [10]. The Ethics Committee stated in particular : *we can see how the use of tissue typing to save the life of a sibling could be justified. We would see this happening only in very rare circumstances and under strict controls.*

## REFERENCES

[1] Cord blood, also called placental blood.

[2] 'Indirect exclusion test' means that the mutation itself is not excluded, but the origin of the chromosome. If the foetus has inherited none of the chromosomes 4 of the affected grand-parent, it cannot have inherited the mutation. If the chromosome is present, there are 50% chances of being affected.

[3] However, the Oviedo European Convention on Human Rights and Biomedicine (1997), stipulates in its article 7 that " The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided. "

[4] European Parliament, Report Report on the ethical, legal, economic and social implications of human genetics ", rapporteur F.Fiori, November 8, 2001 (CDEI 14418).

[5] Data sources : Eurogapp Project 1999-2000, European Society of Human Genetics, Public and Professional Policy Committee, Provision of Genetic Services in Europe - Current Practices and Issues, Background Document, 3 May 2001, ( CDEI 6484), and Sénat, Documents de travail du Sénat, L'Assistance médicale à la procréation et la recherche sur l'embryon, 2000 (CDEI 14307).

[6] Deutscher Bundestag, Schlussbericht der Enquete-Kommission "Rechet und Ethik der modernen Medizin" (CDEI 6914).

[7] Source : Health Council of the Netherlands, Committee on in vitro fertilization, 1998 (CDEI 5138).

[8] Human Fertilisation and Embryology Act.

[9] HGC and HFEA, Outcome of The Public Consultation on Preimplantation Genetic Diagnosis.

[10] Ethical Issues in the creation and selection of preimplantation embryos to produce tissue donors.