From Random Procreation to Standardized Reproduction

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My paper will be more concrete than those of the previous speakers. It is almost a scientific paper, but not altogether. I shall project some slides, but it should in any case be easier for everyone to follow. Why more concrete? Because since the birth of Dolly the sheep, two years ago, the ethical debate on the possibility of cloning human beings has been hindered by stumbling blocks of a contradictory nature. On the one hand, despite endless discussions, no one has come up with good enough reasons to support human cloning. But, on the other hand, no one has produced undeniable reasons for opposing human cloning. So I would like to show you that there is a form of human cloning for which many good reasons can be found (medical, social and others), and that this form of cloning – embryo cloning – can be included among the aims of medically assisted reproduction. I mean that we can envisage the transition from assisted reproduction, offered in cases of sterility, to techniques whereby fertile couples can choose their babies. Until now the goal of medically assisted reproduction was to defeat human sterility, but it will gradually become more and more oriented towards knowing in advance the genetic make-up of the children that will be born. And I shall show you that in order to do this it will be necessary to engage in embryo cloning. But I should mainly like to stress the fact that cloning, contrary to what common knowledge holds, is not genetic manipulation: quite the opposite, it is a process of genome conservation (even at this meeting I have heard people say that cloning is genetic manipulation). I even heard Bernard Gert say that human cloning is significant only if related to genetic engineering. The term genetic engineering usually means genetic manipulation of the embryo. I should like to remind you that the feasibility of all these techniques still needs to be proven, despite the boasting and triumphant statements of our colleagues, the geneticists. Yet, I don't subscribe to the idea that cloning is significant only if applied to genetic engineering. I think it could be useful in the field of genetic identification: you don't interfere with anything, you simply observe,

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you study the embryo, you establish certain parameters to detect how it would evolve if it were allowed to develop into a child and then you select the embryos according to these criteria, since modern assisted reproduction techniques almost always allow us to dispose of more embryos than we need. If medically assisted reproduction can rightly be included in the sphere of reproduction – and this to me seems evident – it is because there is a vast number of embryos, because they are available outside the human body, *in vitro*, and because there is no added suffering in the process of embryo selection. Furthermore, the act of cloning applied to an embryo (and this has already been said) is not at all the same thing, from a moral standpoint, as the cloning of an adult or of a child.

The first victory of assisted reproduction strategies was that they enabled us to improve our chances of achieving fertilization: it improved our odds ratio. Increasing the number of female gametes available, we were gradually able to reduce the number of male gametes necessary for fertilization, while devising mechanisms to favour the union of the gametes. Thanks to these mechanisms today fertilization is successful in almost all couples. This is a completely novel phenomenon, and may allow us to pursue a new strategy, one aimed not so much at ensuring a higher probability of successful fertilization, but rather at improving the chances that the child conceived thanks to medically assisted reproduction techniques will be normal. This will require a considerable number of embryos and thus of eggs to fertilize.

Let us remember that, by means of sexual intercourse (the natural way, that is), one oocyte alone is exposed to two hundred million spermatozoa entering the vagina. Thanks to artificial reproduction techniques – first insemination, later *in vitro* fertilization – we have succeeded in increasing the number of oocytes, that is of egg-cells produced by women subjected to hormonal treatment. It is quite usual to have between ten and twenty. Thanks to the technique whereby a single spermatozoon is injected into the cytoplasm of the oocyte, we now have a ratio of one to one in the number of gametes. I believe that this strategy, which has been used for several decades now and which aims to increase the number of female gametes, reducing the number of male gametes necessary for fertilization, has had its day: we shall never be able to do better than place a spermatozoon into an egg. And we can even introduce an immature spermatozoon into an egg which is not mature at the time it is collected.

