Reply to the President of the French Republic on the subject of reproductive cloning

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Introduction

In the natural state, asexual reproduction can be observed in plants and in certain invertebrate animals ; it gives birth to genetically identical individuals. On the contrary, sexual reproduction produces individuals who are all genetically different. Th is diversity, which is the source of evolution and natural selection, is so important that it is to be found in almost all animals, worms, insects, vertebrates. For several decades, in order to gain an understanding of early dev elopment and cellular differentiation, biologists have been experimenting on asexual reproduction in vertebrates, beginning with amphibians and continuing with mammals.

Applying such methods to laboratory animals or livestock could lead to useful developments for medical research, biotechnology and perhaps even for agro-food production. Recently, a successful experiment in asexual reproduction of an adult ewe has been re ported. Although results have yet to be confirmed by other laboratories, the possibilit y of applying this work to humans is already an issue.

The President of the French Republic has put these matters to the National Consultative Ethics Committee for Health and Life Sciences (CCNE) and requested a complete analysis of our normative regulatory framework and also proposals for modifications whi ch might be required to avoid any risk of such technology being used to clone humans (...).

Cellular cloning, i.e. producing populations of genetically identical cells, is already in frequent use fo r humans and has led to important applications for research, diagnosis, and therapy. Several CCNE Opinions since 1986 were given as to the conditions in which such techniques and cell populations could legitimately be used (Opinion n°8 of 15/12/1986 ; Opi nion n°9 of 23/02/87 ; Opinion n°16 of 16/10/1989 ; Opinion n°21 of 13/12/1990).

Some of these cell populations are embryonic in origin but cannot be assimilated to an embryo since they are incapable on their own of developing into a child. A CCNE Opinion on the specific subject of this kind of cell will be presented in the near future.

It should be remembered that a law dated 29th July 1994, in agreement with the CCNE's Opinion n° 8 dated 15/12/1986, proscribes creating *de novo* human embryos unless it is in

the context of a parental project. The possibility of obtaining such cell populations in this way is thereby excluded.

The CCNE's deliberations in response to the President of the Republic's request have focused on problems raised by the use of asexua l reproduction in humans for the purpose of giving birth to a person.

The Committee's first concern was to set the issues raised after the birth of Dolly the ewe in the more general scientific context of research on cloning vertebrates.

In order to avoid any risk of confusion about terms used to describe various realities, the various forms of reproduction, sexual or asexual, are presented and defined. Reasons which might motivate recourse to asexual reproduction in the human species ar e reviewed.

The s ignificance of using cloning to give birth to humans and an analysis of reasons for doing so that have been put forward are subsequently considered from philosophical and ethical points of view. Central to this reflection is the concept of the dignity of the human person which is the very foundation of the CCNE's outlook since it was created.

In conclusion, the CCNE sought to investigate the question of whether respect for ethical values which might be violated by cloning human beings is adequately protec ted by existing legislation.

I - Scientific and technical aspects

GLOSSARY :

Genome : The entire array of genetic material of a cell or organism. The genome is essentially nuclear, composed of the DNA of chromosomes. However, some cytoplasmic organelles also have a genome. In animals, only mitochondria are in this category.

Mitochondria : Organelles located in cell cytoplasm which accomplish several biochemical functions, inter alia the generation of energy. A small portion of proteins and the protein synthesis equipment of these organelles are encoded by the mitochondrial genome which is apart from, and much smaller than the nuclear genome.

Genotype : Genetic constitution of an organism.

Phenotype : All of the visible characteristics of an organism, controlled by the expression of the genome during development and some environmental factors.

Asexual reproduction : Creation of organisms from a single parental organism by scissiparity, budding, etc. without any new genetic material being added. All o f the organisms produced by asexual reproduction of a given organism have an identical set of genes in the nucleus of their cells : they are clones. They may however differ in form and properties because of largely unknown phenomena, such as somaclonal va riations in plants.

Sexual reproduction : Creation of organisms from two parents, one male and one female, whose genetic material is randomly mixed, so that descendants are all genetically different, with the exception of identical (monozygotic) twins.

Pr ocreation : Sexual reproduction in humans. The result is the formation of a zygote (later to become an embryo) arising out of the fertilisation of an ovum (or oocyte) by a spermatozoon.

Germinal cells : Cells from which gametes originate and gametes themselves, which play a

role in sexual reproduction. In animals, female gametes are called oocytes or ova, and the male gametes are called spermatozoa.

Somatic cells : The cells of an organism to the exclusion of germinal cells.

Egg : The term non fertiliz ed egg is frequently used in English language literature. It should be understood to mean ovum or oocyte.

Embryo : Organism in the process of development ; that which is beginning to exist but is not yet completed (Definition in the Dictionnaire Robert de la langue française). An embryo has the potentiality of developing into a complete organism and contribut ing to the formation of all its component parts.

Totipotency, totipotent cell : Capacity of a cell (embryonic) to contribute to the develop ment of all the parts and organs of a complete organism. In vertebrates, only zygote and initial embryonic cells are totipotent, whereas in plants all cells are.

Differentiation : Process through which a totipotent cell acquires progressively the characteristics of cells constituting the different tissues of an organism (e.g. brain, heart, liver, etc...).

***In vivo* : In an organism**

***In utero* : In a uterus**

***Ex vivo* : In a cell culture**

***In vitro* : In a non-cellular environment**

Clone : Originally, a term used in microbiology and cellular biology to designate the entire array of cells derived from a single parent cell, and thereby genetically identical to it.

A gene integrated to a parent cell by genetic engineering is to be found in all the daughter cells and is therefore cloned (cloning of a gene).

By further extension of this term, cloning is the word used to designate pure production of identical macromolecules (for instance monoclonal antibodies) encoded by the same gene.

Finally, are designated by the word clone the entire collection of organisms derived from a single organism and which all possess an identical set of genes in the nuclei of their cells. As the case may be, the determinants of cytoplasmic heredity (i.e. the mitochondrial genome in animals) of the various individuals forming a clone may be identical or different.

Cloning : As it applies to an organism, cloning is producing a single individual or a population of individuals possessing in the nuclei of their cells a set of genes identical to t hat of the organism from which cloning was achieved.

A - Scientific context of recent cloning experiments on mammals

Selective advantages of diversity have privileged sexual reproduction during the course of evolution

The genetic stock of every individual is contained in the nucleus of each of his cells and more specifically in the DNA molecules which are the main component of his chromosomes. Half of these chromosomes, the number of which is fixed for each species (2 n), are transmitted by each paren t at the time of sexual reproduction, when the gamete nuclei fuse to constitute the nucleus of the egg.

