

## **CLONING. BETWEEN SCIENCE AND ETHICS.**

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## INTRODUCTION

The cloning of a sheep carried out in an industrial research project (1) aroused unusual interest not so much because of its zootechnical significance, as for the prospects opened toward the cloning of human beings.

The title of the present paper is "Cloning:between science and ethics". It is however difficult to keep strictly within this frame as human cloning by nuclear transfer (see below) has perhaps not even been seriously attempted. It is inevitable that the present essay should move around science, ethics and fiction.

This is indeed the feature which has shown itself to be most provocative to the moral conscience not only of the general public but also of theologians, philosophers, scientists and world leaders. The search for human cloning appears as a limit case in the ethics of scientific endeavour. From the moment of the announcement of the sheep cloning there appeared statements from the Holy See reaffirming the teaching of *Donum Vitae* (2) and rejecting the possibility of cloning of humans (3). The Pontifical Academy For Life published a booklet developping to some length the reasons for this stand. (4)

## CLONING AND CLONES

The word "clone" stems from the greek **klon** which is used for the twigs employed in vegetative reproduction of plants. According to the Oxford Dictionary 1995 "clone" may also be taken to mean "a person or thing regarded as identical with another".

Cloning was for a long time viewed as a special property restricted to some varieties of living beings. August Weissmann was perhaps the first who realized that multiplication by autocopy should be regarded as one of the fundamental features of all living matter. In 1893 Weissmann held that the chromosomes whose fission was at his time a novelty, were a special instance of what he termed "biophores", that is "the smallest units that show the primary vital forces, that is assimilation and metabolism, growth and multiplication by fission" (5). In 1940, Erwin Schrödinger published an essay in theoretical biology where he had the foresight to compare the preservation of organization - a striking property of living matter - to the "crystallization of an aperiodic crystal" (6). Thus, even before the great breakthroughs in molecular genetics, "self copying" had ceased to be a marginal phenomenon and had taken its place as a central biological concept. In the seventies the expression "cloning" came to be widely applied to the artificial replication of genetic material such as plasmids in bacterial cells.

Cloning of mammals appeared interesting especially for the cattle industry. It was first attempted by separation of blastomeres in early stages of development. Some important successes were reported (7). One report was published of an experiment which involved a cloning-like handling of a human embryo which was heavily assailed on ethical grounds (8) and which does not appear to have had any follow-up.

## NUCLEAR TRANSFER

### 1.- Preliminary remarks.

More recently, cloning by blastomere separation has been largely abandoned and substituted by the transfer of somatic nuclei into enucleated oocytes, a procedure known as "somatic cell nuclear transfer" which departs from the strict definition of "cloning" but shows much wider biological and zootechnical implications.

Nuclear transfer was successfully employed in Amphibia more than twenty years ago by Gurdon. He showed that nuclei of tadpole cells when implanted into enucleated oocytes could steer development until the adult stage (9). When cells from adult frogs were employed however the maturation did not go beyond the tadpole stage (10)

These discoveries stimulated the search for analogous phenomena in mammals. It was felt that an eventual success in these might have industrial significance. The early literature is reviewed by Prather and First (11). Nuclear transplants of early blastomeres in pig, rabbit and sheep could be made to develop to term provided a metaphase oocyte was used as a recipient. It was natural that the the first attempts should be oriented at substituting the egg nucleus by nuclei of early blastomeres, because the assumption prevailed that "reprogramming" would be more easily attained if the implanted nucleus was at an early developmental stage.

### 2.- Fertilization and activation.

Normal fertilization takes place at the time of metaphase II. Under physiological conditions, fertilization is immediately followed by "activation" of the oocyte. This involves electrochemical changes at the surface of the oocyte and ejection of the cortical granules and is followed by a gradual lowering of the MPF level (see below). The overall effect of these changes is to block polyspermy.

### 3.- Transfer of nuclei.

Metaphase II is associated with a surface bulging of the egg where the dividing nucleus comes to be located. Punction at this place is followed by ejection of the nucleus, so that such oocytes are especially suitable for the obtention of "cytoplasts" (enucleated oocytes). These can be fused with intact cells (caryoplasts) by means of an electric shock. The procedure results then in the introduction of a new nucleus into the oocyte.

Along with nuclear transfer, activation can also be induced by electric shock either before, during or after fusion.

### 4.- Nomenclature of the cell cycle.

It seems necessary at this point to give a very brief account of the nomenclature employed to describe the changes accompanying mitosis.