The main advances in assisted reproduction have consisted in favouring interaction between the gametes, in replacing the cerebral commands governing ovulation, in being capable of preserving gametes and embryos for a long time in liquid nitrogen, in resorting to immature gametes if necessary. And here we come to the last step: identifying viable embryos, or rather

normal embryos, which is not exactly the same thing. Since this is the stage we have reached today, there is a new strategy which will need to be developed, based on the availability of a large number of embryos in the laboratory.

I should like to remind you that in order to exert quantitative control over the number of "products" (children per family), even before assisted reproduction, we have birth control. In other words, today a couple, and a woman in particular, can choose to have a child only when she wants to. Techniques of medically assisted reproduction allow women to become pregnant even in cases of sterility, and thanks to obstetric and perinatal care such a pregnancy will lead to a live birth. I would like to remind you that two centuries ago half of the children born alive died before reaching the age of five: a real revolution has therefore taken place in the field of human reproduction.

The result is that couples – and women in particular – in industrialized countries no longer want to have seven, ten or fifteen children. With a few rare exceptions, they have 1.6 or 1.8 children, in some cases even 1.4 or less. And this is important, since that one child is going to be treasured and valued even more highly, and the mother will want the child even more.

Let us now have a look at the qualitative aspects of this management of human reproduction, in particular of pre-implant diagnostics, by which I mean the genetic analysis of embryos available after the fertilization procedure but before they are implanted in the mother's uterus. This analysis will ascertain which embryos are *normal*. Many embryos are available simultaneously for this selection and this will, potentially, allow us to dispose of a broad-ranging inventory of genetic characteristics from which to choose the embryo. There is a slight emotional factor involved in the elimination of a fertilized embryo, which our Anglo-Saxon colleagues call a *pre-embryo* precisely to underscore the fact that there should be little emotional value attached to it. More importantly, though, these embryos (pre-embryos) are outside the woman's body which means that their elimination is not a medical affair and can de done very easily. Furthermore, as we have seen, couples nowadays only want one or two children.

One could envisage that, in the future, there may be a demand for pre-implant diagnostics on an embryo, especially in the case of couples at risk: currently this type of genetic selection is performed on the embryos of many couples known to be genetically at risk in many countries in the world. But one could also envisage the same procedure being used in the case of sterile couples, who have undergone *in vitro* fertilization due to sterility: if we already have embryos in the lab it would be a shame not to take advantage of the available genetic techniques to select the embryos. This

is a procedure being adopted in the United States for women aged 38 or over: in some centres they are systematically offered embryo selection. Lastly, one could even accept a situation in which couples are offered *in vitro* fertilization with the sole aim of benefiting from the embryo selection procedure.

Talking about human embryo selection, I usually use the word *eugenics* and usually people tell me that this is not eugenics. Yet, if we read the definition given by Francis Galton in 1904 ("study of those socially controllable factors capable of elevating or lowering the racial qualities of future generations, both physically and mentally"), we shall immediately realize that this is exactly what it is about. There is no contradiction, the only disturbing element is the expression "*racial qualities*". But I'd like to remind you that it's not used in a racist sense: in Galton's times the term race was used more or less the way today we use the term species, without racist implications. This definition can thus be perfectly well adopted today, just as I consider it appropriate to use the term eugenics. I'm not talking about the activities of the Nazis. I'm referring to a form of eugenics that held sway in democratic countries in the early part of the 20th century, from 1907 to 1933, let's say, in the United States and in certain European nations: there, individuals judged unfit to procreate children of quality were sterilized, and this was done with the assistance of physicians in those democratic countries.

It was highly unlikely that this classic form of eugenics would have ever been effective, the main reason being that when one sterilizes a man or a woman it is a random process, governed by chance. There are so many mutations involved in the process of gamete production, *gametogenesis*, that there is practically no sense at all in intervening before the production of embryos. Equally, *meiosis*, that is the cell-division procedure that gives rise to gamete production, distributes the genes in a random and unpredictable manner. There are furthermore psychological aspects that cannot be controlled: a man will form a couple with a woman in an unpredictable way and we have no way of knowing which of the millions of spermatozoa will actually fertilize the ovum. Human fertility is very weak and this means that eugenic practices need only do very little to "raise the quality of future generations". Add to this the fact that environmental factors can interfere with genetic factors and, luckily, with individual and social resistances against eugenic planning which has always been an authoritarian process.