The egg, a totipotent cell from which the new organism will develop, thus contains the chromosomal stock which is characteristic for the species. Genes from parents are brought together in the egg in an unique assortment, that depends largely on chance.

Not all multicellular organisms reproduce through specialised sexual cells, i.e. gametes, also called **germinal** cells, in contrast to **somatic** cells whic h are the constituents of all other tissues. Some fairly simple animals such as sponges and coelenterates (e.g. hydrae, corals) can reproduce asexually by budding or scissiparity. In plants, this mode of reproduction called propagation is quite commonpla ce and is achieved through cuttings or suckers. Methods for cultivating plant cells have progressed greatly in recent decades and it has been found that each plant somatic cell is virtually capable of producing the entire plant.

With this kind of reproduct ion, which is in fact cloning, the genetic stock of the species contained in its chromosomes is transmitted to newly formed individuals by **mitotic** division, a process which ensures in principle the exact replication of chromosomal DNA in somatic cells.

The formation of germ cells required for sexual reproduction is a much more complicated process than the one leading to asexual reproduction. It is therefore remarkable that, even if they are capable of asexual reproduction, practically all eukaryotic organisms (1) , be they single celled or multicellular, have developed in the course of evolution cellular strategies which enable them to produce the germ cells necessary for sexual reproduction.

The complex machinery involved in gamete production, i.e. **meiosis** , which reduces by half the number of chromosomes in the sexual cells, has the advantage of contributing the possibility to manipulate and recombine the genes of the species. It is therefore likely that the successful evolution of sexual reproduction is base d on the fact that it played a crucial role in allowing new genes and new genetic combinations to develop and thereby produced unique individuals within each species and, beyond the bounds of the species, the infinite variety of forms and functions to be found in today's living world.

The reshuffle of genes inherited from father and mother during gamete formation is accomplished through two different mechanisms. One of these is random distribution of the homologous chromosomes of paternal or maternal origi n in each gamete after meiosis. That alone in principle enables the stem germ cells of each individual to produce 2 n genetically different gametes. In humans, for instance, whose haploid number of chromosomes is 23, each individual can produce at least 2 23 = 8.4 x 10 6 genetically different gametes. In fact, this number is much greater because of the second mechanism, responsible for gene assortment during meiosis, **genetic recombination** (also called crossing-over) in the course of which homologous chromo somes exchange fragments, when they pair off during the first prophase of meiotic division. On average, between 2 and 3 recombination events occur in each pair of chromosomes during human meiosis. Through this process, the genetic constitution of the gam ete chromosomes is truly mosaic.

Genes and cellular differentiation

The mitotic divisions of cells from the egg ensure that the genome remains stable as it is transmitted from parent cell to daughter cell, unless there are DNA replication errors or misha ps at the time of chromosome segregation in daughter cells.

One of the crucial queries about the development of an embryo from the egg is how cells with the same genes can produce cellular phenotypes as different as a neuron, a blood cell, or a muscle cell for instance. Such differentiation can only be the result of differential activity of genes contained in these various cellular types. Furthermore, the differentiated state of cells is generally considered to be stable, or even irreversible, so that the question arises about the kind of mechanism that regulates gene activity during differentiation. Are genes, quiescent in some types of cells, inactivated once and for all or can they be

reactivated in a different cytoplasmic context ? Are some genes lost during cellular differentiation ? What is precisely the importance and nature of the nuclear-cytoplasmic relationship?

Such are the issues which embryologists became aware of in the fifties when they realised that, without the help and contributio n of genetics, an understanding of developmental mechanisms would remain out of reach.

With the aim of discovering whether or not nuclei of differentiated cells retain genetic potentialities as do those of totipotent embryonic cells, Robert Briggs and Thomas King (then working in the Institute for Cancer Research of Philadelphia) started ex periments, in the early fifties which later became classics.

The oocyte of *Rana pipiens,* whilst in the process of meiotic division, is pricked with a fine glass needle, the effect of which is to provoke activation. This series of cytological and biochemical events is normally connected to penetration by a spermatozoon and is essential to trigger embryonic development. Activation brings meiosis to an end ; the are a of the ovum which is close to the cytoplasmic surface and contains the chromosomes could then be extracted from the oocyte with a glass needle or destroyed by UV radiation. Briggs and King introduced the nucleus from one of the yet undifferentiated cell s of a young embryo at the blastula stage into the enucleated cytoplasm of the active oocyte (a blastula is made up of still totipotent cells which are formed during the early divisions of the egg). A percentage of eggs which had been reconstituted in this way with a somatic cell nucleus developed normally into tadpoles.

Nuclei of embryonic cells from the blastula had therefore retained the properties of the nucleus of the egg (Briggs and King, 1952). If nuclei were removed from more developed embryonic c ells, their capacity to control embryogenesis decreased irrespective of whether the nuclei were taken from the endoderm (Briggs and King, 1957) or from other embryonic tissues in the gastrula or neurula stages (Di Bernardino and King, 1967). According to King and Briggs (1956), this capacity had entirely disappeared in somatic cells in the caudal bud stage which precedes the emergence of the tadpole. At this stage, the only cell nuclei with the capacity to replace the egg nucleus were germinal nucl ei (whose fate is to go through meiosis and contribute gamete nuclei). Such nuclei, when transferred to an active enucleated oocyte, gave rise to normal development in 40% of embryos which started to develop (Smith, 1956).

John Gurdon repeated these experiments with Xenopus and also found that as embryogenesis progresses, somatic nuclei progressively lose their capacity to promote complete and normal embryonic development. He noted however that in this species, nuclei stay totipotent longer than in Rana. Furthermore, he demonstrated that certain tissues, even well differentiated as in intestinal epithelium from Xenopus tadpoles, could supply nuclei capable of orchestrating full embryonic development. In this way, out of 726 nuclei from intestinal cells t ransferred to activated oocytes, 10 (1.4%) led to the development of tadpoles (Gurdon 1962) and 7 metamorphosed into adult toads (Gurdon and Uehlinger, 1966). These nuclei, although from differentiated cells, had therefore retained totipotency.

These expe riments were criticised by King and his colleague who considered that intestinal cells of a tadpole, still containing vitellus, were not from a truly differentiated tissue. They also commented that sampling could have been contaminated by germinal cells present at that time in the intestine, on their migration pathway to the gonads (Di Bernardino and King, 1967; McKinnell, 1978; Briggs, 1979). In response to this criticism, Gurdon cultivated epithelial cells of the web membrane of an adult toad and tran sp lanted the nuclei of these cells into enucleated oocytes. None of them were able to undergo embryonic development beyond the neurula stage. At this point, Gurdon et al. came up with the idea of serial nuclear transplantations using the nuclei of these gas trulae. These nuclei produced numerous tadpoles (Gurdon et al., 1975) which were not however able to feed or metamorphose.