In their division process cells go through a series of stages which together constitute the "cell cycle". The nuclear changes detectable with the light microscope and which go from the breakdown of the nuclear envelope through the lining up of the chromosomes in the metaphasic plate and until the reconstitution of the nuclei of the "daughter cells" (each endowed with the number of chromosomes which characterize the species, which is referred to as the diploid number), are grouped together as the M phase (mitosis). This is followed by an interval or "gap" the duration of which may be of minutes up to years, G1, during which time transcription of DNA, translation of RNA into proteins and cell functions in general, take place. If and when the cell is going to pass through another mitosis, the nucleus doubles its DNA content by synthesis of the compound: this is the S phase of the cycle. Thereafter the nucleus remains apparently inactive through a short interval or gap, G2, at which period the cell has a number of chromosomes which is twice the normal (tetraploid nuclei). G2 ends by the nucleus entering again the M phase as described above.

Thus the sequence of stages of the cell cycle might be written G1-S-G2-M-G1- etc.

### 5.- Oocyte cytoplasm changes and the reception of nuclei.

The fact that successful transplant seemed conditioned by the cell cycle stage of the recipient oocyte stimulated studies of the cytoplasmic conditions of metaphase oocytes. It was shown that they have a high level of "maturation promoting factor" (MPF), which is really a family of kinases (phosphorylating enzymes) which are determinant in the nuclear changes that characterize normal mitosis(12,13) and exert an important action upon implanted nuclei.

These effects may be summarized as follows.

When a nucleus is implanted in a metaphase II oocyte, the cytoplasm with high MPF level will induce the break up of the nuclear membrane, and the premature condensation of chromosomes. These phenomena are followed by reconstitution of the nuclear envelope and DNA duplication. This last process is independent of the point of the cell cycle at which the caryoplast may find itself. (14). As a consequence nuclei implanted at S or G2 will suffer an anomalous increase in their DNA content (aneuploidy) and will become incapable of steering a normal development. On the contrary nuclei in G1 will duplicate their DNA until the level that corresponds to a normal nuclear division.

If instead of having the nuclear transplant coincide with activation, some hours are allowed to elapse after the latter, the MPF level will have lowered and neither nuclear envelope breakdown nor premature chromosome condensation will occur. Under these circumstances G2 nuclei will not replicate their DNA, while nuclei in S or G1 will complete replication in a normal manner.

In short whatever the MPF concentration, G1 nuclei can give origin to euploid nuclei whether they were transplanted at the time of activation or several hours later. This means that successful transplantation of G1 nuclei is to a degree independent of the state of the recipient cytoplasm. On the other hand, G2 or S nuclei are useful for transplantation only when they are inserted several hours following activation.

Apart from the low yield of the procedure, implantation of embryonic nuclei placed a restriction on the practical uses of the technique from the moment that the phenotypic features linked to the blastomere caryoplast could not be known with certitude. However these studies marked an interesting advance: they meant that even in the absence of any sexual intervention and employing an asexual agamic form of reproduction, animals could be manufactured which were genetically identical.

#### 6.- The strategy of the Roslin Institute group.

The Roslin Institute group focused their attention on the state of the caryoplast rather than upon that of the cytoplasm. They tried to obtain nuclei in G1 or rather in G0, that is nuclei which had been induced to "exit" the cell cycle through nutrient deprivation in the culture fluid. This was not possible to achieve with early blastomeres which go through very short G1 phases, so that the cells in this stage are always scarce, while S or G2 cells are abundant. The latter are either tetraploid or find themselves in the process of DNA replication. Both these circumstances favour the occurrence of aneuploidy under the action of MPF, so that the probability of developmental failure is high. Campbell et al (15) turned to nuclei obtained from cultured cell lines where mitoses can be synchronized with relative ease. Technical procedures are available which allow to arrest the cycles of cultured cells either in G1 or G0. The first trials were done with

cultures derived from embryos or fetuses. The success obtained stimulated them to try with cells from adult animals. (1)

Success in nuclear transplantation in the sheep is probably due to the modality of development present in the ungulates. In this group the first four cleavage divisions (up to the state of eight to sixteen blastomeres), occur before the zygote genome has entered into action (Zygote Genome Activation ZGA) (16). This means that during this period there should be no need for DNA transcription. Nuclei would go then through several mitotic cycles before having to enter transcription, and would thus have several cycles available to undergo "reprogramming". In the rat or the mouse ZGA sets in at an earlier stage (one or two blastomeres), which might be the reason for the difficulty in obtaining successful transplants in these species. Human eggs are intermediate in this respect, ZGA being slightly more delayed than in the murines (at the stage of two to four blastomeres (17)). This circumstance deserves attention because it suggests that the adjustment of conditions for nuclear transplantation to the human might require a considerable amount of experimentation on embryos.