We can compare the advantages of the various eugenic procedures in relation to the objective pursued. Firstly, the oldest of all eugenic methods, the one used by the Greeks, which consisted in suppressing the newborn at birth. This was not particularly well accepted, either by the couple or

by society at large; furthermore, it had absolutely no effect whatsoever on improving the genetic make-up of the population. One can also pursue the same objective, but addressing the potential parents, with genetic counselling, which is fairly well accepted by society since it is not really seen as an authoritarian process. This means helping the couple, advising them on the decision to take, although no couple is ever particularly satisfied when they are told that it would be best to abstain from procreation. But, yet again, no genetic improvement of the species will ever be achieved by these methods, nor by sterilization, which has been practiced for a long time (and is still practiced to this day in certain countries).

Abortion (and by this term I refer here to a medical intervention that discontinues a pregnancy when it has been ascertained that the foetus displays an abnormality) is not terribly well accepted by society, and it never leaves the couple satisfied. Furthermore it is of no interest from the point of view of eugenics. But, on the other hand, the technique of embryo selection, meaning that no embryo that does not meet a specific definition of normality is transferred into the uterus, is a technique that is socially acceptable and is also accepted by the couple. If the couple has fifteen embryos and wants two children, they will prefer that these two are chosen from among the normal embryos. In this case there is also a possible effect of genetic improvement of the species if the scale on which the procedure is performed (large number of embryos and couples to be treated) is vast enough.

If some embryos are homozygous for a severe abnormality they will be excluded. Among all the embryos that are observed under a microscope (in our example there are fourteen), first of all we shall rule out these four, considered the most abnormal despite the fact that some of them are heterozygous and therefore will only be carriers of the disease. Then we have a group of five embryos who are all at risk, meaning that they are not exactly abnormal, but they do carry the genes that make them susceptible to certain diseases. These embryos will be ruled out as long as we can dispose of other embryos of better quality. The study of the susceptibility to risk factors is undoubtedly the future of genetics: it will soon eradicate all single-gene diseases that we are beginning to investigate and identify. There are not many of them; polygenic diseases, on the other hand, are far more numerous and will require much more research before we have finally mapped them in the genome.

After that we will identify the second-choice embryos, the ones that are not bad, but do in any case present some small flaw. This form of diagnostics calls for an in-depth analysis of the genome which has not yet been achieved: what I am showing you here is a projection into the future. In the end we

are left with, say, three *normal* embryos which we shall transfer into the uterus. One could at this point, since we know the sex of these embryos, take advantage of the knowledge and suggest to the couple that they can choose the sex of their baby. That's not an entirely innocent procedure.

What is the advantage of this selection of embryos as compared to the prenatal diagnostics that we already practice today? In prenatal diagnostics there is only one foetus in the mother's womb and the foetus is examined in search of a single specific pathology (for the simple reason that, if one were to search for ten pathologies in each foetus tested, we would always end up by finding something and have to eliminate them all). This can only be done very rarely since pregnancy isn't that easy to achieve in a woman. A woman can get pregnant, generally speaking, once a year. This means that overall the number of embryos or foetuses one could subject to foetal genetic analysis every year would only be one per woman.

When you perform an embryo selection, the number of embryos present at the same time in the test tube, *in vitro* in other words, is usually about ten, sometimes more if the woman is young. So we have a lot of embryos available for testing. And this test can be repeated several times a year. In other words, every year we shall dispose of several dozen embryos in order to diagnose a variety of different conditions: using the selection procedure our diagnostic potential is incomparably superior to that offered by prenatal diagnostics. I believe that this is truly important to understand that we are entering a new age in human selection processes: the potential is incomparably greater than it was with the old techniques.