Another spectacular experiment involved a nucleus taken from the erythrocyte of an adult toad (which once differentiated neither mu ltiplies nor synthesises mRNA). This nucleus was transferred to an enucleated oocyte and re-acquired the capacity to divide and direct the development of an egg up to the tadpole stage (Orr et al., 1986; Di Bernardino, 1989).

Differences in results arrived at by Briggs and King, on the one hand, and Gurdon on the other hand are very likely due to the species used in the experiments. Transfer of a differentiated cell nucleus into the cytoplasm of an oocyte certainly requires r e-adaptation. In the egg, th e rate of cell division is faster than in differentiated cells. Delay in DNA replication in transplanted nuclei is the cause of chromosomal breaks frequently observed in the cells of cloned tadpoles. Sally Hennen (1970) demonstrated that nuclear tran splantation success is significantly enhanced if the egg is cooled after it has received the donor nucleus which adapts better to its new cytoplasmic environment. Treatment of nuclei with spermine, which has an effect on nuclear histones and makes chroma ti n accessible to DNA duplication and transcription, also enhances the success of such nuclear transplantations.

The conclusion from this experimentation is that, in tissues used as the nuclear source, cellular differentiation has not impaired the genome capacity to be activated and to differentiate into most (if not all) cell types of the species concerned. A numb er of genes which are inactive in skin or blood cells can be used if their nuclei are subjected to new activating influences supplied by cytopla sm of other cells. In other words, these nuclei can be re-programmed, thus demonstrating that genome stability is retained during cellular differentiation.

Does this conclusion apply generally ? Probably not. Indeed, following research by Susumu Tonegawa (1983) and Mark Davis (Davis and Bjorkman, 1988), it has been known that the differentiation of B and T lymphocytes involves structural modifications of gen etic material such as the elimination of DNA fragments and the bringing together of regions, initia lly separate in the chromosomes, which carry the genes for immunoglobulin and T cell receptors.

It is possible that chromosomal rearrangement and transposition exist in other differentiated cells. Such modifications are of course irreversible and could lead to permanent deficiencies in the capacity of the nuclei of these cells to control embryonic development.

Nuclear re-programming in somatic hybrids and in cancer cells

The oocyte's cytoplasm does not have the exclusive privilege of being able to re-programme the activity of differentiated cell nuclei. Some occasionally spectacular changes in gene activity were induced in the sixties by the fusion of two somatic cells with different phenotypes and physiological activities (Barski et al., 1960 ; Harri s and Watkins, 1965).

The alteration of cell plasmic membranes in culture by certain inactivated viruses or by substances such as polyethylene glycol induce membrane fusion of adjacent cells. The result is a heterokaryon (also known as a somatic hybrid) i n which the nuclei of fused cells stay separate whereas their cytoplasm is mixed.

For instance, it is possible to induce fusion between a fibroblast, which has an active metabolism and fast rate of proliferation, and the nucleated erythrocyte of a chicken, which has ceased to divide and whose chromatin has no transcriptional activity. Shortly after the cytoplasm of the two cells has merged, the erythrocyte nucleus regains transcriptional activity (i.e. some of its genes produce messenger RNA) and later ev en enters into the DNA synthesis phase and divides. It is known now that the fibroblast nucleus acts through proteins (called transcription factors) synthesized by regulatory genes, and that these proteins initiate and maintain transcription of other gene s. These proteins, synthesised from messenger RNAs in the cytoplasm, are able to migrate into the cell nucleus where they

act as regulatory genes. In heterokaryons, these transcription factors, which are coded by the fibroblast nucleus, enter the erythr oc yte nucleus and reactivate it.

Due to this pioneer work, it is possible to understand that the oocyte cytoplasm contains transcription factors that accumulate during oogenesis through the activity of the female gamete nucleus. These factors are responsible for the initiation of the fir st phases of development since they trigger a specific cascade of gene activities within the nucleus of the egg. Experiments involving transplantation of differentiated cell nuclei into the oocyte show that this gene regulati on is effective in a highly heterochronic nucleo-cytoplasmic system, i.e., a system where nucleus and cytoplasm come from cells at very different stages of their development. This is also the case in heterokarya where associated cells may have arrived at the same ontogenetic stage after following distinct differentiation routes.

This somatic hybrid technique, extensively used, provided significant information on the extent and limits of phenotypic plasticity in differentiated cells in these specific exper imental conditions (e.g. Blau et al., 1985). These results are not within the scope of this presentation. It is however worth noticing that this technique led to two major applications : the method for producing monoclonal antibodies (Koller and Milstein , 1975), and the mapping of a number of genes on human chromosomes. When heterokaryon nuclei divide, they fuse and produce hybrid cells called synkaria, the nuclei of which contain chromosomes from the two initial cells. If these cells belong to man and mo use respectively, human chromosomes are progressively eliminated during successive divisions, for reasons as yet not understood. The disappearance of an enzymatic activity for instance, when a human chromosome is eliminated, makes it possible to locate th e gene for that enzyme on this chromosome (this method was developed by Weiss and Green, 1967). Numerous references on the subject can be found in Ruddle and Creagan's review, 1975).

Functional plasticity of differentiated cell genomes is also evidenced b y certain characteristic modifications of cancer cells in which normally silent genes are reactivated or in which genes characteristic of other cells are activated. For instance, some liver cancers synthesise proteins normally found in the foetal liver, and bronchial cancers secrete pituitary hormones (Schapira, 1963; Abelev, 1971; Texier et al, 1991).

Cloning of Mammals - The situation before Dolly

Experimental production of twins

For almost 20 years, the experimental production of twins, similar to those which appear spontaneously from a single egg, has been possible. In ovines and bovines, an 5 or 6 day old embryo (in the morula stage) is divided into two equal parts. With both ewes and cows success was achieved by Willadsen (1979-1989). The he mi-embryos once re-implanted in a carrier female turn out to be highly capable of regulation and they develop into a normal lamb or calf.

Nuclear transplantation into the oocyte

Nuclear transplantation has been successful in the mouse after the pronuclei of spermatozoon and ovum have been expelled before fusion and replaced by those of another egg (Mc Grath and Solter, 1983, 1984). These reconstituted eggs cleave normally and are later implanted into a pseudopregnant female where they complete their dev elopment. Genetic characteristics of mice born from such eggs are of course those of the implanted nuclei.