#### 7.- The production of a sheep.

In the successful experiment reported on February 1997 (1), oocytes of Scottish Blackface sheep were employed. They were gathered by washing between 28 and 33 hours after the administration of a dose of gonadotrophin releasing hormone. Under these circumstances development of the oocytes becomes arrested at Metaphase II. Five to six hours after enucleation, fusion was carried out by electric shock.

Small pieces of mammary gland of a six year old Finn Dorset sheep in the last trimester of pregnancy were dissociated into their constituent cells by standard techniques, and placed in culture medium. A total of three to six passages into fresh culture medium were done at intervals of seven days. The culture was then set in G0 stage by decreasing the amount of serum in the medium from 10% to 0.5% for five days.

277 cases of apparently successful fusion were carried out. Only 29 progressed to the stage of morula or blastocyst and could be transferred to host sheep. Only one (3.4% of 29, and 0.3% of 277) came to term - the sheep Dolly.

Similar attempts were done with cells obtained from cultured embryonic and fetal cells. The total number of fusions communicated in this paper (including the 277 already mentioned) was 834. They resulted in eight sheep, somewhat less than 1%.

The crucial point in the experiment was of course to demonstrate that the sheep produced by nuclear transfer had the genome of the caryoplast. The main evidence was provided by the phenotype of the animal (white face correspondig to Finn Dorset variety), and an analysis of the DNA microsatellites (18,19,20), which showed a considerable degree of coincidence between the pattern of Dolly and that of the caryoplast.

A point has been often raised which should be cleared. An almost exact copy of an adult animal had been obtained. However it could not be established whether the caryoplast responsible for the development of Dolly was a fully differentiated mammary gland cell or rather a "stem cell". The answer to this question might be valuable toward determining the effective reprogramming capacity of adult nuclei, and would thus be important in the study of the biology of differentiation. On the other hand, from a zootechnical point of view the doubt does not have great weight, from the moment that an animal had been produced whose phenotype was known in advance to the experimenter.

## PUBLIC REACTION

The announcement by the Roslin Institute created widespread excitement, amounting at times to shock at the perspectives opened to procreation. In many quarters it was believed that human cloning was already at hand.

### 1.- The media.

On March 4, less than a week after the announcement from the Roslin Institute, U.S. President Clinton held a press conference and put the news at a level comparable to the development of nuclear energy.(21) Even more, Clinton went on to say that "many of us would feel deeply troubled thinking that we might be cloned", and announced an urgent investigation into the legal and ethical implications of human cloning. This work would be entrusted to the National Bioethics Advisory Commission (NBAC). At the same time the use of federal funds for human cloning research was prohibited while private funding agencies were asked to join the moratorium.

From this very week on, and for several months a profusion of comments appeared both in the world press and in scientific journals.

Gina Kolata, in the New York Times of February 23,(22) quoted Ronald Munson of the University of Missouri who pointed to a paradox which might be taken as representative of present day science: "There is something ironical about this. We have here an incredible scientific advance. What was it that prompted it? It was the desire to produce a certain class of sheep milk. It is theatre of the absurd..." We might note that this "absurd" is connatural to modern scientific developments: nobody can accurately foresee the results of a scientific discovery, because the latter brings up changes in the very reality which will be faced in the future.

The same article quoted Neal First, eminent specialist of Wisconsin, for whom the discovery was a zootechnical advance more important than that of artificial insemination, and on the other hand Lori Andrews, a bioethicist who warned of the danger of people being cloned without their consent.

On the February 24 issue of the New York Times (23), Kolata brought up the acid comment by Ursula Goodenough widely reputed as a cell biologist, that in the future there might be no need for men; whereas Lee Silver of Princeton pointed to the practical difficulty of exerting any legal control on a technology which was apparently so simple to carry out.

The Roslin Institute group had been very cautious and expressed opposition to human cloning. (24) They pointed out however that genetic intervention combined with cloning opened wide horizons to the industry, an idea which was developed also in the March 15th issue of "The Economist", in an article of great information value. (25)

Scientific journals of great prestige - it suffices to remember Nature, British Medical Journal and the Lancet (26,27,28) - published editorials and letters from readers where possible beneficial applications of human cloning were discussed, and the time delay for its possible introduction into practice was estimated. While British Medical Journal in its March 29 issue (27) was inclined to believe in a relatively remote application, Nature in February (26) anticipated a short delay for human cloning.