What can we do to increase the current medical effectiveness of this embryo selection procedure, called pre-implant diagnostics (PID)? Today only a few hundred children in the world have been born with this procedure of PID, since the technique is very cumbersome and not very widespread in its application. But for the future one can envisage the possibility of choosing among a large number of embryos: instead of selecting from among ten or twenty, we shall be able to choose from a hundred or more embryos. In order to do this we shall have to increase the number of ova produced by the woman. I shall talk later about the techniques that will allow us to do this, although they are already being experimented in animals.

Once we have the embryos available, we shall be able to multiply the genetic characteristics that we are searching for. Human genome programmes are being developed in many countries; they will supply us with genetic probes to investigate a number of genetic mutations, of particular features of the genome, so that we can envisage studying several hundred in the future. To increase the amount of genetic information obtained from

each embryo it will be necessary to increase the number of tests we perform on a cell, or increase the number of cells tested. Later, I will show you how this can be done. I believe that we will end up by cloning since the main problem with these cumbersome and expensive techniques is the following: once you have ascertained that an embryo is a *quality embryo*, it only has one chance out of ten to become a baby after being transferred into the uterus. This is a productivity rate that is absolutely incompatible with the economics of healthcare: a chance in ten of a good embryo becoming a normal child is a totally unacceptable efficiency ratio. What will happen is that this embryo, the selected embryo, will be multiplied so as to increase its chances of becoming a single child: several identical embryos will be cloned, and one at a time they will be unfrozen and implanted into the woman, one at a time at each monthly cycle, until one of them succeeds.

To show you that this procedure is neither science-fiction nor something belonging to the distant future, let me tell you that there are already similar procedures being developed in animal studies. Let's see how you can increase the number of embryos, the number of ova to be fertilized. We could intensify hyperovulation hormonal treatments in the woman, but there is a limit to this and we would not succeed in producing a vast increase. We could repeat the cycles of *in vitro* fertilization with this diagnostic procedure and freeze the embryos, but this would be hard on the couple. We could produce ova *in vitro*, from oocyte laboratory cultures: highly promising experiments in this field have been performed in several countries. We could also grow small ovarian follicles in large numbers and raise ova from them. We could envisage ovarian grafts after freezing, even xenografts, ovarian fragments from another species, not the human species. This has already been done. Gosden recently grafted human ovaries onto the same woman, but he also grafted sheep ovaries and monkey ovaries onto mice, obtaining ovarian growth and proving that the procedure is feasible.

To multiply our diagnostic potential we can perform a variety of different tests: we can examine a single cell for a wide range of different characteristics (we can already investigate twenty different DNA sequences in a single cell). But we could also multiply the embryo cells to be examined, since we know how to cultivate them to blastocyst stage (five or six days), thus producing for our test purposes dozens of cells. But even better, we can do what Bongso did in Singapore six years ago, something very few people have talked about: from a five or six day old human embryo cell (a blastocyst), grown in culture for three weeks, he obtained three million cells. On such a vast number we could run all the tests we want. Since the human genome is made up of a hundred thousand genes, with three million

cells available it's certainly not going to be a lack of cells that is going to stop us from running all the tests we want.

Then it is necessary to increase the probability of a live birth after the selection process. Research work has shown that embryos selected for their normal chromosome make-up stand a greater chance of yielding a live birth, simply because chromosomal abnormalities are the cause of miscarriage.

But we could equally increase the probability of live births by other means: multiplying the number of embryos (which is something we have known how to do in mammals for twenty years now), promoting cell division, or transferring embryo cores into enucleated ova. If we clone before implantation we could even obtain an abundance of absolutely genetically identical embryos.

It's worth remembering that embryo cloning has already been performed in primates: baby monkeys have already been born with this technique. Thus, we know primates can be cloned with this procedure.