In mice, nuclei from embryos in the 8-cell stage or from the inner cell mass of blastocysts, do not allow the development of enucleated eggs (Tsunoda and Kato, 1993; Cheong et al., 1993). However this is not so for all mammals. For instance, in domestic animals similar experiments were a success as early as 1986, when Willadsen produced the first mammal, a lamb from an oocyte which had received the d iploid nucleus of a blastomere.

In bovines, the first calf born of embryonic cloning was produced in the USA the following year (Prather et al., 1987). In 1989, INRA (Institut National de Recherche Agronomique) was successful in producing lambs by nuclear transplantation and, in 1990, obtained the birth of a first clone of 6 genetically identical rabbits from a single embryo (Heyman et al., 1990).

Finally, in 1993, INRA announced the production of a clone of 5 genetically identical calves from a single embryo (Chesné et al., 1993). At the present time, more than 70 calves have been produced for experimental purposes by INRA using embryonic cloning techniques.

These experiments make it possible to detect and analyse developmental features which are not gene tically determined. They also reveal some unexpected differences in animals produced by artificial insemination, which display higher birth weights than normal.

Most of the ongoing research is occurring in North America (USA and Canada), in Europe (United Kingdom, France, Germany, Netherlands, Denmark, Italy, Belgium...), in Japan and Australia. According to a 1996 evaluation, no more than about 1000 calves were produced using cloning from embryonic nuclei at the morula stage.

Embryonic cloning progresse d further when the development of a bovine egg was achieved after transplantation of nuclei taken from the inner cell mass of an embryo in the blastocyst phase (Keefer et al., 1994).

More recently, complete embryonic development was obtained in sheep, with donor nuclei from an embryonic cell line cultivated in vitro through several passages (Campbell et al., 1996).

Experiments performed by Wilmut et al. (1997)

These experiments marked a new technological breakthrough as regards the cloning of mammals. Lambs developed following transplantation in oocytes of nuclei from 9 day old embryos, from 26 day old foetuses, and even from mammary gland tissue from a gestating ewe. This success was due to recognition of the fact that the major difficulty in such ex periments is for a somatic cell nucleus to adapt to ovocyte cytoplasm and to respond to its signals. Implanted nuclei are generally in the S phase (DNA synthesis phase) or G2 (which is the phase immediately after S) of the cell cycle. Oocytes in which n uc lei are transferred are generally in the metaphase of the 2nd meiotic division (close to cell division). This chronological discrepancy leads to induction of an immediate DNA replication in the implanted nucleus followed by premature chromosomal condensa tion. These events are generally linked to an abnormal distribution of chromosomes in the daughter cells that become aneuploid (i.e. they contain an abnormal number of chromosomes). Aneuploidy very frequently leads to arrest of embryonic development.

Wil mut et al. (1997) took the precaution of cultivating the donor nuclear cells in conditions which ensured a state of non-proliferation, i.e. **quiescence** . This is easily obtained by starving the cells. The cells become arrested in the phase of the cell cycle phase known as G0 (i.e. the resting phase when the cells are not dividing). This state probably confers on the somatic nucleus the capacity to sync hronise DNA replication with the ovocyte programme. It also probably leads to the rearrangement of the chr omatin organisation which occurs throughout the period of egg cleavage in mammals (Thompson et al., 1995). However data gathered so far does indicate that, after nuclear transfer, the structure of the nucleus is not that of the zygotic nucleus. (Christian s et al., 1994 ; Chastant et al., 1996).

Success obtained by Wilmut et al., (1997) with nuclei from the adult mammary gland should not obscure the fact that the nature of these donor cells is not precisely known.

There could be cells which, even in adults , retain some pluripotentiality. There are such cells in almost all tissues.

Furthermore, it should be noted that the success rate of recently reported experiments is extremely low : 1 lamb born out of a series of 277 transplantations of mammary gland nuclei.

What potential biotechnological applications could arise out of embryonic cloning of domestic animals ?

It must be noted that, at present, the yield of this biotechnology is rather low in spite of having tripled during the last five years. On ave rage, 10 calves are born out of a hundred embryonic nuclei, as against 3% in 1992. For specific research projects, clones of 3 to 6 calves can now be produced on a regular basis.

In the fairly near future, animals produced by these cloning techniques can be useful in a variety of ways.

In particular, it will be possible to reduce the numbers of animals in comparative veterinary treatments, herd management methods for cattle, or social and feeding behaviours studies, since uniform sets of animals can be c onstituted.

New possibilities will be offered to improve breeding programme efficiency, for instance by earlier selection, to introduce a particular trait into selection schemes (such as resistance to disease or adaptation to a given environment), to ameliorate the g enetic potential of females... In poorly reproducing strains mating between a larger number of animals, even though they would be produced by cloning, would increase chances of preserving genetic diversity.

The above applications only require a limited number of copies of the same individual : they mainly concern research and technical support given to breeders.

If they were used in animal husbandry, identical reproduction in large numbers would increase the risk of depleting genetic diversity. If however, techniques were to be improved to such an extent that in the long term clear economic advantage were likely , legislation similar to the law presently regulating artificial insemination technology would have to be drafted.

Prospects of uses in human therapy are particularly important :

- validating protocols for medical treatment would require a smaller number of better defined animals.

- cloning after homologous recombination would make it possible to create animal models for human diseases in other species besides mice and rats.

- transgenic animals, engineered to produce molecules of pharmaceutical utility or as organ donors for human transplants, could be multiplied easily.

In conclusion, beyond possible biotechnological applications and application to the production of biologically active substances, recent developments in cloning techniques deserve evaluation in the domain of fundamental sciences.

Biological problems which in the fifties led scientists to carry out the first experiments in transplantation of somatic cell nuclei in the ovular cytoplasm, can be formulated in the following way : what are the mechanisms which co-ordinate, during embryo nic development, differential gene activities in cells arising from the division of the totipotent

fertilised egg ? This fundamental problem is at the very centre of the mechanisms of embryonic development ; it conditions the way in which the cells of an adult later function ; it is at the core of the dysfunctions causing tumours.

Progress since 1950 has demonstrated that the cell differentiation process does not necessarily impede the functional potentialities of the genome which, even in an adult cell, can control complete embryonic development if placed in favourable circumstanc es. But is this true for all adult cells ? What exactly are the conditions required for reprogramming the genes of a differentiated cell in the cytoplasm of the oocyte ?

These are only a few of the questions which remain to be solved. Thanks to recent progress, we can begin to seek answers. Cloning experiments which led to Dolly's birth are part of the long chain of important biological issues which began almost 50 years ago and which are still a rich heuristic source.