As was to be foreseen the reaction in scientific journals was influenced by the fact that a rigorous banning of human cloning would require severe limitations to the experimenting in human embryos. It was noted that there are some potentially beneficial results of experimentation in human embryos that might be affected; and on the other hand that cloning offers a hypothetical way to deal with such conditions as intractable azospermia or mitochondrial disease. (29)

It is clear however that the experimental steps necessary to attain human cloning with reasonable security would require the instrumental use of many human lives. Kahn in Nature (30) already in February, evoked the kantian requirement of never using a person as a means or instrument. He added a comment which has a permanent value: "The results of Wilmut et al. undoubtedly have much merit. One effect of them is to oblige us to face up to our responsibilities. It is not a technical barrier that will protect us from the perspectives I have mentioned, but a moral one, originating from a reflection of the basis of our dignity. That barrier is certainly the most dignified aspect of human genius".

All around the world a large number of more or less fanciful articles referred to the importance of the cloning event. Hot discussions were started in Internet, and even patently fraudulent cloning offers were made. Few large cities in the world will have been free of published comments of clones of small Hitlers or of slaves produced with perverse ends. Finally the disquieting perspective has been opened of clone fabrication with the purpose of building up organ or tissue banks.

Some recurrent themes appeared: the exciting zootechnical prospects, the important biological discovery, the social and cultural impact of an eventual human cloning and the new ethical and legal issues which came to the fore.



## 2.- Myth and Science.

History suggests that artificial production of human beings may have some symbolic value capable of reaching hidden depths of the human mind. This has become again apparent in recent times in connection with the advances in molecular genetics.

Daniel Callahan of the Hastings Bioethics Center reminded - as quoted in The New York Times (23) - that a considerable amount of discussion on cloning had arisen already in the seventies, probably connected with the early clonings of bacterial genetic material. That was the time of appearance of "Sleeper", the Woody Allen film, and "The Boys from Brazil" and also of the publication by David Rorvik of "In his image: the cloning of a man". This was also the time at which thinkers like Hans Jonas had dealt with the subject in penetrating analyses (31)

It seems as if genetic engineering has given new life to an old myth related to the production by man of other beings in his image. A modern version arises from an interesting paper issued by Joshua Lederberg, Nobel Laureate for his contributions to bacterial genetics.(32)

Lederberg held that planning founded upon prevision which is the hallmark of human intelligence was almost absent from the sphere of the prediction and modification of human nature, and that in these times a new theory of evolution is needed to permit the modification of a system that plans imperfectly its own future. Science and technology are rapidly changing the life conditions for mankind, whereas natural selection is far too slow a process to face up to these changes, while chemical modification of the genome may be a very complex endeavour. Under these circumstances argued Lederberg, man is on the point of entering an evolutionary perturbation of large proportions, which is not algeny (gene alchemy), but vegetative propagation by cloning. "If a superior individual is identified...why not copy him directly, rather than going through all the risks of recombinatory fragmentation, included those of sex?...Leave sexual reproduction for experimental purposes; when a suitable individual is obtained, propagate him (her) by cloning..." The idea is extensively developed by Lederberg, but the quotation is sufficient to give an idea of his proposal.

This is a radical proposal in eugenics. It presupposes a special kind of authority of some human beings upon others or upon the rest. This power is founded on scientific and technological know-how. Science abandons its usual role of rational prediction of phenomena and ventures into the task of global orientation of the destiny of mankind. Lederberg is proposing a seemingly simple way to change the future of humanity, even though the collateral consequences of this kind of intervention cannot even be fathomed.

It may be said that the proposal, in spite of its scientific conceptualization and language, claims for science some aspirations that have been more proper to magic, and it is possible that cloning finds an echo in some non rational stratum of human mind.

Actually the "production" of men is a theme that has exerted a strange fascination for a very long time, from Simon the Magician in the apostolic legend up to the writings of Paracelsus. The Jewish Kabbala imagined the "golem" a humanoid creature obtained by touching a clay figurine with a piece of parchment upon which was inscribed the mysterious tetragram of the Divine Name. (33)