Ovarian conservation, in my opinion, will play an important role in the future, in our animal experiments. Ovaries are removed and frozen; after a certain period of time they are unfrozen and implanted into a female, the same one or another, even a female of a different species, and they develop. Practically speaking, human *in vitro* fertilization offers us the possibility of harvesting small ovarian cortical fragments from young women, to set them aside and use them twenty or thirty years later. Today PID is not a very effective technique since we have to make do with about a dozen ova which leaves about six embryos after each fertilization attempt. Embryo selection allows us to choose about half the embryos (if we only look for the major pathologies and don't give ourselves too many qualitative criteria to abide by). After transferring these three embryos we would obtain only 0.3 children per test, which is a very poor result.

I imagine that in the future, using the methods I have just described, we should be able to dispose of about a hundred ova per woman, especially if we freeze ovarian fragments taken from young women. Using this procedure we could obtain dozens of embryos. Genetic selection would then allow us to select only one or two: we could become much more demanding than we are at present, we could eliminate a large number of them, since we would have so many resources available. Then we could produce copies (clones, that is) of the *best* embryo, and be sure that we would obtain at least one live birth. We would then have to be obliged to destroy the remaining frozen clones, in order to abide by the ethical considerations that forbid us from producing an army of identical children, at first at least ... .

I think that, if we are to restrict this type of eugenics based on embryo selection, we should not define what we mean by severe pathologies: you know that this is not done nowadays in the case of prenatal diagnostics performed on pregnant women. There is no legal definition of a disease that would justify the elimination of a foetus. In each case the final decision is the result of consultation between physician and patient, and every time the decision is taken in consideration of the particular situation. Although there may be a general consensus among geneticists, there is nothing codified by law. In any case, excesses are unlikely since the woman carries only one baby in her uterus and its elimination is a very painful process, both physically and morally. There is a sort of natural regulation against eugenics, since pregnancy is a unique event and it occurs inside the mother's body: if it took place in a test tube it would not have the same implications. In the case of embryo selection, a definition of those pathologies authorizing PID could provide a safeguard. But we could not have a transparent, or visible safeguard since it would be contrary to human rights to put in writing that certain human beings can be eliminated. Thus, there would only be one way to restrict embryo selection if we are to avoid falling into the trap of perfect eugenics: restricting the number of pathologies that we can look for in the embryos of each couple, without defining them. This is what I proposed, this is what the French law imposes, but France is the only country that contemplates such a legislation and I don't know how long it will last. Clearly if we restrict PID to a single-gene pathology (a mutation) to be searched for in the embryo, even without specifying which one, we shall enormously reduce the risk of eugenic practices. But we could also accept the elimination of all those embryos that have a chromosome too many, or one too few: in fact, this would have no eugenic consequences since individuals with this type of chromosomal abnormality are hardly ever capable of reproducing. Conversely, as far as mutations are concerned, it would be advisable to look for only one mutation per couple, in all the embryos produced by this couple.

This, therefore, is a proposal.

I should simply like to add that I am currently carrying out a survey among my international colleagues to verify whether they agree with this suggestion. Generally speaking, the French appear to be in agreement with my proposal; this may be the result of the vast number of debates we have had on the topic and also of a very particular cultural attitude encouraged by our Ethics Committee. Conversely, our British colleagues, and even more so the Americans, find that this proposed restriction would be stupid: if you are scientifically capable of detecting fifty pathologies, they say, why not make use of this ability to ensure the greater happiness of child and

parents alike? I fear that it will be thanks to simplistic reasoning such as this that we shall allow a new type of eugenics: "soft", generous, democratic eugenics.

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BIBLIOGRAPHY

J. Testart, B. Sele, Toward an efficient medical eugenics: is the desirable always the feasible?, Hum. Reprod: 10, 3086-3090, 1995.

J. Testart, La procreazione assistita, Il Saggiatore, Milano 1996.

J. Testart, Des hommes probables. De la procréation aléatoire à la reproduction normative, Le Seuil ed., 1999.