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B - The issue of applying cloning techniques to the human species

In the past several years, it has been regularly announced and become the subject of much speculation that human cloning is possible and even imminent. The expression cloning covers some very different techniques which will be described as a first s tep. Furthermore, for as long as the issue of po ssible use of cloning techniques in the human species has been discussed, that is since several decades or even more than a century, various imaginable applications in the field of medicine have been mentioned. We shall therefore review the indications for application to the human species which are most frequently put forward in various statements or commentaries, regardless of an ethical analysis of these indications which will be the subject of a special chapter (chapter II).

DIFFERENT TYPES OF CLONES

Different processes, spontaneous or experimental, may lead to clone populations:

Monozygotic twins : cleavage and separation of an embryo composed of several cells into two (or more) independent parts, each of which can potentially generate genetically identical but separate organisms.

In domestic animals , the phenomenon occurs spontaneously, but very rarely. For about twenty years or so, it has been possible to produce identical twins experimentally in cows and ewes.

In the human species , monozygo tic twins are a rare natural phenomenon, occurring spontaneously and infrequently. There is a stable rate in all populations of about 4 per 1000 births. Experimental cleavage of human embryos was performed in 1993 and reported in the annual conference of the American Fertility Society by two scientists working in the George Washington University research laboratory. They undertook in vitro human embryo cleavage on 17 embryos recognised as triploid on fertilisation (2 male pronuclei and 1 female pronucleu s) and therefore incapable of normal development after transfer. They separated the embryos in the 2 to 8 cell stages, into 2, 3, or 4 parts which they introduced into artificial striated membranes (zona pellucida) and then cultivated *in vitro* . Forty-eight new embryos were produced and developed, some of them as far as 16 or 32 cell stages. This work was never printed in any scientific peer reviewed publication.

Cloning by embryonic nuclear transfer : It is possible to produce in animals clonal organisms by transferring in oocytes (or ova) which have been previously enucleated, nuclei of the cells of a single embryo after a few days of development (see scientific section). It must be emphasised that this type of cloning requires prior procreation to ob tain the nuclei donating embryo.

Embryonic cloning by nuclear transfer from an adult organism , which has just been achieved by the Scottish team of the Roslin Institute ; no procreative act is required and this is an example of asexual reproduction... alth ough it uses a non-fertilised female gamete.

The recipient oocyte and the nucleus donating cell can be from the same female organism, or else the cell donating the nucleus can come from another organism, male or female. Cloning with nuclear transplantation can create embryos whose cytoplasm and org anelles on the one hand, and nucleus on the other hand, have different origins. In fact, the ovular

cytoplasm plays an at least dual role in the formation of the embryo. Firstly, it contains the biochemical sy stems which may activate cell division and reprogram the nuclear genome, and secondly its mitochondria which possess their own genome, contribute some of the energy which the cell needs. This function is partly directed by the mitochondrial DNA which is of purely maternal origin.

COULD THESE DIFFERENT CLONING TECHNIQUES BE APPLIED TO HUMANS ?

The answer to that question depends on the type of cloning.

Creation of twins *ex vivo* by manipulation of an embryo created by *in vitro* fertilisation is possible a nd was tested by American scientists in 1993. It can also be the consequence of certain ex vivo procedures to facilitate implantation of the eggs in the uterus (mechanical weakening of the zona pellucida).

Embryonic nuclei transfer has led to the birth of monkeys which a team of American scientists announced in 1997 but this has not yet been reported in a scientific publication. Such a technique could lead to the creation of monkey clones and could also perhaps be applied to humans .

Creation of clones by t he transfer of cell nuclei from an adult mammal is still exceptional (the birth of a single ewe as yet published, and a few more births announced by the media...) and it is impossible at this point to judge whether this kind of technique could apply to humans. However, if the *Roslin Institute* results were to be confirmed, there is no reason in principle and technically speaking to believe such results could not be repeated with human beings.

However, cloning a human being would demand the availability of a considerable number of oocytes and repeated attempts. The success rate of *in vitro* fertilisation in terms of births per attempt is only 15% for infertile couples. Once embryos have been obtained by *in vitro* fertilisation, implantation rates are approximately 10% per transferred embryo (on average, two or three embryos at a time are transferred). After freezing and thawing, an embryo's chances of successful implantation may be reduced. Oocyte freezing tech nology is very defective. Consequently, if one considers the low efficiency of asexual reproduction for one ewe (one success in almost 300 nucleus transfers) hundreds or even thousands of oocytes would probably be necessary to achieve one birth !

JUSTIFICATION OFFERED FOR NUCLEAR TRANSFER AND CLONING OF HUMAN BEINGS

I] - Reproduction

a) - Increasing chances of pregnancy when a single embryo was produced *in vitro*.

This was the argument put forward in 1993 by the George Washington scientists to justify their experiments on human embryos. A single e mbryo, split, could enable the creation and transfer *in vivo* of several twin embryos. In practice, a single embryo is a rarity and the average number of embryos produced by *in vitro* fertilisation in the last five years was 3.9 (FIVNAT file 1996). Although technically the procedure is available to laboratories specialising in *in vitro* fertilisation, practitioners have not repeated these experiments.

b) - Facilitating pre-implant diagnosis.

The pre-implant diagnosis which is still under evaluation, is usu ally performed on a cell taken from an embryo in the 8-cell stage. Embryo survival is considerably diminished if more than one cell is sampled. In prevailing conditions, one or two cells from embryos

obtained by *in vitro* fertilisation are analysed and once results are known, a healthy embryo is transferred *in utero* .

Creation of several cloned embryos would make it possible, after one of them is cultivated, to obtain a larger supply of cells. Other embryos would be frozen while awaiting results. In the c ase of creation of cloned embryos, there would be destruction of an embryo which had been specifically created for the purpose of diagnosis.

c) - Perpetuating biological lineage if procreation is an impossibility.

It seems that today's society is ever more demanding in its urge for biological descent. *In vitro* fertilisation (IVF), and later ICSI (intracytoplasmic sperm injection), have made it possible to increase gradually the chances of overcoming male infertility whereas before the only options for a couple where the man was sterile if they wanted children, were adoption or insemination with donor sperm. Therefore nowadays, men who only have a few normal spermatozoa can sire children. Even those whose spermatogenesis stops before a mature spermatozo on develops can now, sometimes, father offspring. There are, however, forms of sterility of more consequence : dysplasia or severe testicular atrophy, sexual ambiguity, or even female homosexual couples, where there is no trace of a male germline.