In the second part of "Faust", Goethe (34) takes up the theme drawing from other sources of inspiration. Wagner the pedant disciple manages to create a kind of man "Homunculus" inside a glass flask. He is driven not only by the desire of attaining through this work a deeper sort of knowledge, a more perfect mastery of the world, but more precisely by the purpose of breaking, of debasing the ways of Nature. "Was man an der Natur Geheimnisvolles pries / Das wagen wir verständig zu probieren, und was sich sonst organisieren liess/ Das lassen wir kristallisieren..." "Was wollen wir, was will die Welt nun mehr? / Denn das Geheimnis liegt am Tage..." "Die holde Kraft die aus dem Inneren drang....Die ist von ihrer Würde nun entsetzt..." ("That which was praised as full of mystery in nature/ we dare to test by reason, and that which used to let itself be organized/ do we now allow to crystallize....What more do we desire, what could the world still desire? / For the secret has been brought to light....The sacred force that swelled from the interior...is now deprived of its dignity..."). The poet expresses here a drive toward debasing nature and changing it into a secret without a mystery: Wagner feels radically assured of the triumph of rationalism over nature. But at the very moment when he exerts in such a manner his power, Homunculus escapes to live his own life and leaves his master abandoned to his doubts and to his books.

In this as in other versions of the theme, the "fabrication" of a man is achieved with the help of evil spirits, even of Satan himself. The act itself is understood as a theft of God's power, an usurpation of the place of the Creator.

As is sometimes the case, science, even science fiction, inherits the passion for power that is the driving force of alchemy or magic. Even the saying by Francis Bacon that "scire est posse", "knowledge is power", might have been written at the door of the laboratory where Faust's disciple received the help of Mephistopheles. It is possible that science, liberated from the power of magic may have found a firmer ground in experiment and reason. But it may be that in some recesses of the soul, the same basic desire is still alive, which is not to fabricate sheep, not even to fabricate men, but to play at being God.

The public mind has felt intuitively that the fabrication of a man would be trespassing upon a boundary, something like the profanation of a sanctuary. This act of arrogance both fascinates and horrifies, and lightens up the fires of imagination.

### 3.- Official statements from international organizations.

It is now necessary to turn to the statements issued by organisms that have responsibilities in the normative aspects of this question.

The European Parliament was especially categorical (35) stating that clonation penetrates a new ethical sphere and that it represents a serious violation of fundamental human rights, is contrary to the principle of equality among human beings, from the moment that it allows a eugenic and racist selection of the human species, offends the dignity of the human being and requires experimentation on humans. It declares furthermore that each individual has a right to his genetic specificity and that cloning should be prohibited. It asks for an explicit condemnation of human cloning at world level.

This declaration developed and reinforced others from the same source which have been suggesting a deep trouble on the problem of the human genome and its manipulation.

At the end of 1996, The Director General of UNESCO issued a document of limited distribution - "Declaration on Human Genome", which should be submitted with the corresponding modifications to the 29 General Conference, September 1997. (36)

Nº 27 of this Declaration contains the statement: " Even though it is necessary that research on human genome be continued, it is necessary to say that it can also open the way to serious deviations which are contrary to human dignity and to the fundamental rights which are its corollary".

Nº 29 adds: "...freedom of research cannot be absolute and if necessary it should undergo limitations. This is especially the case when its expression may be contrary to the respect for human dignity where its legitimation is founded"

Nº 33 says: "...The conjugation of these three fundamental principles, dignity of the human person, freedom of research and solidarity among men allows to design an equilibrated architecture for a future declaration on human genome..."

In its normative part (art.5), the Declaration states that "...no scientific advance might be allowed to prevail upon the dignity and rights of the human person..."

These statements reiterate the theme of "human dignity" and the "dignity of the human person". In relation to them they allude to "a new ethical sphere", to "the protection and security of human genetic material", and to the foundations of freedom of scientific research.

## A SKETCH OF AN ETHICAL EVALUATION.

The following sections will deal with two aspects touched upon by these documents, namely, "Cloning and the dignity of the person", and to "The new ethical sphere".

### 1.- Cloning and the dignity of the person.

The concept of respect of human dignity is here taken at its "minimalist" meaning which prohibits the instrumentalization of human beings.

#### Instrumentalization of procreation.

An act of cloning can only be performed within a constitutively eugenic project. If a nucleus belonging to a human of known phenotype were to be taken for transfer, somebody would be making a selection affecting the whole phenotype of the resulting individual. The existence of a guiding criterium for cloning transforms the "clone" into an instrument oriented to obtain some definite goal. This may be as simple as defining the sex, or as complex as the production of an individual who might be inscribed into the planning of the future of the human race as sketched by Lederberg. The whole process of procreation is taken instrumentally. Between this and systematic eugenics of tragic memory there is not a precise demarcation line.