Will su ch couples also claim the right to biological filiation ? It should be noted that if the technology used in sheep were applied in that form to humans, the end result would be monoparental reproduction (100% of nuclear genetic inheritance from the fathe r) and not biparental with genetic contributions from both mother and father. However, the demand for pregnancy from menopausal women, or for embryo or oocyte donation to overcome sterility, are demonstrations of the extraordinary capacity for maternal r e-appropriation of the embryo through pregnancy, even though in this case the surrogate mother is not the biological mother. Furthermore, in the case in point, the mother would at least contribute her mitochondrial genome to the embryo.

It does seem therefore that one cannot exclude the possibility of social demand for legitimating the use of such techniques, at least for couples in which one spouse has no fertilising gametes. For that matter, cloning could also satisfy a gamete-less wo man who wishes to be biologically perpetuated through self-cloning using the enucleated oocytes of a donor.

More recently, in *Nature* , there was speculation on the subject of reproducing through cloning a dead or dying child. Statements in various fora also considered the possibility of reproducing exceptional people..., or of loved ones...

d) - It is to be noted that nuclear transfer of an embryonic nucleus could also be considered in human beings for reasons totally foreign to cloning, in an authentic procreation , for gene therapy in the case of mitochondrial disorders (2).

I I] - Grafts

Preparation of immuno-compatible cells for cell therapy.

Cell grafts are indicated in a broad variety of diseases and pathological situations : to cover burn surfaces, transplantation of hematopoietic stem cells for leukaemias and other diseases of the blood; neuronal cells in Parkinson's disease, possibly Hunt ington's chorea; endocrine pancreatic cells in diabetes, etc. Furthermore, one of the gene therapy strategies develop ed nowadays is based on grafting cells corrected *ex vivo* . When cells for transplantation come from someone who is not the beneficiary (i.e. an allogeneic graft) tissue incompatibility impairs effectiveness and safety. Availability of embryonic cells which are genetically and therefore immunologically identic al to those of the patient would greatly facilitate such procedures and it is very likely that they would be more effective. Cloning by

nuclear transfer from an adult organism should make it possible, if necessary, to prepare such cells in the space of a few months. With this kind of scenario, an embryo would be created using a recipient oocyte and the nucleus of one of the patient's somatic cells. This embryo could then be cultured *ex vivo* and after a few days, an attempt could be made to culture cell populations in which differentiation could be induced *ex vivo* and which could therefore be used for grafting. However, experiments in creation and differentiation *ex vivo* of embryonic cells are difficu lt and have not yet been successful in any species except mice.

Consequently, if isolation of differentiated embryo cell lines *ex vivo* turned out to be impossible in humans, a possibility could be implantation of an embryo to a recipient uterus so that it could develop until cells for grafting appeared. These cells would then be isolated after embryonic development was arrested. It sh ould be noted that such techniques are prohibited by law at this time, since they would require creation of embryos for a p urpose unconnected to a parental project.

For the sake of completeness, we mention that some opinions went so far as to consider that copies of living persons could be created by cloning and preserved with the sole purpose of using them as potential sources for organs and cells to be grafted if required.

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C - Commentary on media reporting on the subject of cloning

Before going on to ethical consideration of the serious issues which arise, it seems necessary to comment briefly on the manner in which the subject of cloning was dealt with so far by the media.

In its Opinion n° 45 of June 1995 concerning ethical problems raised by the transmission of scientific information in the fields of biological and medical research, the Committee drew attention to worrying lapses which could seriously damage the quality o f the message. The conditions in which was divulged Dolly's existence are one of several new illustrations of this trend.

Nature accepted an article from the Edinburgh team who had cloned Dolly on 20th January 1997 for publication on 27th February. A number of scientific journalists were given information in advance with the usual moral obligation to apply an embargo until the dat e given. *The Observer* , unilaterally disregarded the embargo to be the first with the news in its issue of Sunday, 23rd February. Forthwit h, all the press agencies followed suit. Ian Wilmut and his colleagues then improvised an immediate press conference. Nevertheless, the information was spread world-wide before appearing as the princeps article in a scientific publication with peer revi ew, on the basis of a mere article in a weekly magazine.

This indisputable breach of ethics followed for scientific information of course had detrimental effects on the quality of data transmitted. Thus, all the articles emphasised that the fundamental s cientific novelty evidenced by Dolly's existence was the reactivating of totipotency of fully differentiated adult somatic cells, but omitted the important comment by Ian Wilmut et al. at the end of their article in *Nature* (p. 812) : We cannot exclude the possibility that there is a small proportion of relatively undifferentiated stem cells able to support regeneration of the mammary gland during pregnancy. Furthermore, in that same article, the erroneous duplication o f a photographic illustration (whic h was later corrected)

prevented any comparative appreciation of the phenotype of cells whose nucleus was transplanted.

One cannot fail to notice, on this occasion as on many others, the reprehensible breach of ethics of scientific information and the concomitant fact that considerable economic and financial interests are present. News about Dolly had the most excellent ef fect not only on sales figures for that issue of *The Observer* , but also on stock exchange appreciation of share values of the biotechnol ogical firm PPL Therapeutics for which the Edinburgh *Roslin Institute* research team also works. Simultaneously, the British Ministry of Agriculture made public its intention of ceasing to finance this research, according to a decision taken apparently some months previously. There is some justification for considering the whole affair as a confirmation of several misgivings expressed by the Committee in its Opinion of July 1995.

But a further point is even more disquieting in our view. It is worth emphasi sing that an attempt by a team of USA scientists to clone human embryos in 1993 - an attempt which had generated much justified and extreme alarm at the time - was never published in a scientific periodical, nor did it give rise to any public systematic a nd ethical debate which would have guided public opinion in its thinking during the years which preceded Dolly's birth. There are here, it seems, unless sufficient watchful attention is paid to the subject, indications of what may turn out to be a particu la rly pernicious system of transmission of scientific information in the field of biological and medical research, characterised by an alliance of media scoops and silence from laboratories and medical practitioners. Is there not a periodic deluge of artic les and commentaries on sensational media oriented aspects of research to an extent that generates satiety and confusion, to which all too frequently is allied an absence of information on health issues of crucial importance for society and disquieting di sc retion regarding the development of work which suddenly bursts upon the public at large in the form of premeditated scoops about upsetting *faits accomplis* ? In our view, it is almost exactly the opposite which should be motivated by ethics in scientific information and democratic regard for a responsible citizenry.

I I - Ethical considerations

The intense emotion generated the world over by the now plausible prospect of cloning human beings, and vehement condemnation of any such possibility based on ext remely diverse convictions, could suggest that any ethical question posed would be a foregone conclusion. Nothing however could be more damaging than to draw conclusions and possibly legislate on such a weighty subject without taking the trouble to fully consider the matter from a philosophical and moral point of view. There are two reasons in particular why this is so :

1) If in the final analysis, it appears necessary to prohibit by law any reproductive cloning of human beings, it is highly important t hat the ethical arguments on which such a decision is based should rest on very firm ground in the eyes of international and national opinion. In this way, concerted action can be taken to that effect on a global basis which is the essential condition of its efficacy. Evaluation of attitudes and arguments put forward must therefore be undeniable.

2) This effort to reflect on the subject cannot be deferred on the pretext that cloning humans is so far no more than mere hypothesis for which conditions of a chievement are far from complete. The history of biomedical research has amply demonstrated the need for ethical reflection as far ahead of research as is possible so as to prevent a *fait accompli* . Nor can the serious nature of the subject be dismissed because it smacks of fantasy or even science fiction. An inrush of volunteers - some of them very affluent - for cloning, arriving in Edinburgh, shows how witless it would be to equate fantasy to fallacy. The idea of a Nobel prize winner's sperm bank to give birth to a crop of geniuses was also patently a fantastic aberration. It nevertheless became reality and some victims were fooled.

Serious ethical reflection is an obligation when, in one way or another, the dignity of the human being is at stake.

* * *

The ethical problem with which we are now confronted concerns the now conceivable prospect of reproductive cloning of human beings , that is, with due regard to definitions formulated above, an embryo produced by full development of a somatic or embr yonic cell leading to the birth of a child. If the cloned cell was taken from a developed organism, child or adult, the result would be a human being whose nuclear genome would be identical to the original individual's nuclear genome. If the cloned cell was from a developing embryo and immediately transferred *in utero* , the result would present itself in the form of induced quasi-twinning, not even necessarily limited to two individuals. In both cases, human beings would be generated by asexual reproduct ion, and would be carbon copies of each other and of the original organism whose nuclear genome they would carry. In other words, the result is a production of individuals, one or several, almost as identical biologically speaking as identical twins, alth ough they could enter the world at time gaps which could skip one or several generations.

As has been mentioned above, reproductive cloning resulting in the birth of human beings must not be confused with non-reproductive cloning , which does not lead to th e birth of a child. The notion of non-reproductive cloning also covers two kinds of techniques which are either already in use or could be a possibility :

- production and culture of cells of embryonic or adult origin which cannot themselves give rise to the constitution of an embryo. These techniques, which are commonplace and of great usefulness for diagnosis and therapy, raise ethical issues which are n ot fundamentally different from those raised by other aspects of biomedical research. The possible use of cells derived from human embryonic stem cells is the subject of an Opinion of the National Consultative Ethics Committee soon to be presented.

- production of embryos whose development would be arrested in a more or less early phase to obtain immuno-compatible cells for use in cell therapy. However, in this respect, it should be noted that creation de novo of human embryos unconnected with a parental project and for the sole purpose of research is prohibited by a French law dated 29th July, 1994, w hich is due to be reviewed in 1999.

The very different and profoundly novel subject of this document is the prospect of possible reproductive cloning of human beings, which is a complete convulsion of the human condition , the implications of which in ethical and legal terms appear from the outset to bear no comparison with non-reproductive cloning. The following reflections are solely concerned with reproductive cloning.

1. Genetic identity and personal identity : a grave confusion which must be dispelled

A point of clarification is required. In all that has been written on the possibility of reproductive cloning of human beings since Dolly's existence was announced, in France and elsewhere, one finds that is frequently accepted as an obvious truth that complete genetic identity of two human beings would lead ipso facto to their complete psychic identity. It would even seem to be understood by some that an individual produced by cloning is a kind of reincarnation of the clone's original. It is precisel y this imagined identical reduplication of a human me into another body by genomic propagation like plant cuttings which fans the yearning of not a few individuals to escape in this way individual death for themselves or for another cherished person.

It can be stated with complete confidence : the notion that perfect genetic similarity would

in itself lead to perfect psychic similarity is devoid of any scientific foundation. Not even biological identity in an individual can be equated to his nuclear genetic identity, because of the role played by cytoplasmic (mitochondrial) heredity, and more so because of epigenesis in development. It is a known fact for instance that, in two adult identical twins, neither cerebral organisation nor even the organis ation of the immune system are identical in every detail. *A fortiori* , identity in terms of the psycho-social dimensions of a person is even less of a possibility since it is essentially constituted through and from subjective and biographic individuation which is inexhaustibly singular and by essence cannot be reduced to mere genetic programming. Thus it would be absurd to consider that an adult and his clonal duplicate who must necessarily be born much later, and is bound to have a different life histor y, could be to any degree presented as two copies of a single and identical person. To believe such a thing would be to fall victim to the reductive illusion which is borne by the dismal confusion between identity in the physical sense of sameness (idem) a nd in the moral sense of selfness (ipse).

To throw light on what is mystifying about such a representation of the facts is of importance not just theoretically but also in practical terms. It highlights the superficial nature of some insufficiently thought out objections to prospects of reproduc tive cloning in human beings, but also by the same token, underlines the fallacy of fantasies about reproduction of oneself or of a loved one and about survival of identity which seem to haunt many requests for dev elopment of cloning techniques. Insofar as making conspicuous the totally fallacious nature of such aspirations will contribute to discourage candidates who would also be backers, ethics cannot but benefit.

2. Reproductive cloning : an unacceptable upheaval of the human condition

That being said, two kinds of ethical considerations need attention. To first consider the effects of reproductive cloning on people and their relationships with each other, one cannot help being struck by their unacceptabilit y in conscience.

Although to possess the same genome in no way leads two individuals to own the same psyche, reproductive cloning would still inaugurate a fundamental upheaval of the relationship between genetic identity and personal identity in its biological and cultural dimensions. The uniqueness of each human being, which upholds human autonomy and dignity, is immediately expressed by the unique appearance of body and countenance which is the result of the singularity of each genome. It is true that i dentical twins are in a sense an exception to that rule - but this is a rare, fortuitous exception, and is limited to brothers or sisters born at the same time - and neither one can be seen as a copy of the other. They are more similar than non twins, but each of them is an entirely complete self. One can well imagine the kind of social reality brought about by a production of clones, no longer the fruit of chance and exception, and no longer necessarily coexisting in time. These human beings, individual s in terms of their psyche in spite of their genetic similitude, would be seen in both the literal and the figurative senses of the word, as identical copies of each other and of the cloned individual of which they would truly be a copy. In this way the sy mbolic value of the human face and body as the substrate of the person's uniqueness would be undermined. Unlike Dolly, human clones would know they are clones and would know that others see them as clones. One cannot be blind to the intolerable lowering o f a person to the status of an object that would ensue. Who could guarantee that such a destabilising effect on cardinal social representations would not pave the way for attempts at utilitarian creation of human varieties, which means the creation of ne w kinds of slavery, to which some well-known scientists dare to allude with carefree partiality ?