Instrumentalization requires further that somebody "handle" the instrument, especially in the design for which it is to be employed. The role of the "agent", the active role in this procreation is no longer linked to the "parents" who really do not exist, and it is in their stead passed over to the person (or institution) who chooses the caryoplast. The immediate "agent" is the expert (biologist or medical person) who manipulates the cells for cloning.

One important "production factor" is the individual who provides the nuclei. He (she) may be entirely foreign to the actual performing of the cloning, and may never have given cells for that purpose. It cannot therefore be spoken of as a "donor". Of course he never provided with gametes. This is evidently what President Clinton was alluding to in his press conference when he said: "...this new discovery opens the troubling perspective that it might become possible to clone human beings with our own genetic material..." In this act of procreation, the one (male or female - it is clear that one may not speak of "father" or "mother") who provides the genetic material, is entirely instrumental": neither his cooperation nor his consent are strictly required.

It seems that to employ a human being in this way is to make out of him an instrument in a way that is offensive to his (her) dignity.

Among all who take part in this process, the one nearest to her biological role is the woman who will bear the nasciturus. As a consequence it is she who shows in the clearest way the alteration in the "meaning" of the process which has transformed her into an instrument. The woman will always be a "surrogate mother". The embryo implanted into her womb is either genetically identical or genetically alien to her. In neither case could one refer to the nasciturus as her son or daughter. The role of the woman is therefore ambiguous. On the one hand it might be said that she is a mere instrument to carry an embryo to term; on the other, following the sarcastic remark by Goodenough, quoted above, the woman might find herself in the never contemplated situation of being able to carry out procreation in the complete absence of a male.

#### Cloning and "in vitro" fertilization.

Human cloning by nuclear transplant has never been attempted. One might ask under what conditions it might become the goal for medical action. I believe that the most likely application would find itself in the field of "in vitro" fertilization.(IVF)

Whatever the motives leading to the use of IVF may be, it is clear that the rationality of an "interpersonal" act of procreation is substituted by an industrial rationality. In the context of the conjugal act, success or failure may be evaluated from many points of view, which in the last analysis refer to the success or failure of the union. In IVF on the contrary, success or failure are measured by the obtention of the "product".

This is typical of industrial rationality. But it is apparent that the driving force in modern industry is the request or demand for the product. It suffices to imagine reasons why reconstructed embryos might be desirable and demanded, to see and possibly evaluate the pressure of opinion that might be made to bear in order to obtain legitimation of the necessary procedures. One instance might be the need to solve the problem of individuals suffering from azoospermia (this might be a population of considerable size). Another suggested possibility would be to by-pass mitochondrial diseases which are inherited exclusively through the egg cytoplasm, without intervention of the nucleus (29). Finally, - not to lengthen the list - one might take into account the wishes of lesbian couples who do not desire any male participation in their reproduction. It is not possible to make a proper estimate of the magnitude of these requirements, but all of those mentioned here have been already suggested or proposed either in the press or in scientific journals, either as letters or editorial comments.

A modern industry is not content with merely giving satisfaction to demand. It needs research and development (R&D), in order to establish the conditions needed to obtain the optimum product at the lowest cost. In the present case, R&D would be provided by experimentation on human embryos. One foresees the pressure to ease any legal restraints on this activity wherever it has been established. Human embryos in the present context become either "means" to test and improve the procedure, or "industrial left-overs" such as was tragically evident in the recent case of three thousand embryos in Great Britain.

R&D in the field of human cloning should be long and arduous. It might not be enough to obtain seemingly normal new borns. It should be necessary to establish follow-ups perhaps for years to be able to exclude congenital defects of late appearance. This danger haunts the report to President Clinton by the National Bioethics Advisory Commission (NBAC) (37). This document is pervaded by utilitarian and consequentialist ethics, and endeavors to discover areas of consensus inside the American population. In the introduction to Chapter IV, "Ethical Considerations" it is stated: "Virtually all people agree that the current risks of physical harm to children associated with somatic cell nuclear transplantation cloning, justify a prohibition at this time on such experimentation". In keeping with the orientation of the report, it avoids any discussion of experimentation on embryos, and refers to the recommendations of the Panel of the National Institutes of Health on the subject (38). These recommendations show however how tenuous can the barrier be that prevents experimentation on human cloning. According to the Panel the research - in order to receive federal funding - should "promise significant scientific benefit", which does not define a clear boundary. It is true that nuclear transplant is banned, but this recommendation lacks a firm conceptual support, and the whole of the context, even in the most moderate of interpretations, considers the embryos as instruments devoid of anything that might be called inalienable dignity.

Industrial demand is basically an anonymous form of power, the power of the crowd. Nietzsche said that multitudes (Vielheiten) (39) are there to attempt those things which individuals do not dare to do. Industrial demand, by generating publicity and propaganda, gets to the point of making us believe that things which would have horrified us not long ago are truly indispensable; or that it is our right to demand things which only one generation ago would have been forbidden.

#### The condition of the "clone".

There is a strict correlation between the condition of "instrument" and that of "end object" in an industrial process. An industrial object is never properly an end in itself. It is only the end part of a process which should be taken jointly with all the steps that led to it and those which may follow from it. The "clone" has been "manufactured following specifications more proper to industry than to procreation. He (she) was not willed as a person is willed, that is as a being destined to open new possibilities of existence. It was willed by its foreseeable characteristics, just as an object is willed. If the clone does not correspond to prevision the production process will have been a failure. Such would be the case for instance if a clone came to suffer from a congenital condition attributable to the mode of generation, as is feared by the NBAC report. Furthermore the clone will be always in a peculiar situation, a kind of "diminished existence", because there will exist already a sort of "antecedent" of his (her) life. This point was taken also in the NBAC report although it was largely disregarded as lacking empirical support. The argument which goes back to Jonas (31) says that the genome of the clone was previously subjected to adaptive trial in the life of the "donor" of the caryoplast, and was tested in relation to the environment. This is different from what happens with univitelline twins,

because these face life simultaneously and they share the natural uncertainty in front of it. This is what Jonas has called "the right to ignorance": a "delayed twin" knows too much about himself, or at least, he believes so, from the moment that another person exists or has existed who started from the same genetic endowment to face options analogous to those present in his own life. It is not necessary to believe in a blind genetic determinism to concede the possibility that the existence of this individual will bear the mark of such a circumstance. Part of our own human condition is a veil of ignorance which hides our own future from us. The clone is denied the highly valued condition of "equality": paradoxically, the very reason that this individual is genetically identical to someone who preceded it in life, makes that he (she) is necessarily an inferior at the hour of getting to know his (hers) limitations by somatic or psychological disease. The demand for empirical evidence put forward by the NBAC seems contradictory because this evidence would require the carrying out of the very experiment which is subject to scrutiny on moral and ethical grounds.

This "diminished" condition of the clone would be also reflected on the fundamental human relations that give origin to it. Is it not evident that these have a meaning which is quite different from normal kinship? The "clone" has strictly no genetical father or mother. It does not seem possible to ask his (her) grandparents to consider him (her) their son their son or daughter. Neither is there anything resembling a brother besides the caryoplast "donor" which is a univitelline twin. The NBAC tends to undervalue these considerations taking them as "speculative" and linked to special "cultural values". There can be no doubt however that these human beings would be produced under highly abnormal conditions. If somebody desires to venture into this dangerous road with the argument that there is no evidence to support well-founded misgivings, the onus of proof rests entirely upon him.

### Summary.

Summing up it may be said that the eugenic procedure; the presence of an "agent" entirely alien to the human couple; the instrumental reduction of the person who originates the caryoplast; the meaning of manufactured object which applies to a human being so planned and willed; the instrumental "use" of the woman as site for the pregnancy; the experimentation on embryos and children; are all factors which join to build up a radical novelty in procreation, where "human dignity" even in its simplest acception has lost all meaning.

### 2.- The new ethical sphere.

Cloning is an extreme form of intervention upon human beings. Even though many of the comments that are elicited by it are applicable to other technologies, it cannot be denied that cloning is a subject where many of the modern bioethical dilemmas become specially apparent..

### Intervention upon living systems.

Technical action upon "the living" is different in significant aspects from other technological actions (31) from the moment that it is never exerted upon isolated or independent elements, but essentially upon a "system" whose parts are in various - often intimate degrees - of interdependence. Furthermore living systems show always some definite degree of self-regulation. The same considerations apply to various levels of organization of living matter: they are valid of cells, of organisms, populations or ecological niches. They can even be predicated of human communities.

As a consequence interventions determine effects which are not easily predictable either when they occur for the first time, or when the initial conditions are not accurately known. When action is exerted upon a self-regulating system, no linear relation between cause and effect can be expected: the system may "absorb" the perturbation even to the point of annulling it, or it may on the contrary amplify it to a considerable degree. As a rule collateral effects will appear whose magnitude and complexity may obscure the expected effect.

The above mentioned features may not appear evident when one is dealing with an intervention exerted upon a deterministic system and performed under rigorously controlled conditions, such as is the case when many essays have been made to ascertain the most probable responses of the system: this is often the case of the use of pharmacological products for therapeutic purposes. Even then however it is a mere illusion to think that the effect that was aimed at and obtained has been the sole consequence of the action, or even the most important one. The finding of unexpected carcinogen properties in a number of drugs is a very common example. There are of course some effects which are not so striking but which are equally significant. Such may be the case of the detoxifying reactions that set in after administration of some drugs (phenobarbital is a text-book example) and which show even in the fine structure of liver cells with the development of a hypertrophic system of intracellular membranes of the smooth endoplasmic reticulum. As a rule the acceptance of a new drug for public use demands prolonged experiments in animals and careful assays in human subjects, so as to ascertain that the expected beneficial effects are not offset by unwanted reactions of the system.

It is interesting that even when the reaction of the individual organism seems reasonably controlled, side effects may appear which make their apparition at different levels of organization. It would be easy to find examples in animals or plants. But I would like to remember here under this perspective only two well-known examples taken from the life of human communities.



Antibiotics have had a great social impact through their repercussion on life expectancy and age composition of the population. Likewise hormonal contraceptives have affected the birth-rates, the age-distribution of the population and consequently the distribution of economic burdens with effects detectable even in social security systems. Furthermore they have deeply distorted the meaning of human sexuality for a large proportion of humanity, with the consequent negative anthropological and social effects. In all of these cases the impact upon the living system has yielded wide ranging and largely unexpected results.

It is obvious that direct intervention on human germ cells might bring with time effects that cannot be predictable to-day. This raises serious problems of responsibility before a mankind which is still non-existent. Such matters have been addressed at length by Jonas (31) but they will not be dealt with here.

#### In vitro fertilization and cloning.

These should now be addressed in the above mentioned perspective of unpredictable effects. It is not possible to be sure that the artificial interference with the effects of azospermia for instance, would not disrupt mechanisms regulating the genetic equilibrium in the population. Even putting aside the obvious moral objections, it is clear that much additional information is needed before being sure that these techniques would not be damaging to the human species.

In cloning by nuclear transfer the "new ethical sphere" becomes apparent for additional reasons. The procedure is unprecedented insofar as it amounts to "putting together by parts a human being". Up to now procreation appeared linked to the interaction of "natural" units ( the gametes). Even though distorted (in IVF for example), it was at least inserted in the normal process of descent of the species. What would be proposed now is the assembly of a human individual with parts (caryoplast and cytoplast) which are themselves the product of technique, and which were not destined to play any role in procreation.

The achievement is of course thought-provoking. But it cannot be ignored that it opens the road to new interventions on biological material, which might try to make it depart even more from normal physiological processes. It might be reminded that the idea of an "assembly" of a human being from parts which are subsequently animated is not new. This was the contention of a number of XVIII century zoologists and this is also what worried Goethe (40) in the writings of some french biologists of his time who were in general adept to some of the forms of preformism.

### Dignity of the person and dignity of the origin.

The notion of the dignity of the person is much more far reaching than the sole protection from instrumentalization. It has its roots in the unique and irreplaceable character of each human being (41), which by itself takes it away from any chain of means and ends, and leads to the recognition of an incommensurable value which is expressed as moral responsibility toward it.

It should be acknowledged that the ethical problems related to the beginning of human life have been valuable in that they have enriched the notion of the human person. They have stressed the importance of the bodily condition of the person. This is consistent with the definition by Boethius (cited in 41), that person is "naturae rationalis individua substantia". Substance does not denote a static entity, but is rather the act of being itself in its individual condition, as stressed also in the famous expression by Richard de Saint Victor, "intellectualis essentiae incommunicabilis existentia" (cited in 41).

There is however a biological facet of this unity and unicity, and this is closely related to its mode of origin or procreation.

If the corporeal dimension of the person is taken seriously, one must also attend to those features which are inseparable of its condition as a unique biological organism. These are among others its being a discrete unit, a dynamic system with stable developmental pathways (42). But the form of origin of this unit in fertilization and the insertion of this origin in the descent of the species are also inseparable from the uniqueness of the person. The individuality of the human being which is manifest in the body-soul unity is originated in procreation and descent. If these are tampered with, the way is laid open to insert human beings in the chain of means and ends, and to reduce man as a whole to an industrial product.

Man is "corpore et anima unus", which means that it is in my body where I stand endowed with dignity. If this were not the case the very notion of human dignity would be devoid of meaning. Dignity covers therefore those actions or modes of being which are at the origin of the bodily condition of the human being.

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