Allied to the importance of the physical aspects of the human being is the importance of genetic indeterminacy . Respecting the autonomy of a person, and that person's liberty and therefore dignity, is a prescription for accepting *inter alia* one fundamental trait of the human condition : what will become an individual's genetic idiosyncrasy is and must remain essentially out of reach of anyone's decision . The vast lottery of heredity and its inexhaustible uncertainty is in this case a powerful protection for the human being against

parental or social pre-determining decisions. It is true that progress in the field of prenatal and pre-implantation diagn osis pro vides the technical possibility of exempting unborn children from some severe genetic disorders, and also of bestowing upon them certain biological characteristics chosen by their parents. In fact, although this latter possibility is as yet limited, it a lready raises grave ethical problems as regards an individual's autonomy, and justifies legal prohibitions which many countries have already adopted. The possibilities potentially offered by reproductive cloning of human beings is altogether a more serio us concern : predetermination not just of a few, but of all the genetic characteristics of a future human being and thus making of that being a thing produced by those who so decided is what is in question here, be it the cloning of an adult or inducing gem ellarity in the embryonic stage (see part B, paragraph Ia and II). The organism of such an individual would in fact serve as a means of expression of a genome chosen by a third party. Could a project of this nature be judged as being anything but an off en ce against the human condition ?

There is more. It suffices to consider for a short moment the significance of moving away from procreation of a child by the two parents of that child into reproduction of a human being by the equivalent of plant cuttings to measure the dislocation of parenthood, or even of genealogical temporality which such cloning would bring about. There is a paradox in cloning : an individual produced in this way would be the exact chromosomal copy of his originator, but would simulta neously be fundamentally different because production would be of a totally different nature with no fusion of gametes. The possible parental couple become biologically an association between a supplier - male or female - of a cell nucleus, and a supplier of a clone-carrying oocyte. Although anthropologists have described systems of filiation which are very different from those prevailing in our own societies, none of them dispense with two complete biological parents, for the simple reason that they all ar e based on the universal experience of sexual reproduction. Asexual by its very nature, reproductive cloning would therefore inaugurate a mode of filiation highly charged with problems. Furthermore, by blurring family sequences, an individual born by cl oning would be both a descendant and a twin of an adult. The very concept of filiation could become meaningless. As to the coexistence within the same population of individuals born of procreation by two parents, and of others whose chromosomes come fro m a single person by means of asexual reproduction, such a situation could not but lead to inextricable problems of civic identity and also very probably to unfathomable risks of new forms of discrimination.

3. Reproductive cloning : an unacceptable instrumentalisation of a person

No motivation, however convincing it may appear, can possibly legitimate such an appalling project : the end cannot justify the means. However, scrutiny of such possible motivation is well worth while since ethical reflection en counters here the strongest additional reasons for denouncing any reproductive cloning of human beings and also any research likely to achieve this result.

Irrespective of the end purpose alleged in favour of such a project, some of which are presentable and others almost too outrageous to be voiced, they all have in common that their very principle is to plan the birth of human beings not as a result of free choice but as simple instruments at the service of prior objectives which are, despite appearances , totally foreign to them. Reproductive cloning of human beings is therefore unacceptable not just because of its foreseeable effects on the human condition, but also because the very ends in the name of which certain people believe they can justify the scheme is tantamount to making an end in itself of cloning as opposed to the clone. In this way, there would necessarily be an instrumentalisation of the person to be born.

So called medical applications

As though a scheme for reproductive cloning could be viewed as a simple extension of present day or future medical applications of human cell cloning, some tentative allegations are being made to legitimate the project because of possibilities of medical application. Such

claims are a distorti on of the truth. A closer look at these alleged medical justifications reveals that they always conceal insidious or brutal alienation, or even purely and simply the sacrifice of a future person to serve the interests or illusions of others. For this reas on, we believe the notion medical application of reproductive cloning of human beings to be fundamentally inadmissible.

It is hardly worth mentioning at this point cloning programmes in which human beings to be created would be expressly designed to become simple instruments. Such is the case for technical possibilities referred to above (see part B, paragraph Ia and II) when an embryo would be created solely for the purpose of a preimplantation diagnosis or to produce immuno-compatible cells. The c ase is made in even coarser terms in those fantasies describing human beings to be manufactured by cloning to serve as reserves of spare organs for transplantation or to provide labour genetically selected for physical properties suited to certain tasks. In their ambiguous guise of realistic fiction, these ideas contain such monstrous inhumanity that one can only be highly astonished to hear them proclaimed by scientists, some of whom are distinguished specialists. Their attention should be drawn to the et hical discredit which they bring down upon not only their own accomplishments but also on their discipline generally.

Other applications have received mention which, at first sight, concern cloning of individuals as an end in themselves, so that it would appear that there is no question of turning a person into a mere instrument. Such hypothetical uses of reproducti ve cloning are particularly likely to fool well-intentioned persons and must be examined with the greatest care.

The desire to rebuff dea th by any means available

In some cases, the argument of parents wishing to reproduce by cloning a child whose impending early death is unavoidable, has been put forward. As has been emphasised above, a being produced in this way would in fact be a totally different person. Howeve r, by virtue of the child's extreme physical likeness to the deceased, added to the unfounded conviction that a genetic copy is also a copy of the psyche, the clone could appear to be, in the eyes of his parents, a reincarnation of the dead child. Requests for cloning a dying spouse or other loved ones are also formulated. Some individuals, both male and female, have applied to be cloned themselves. In all the fantastic representations which underpin such yearnings, there is the notion that the genome of an individual is endowed with the properties traditionally attributed to the soul, so that its identical reproduction it is confusedly thought to be a reincarnation of the person concerned, to whom imagination promises a new lif e whilst remaining the same person.

Obviously, no one can appoint themselves to rule over the beliefs of others. But in this matter, if the nonsensical identification between a deceased person and his clone were to lead to the birth of a being produced in this fashion, we are no longer in the realm of respecting the belief of others. The issue here is manifest instrumentalisation of a person, and ethics demand that this should be prevented because although very superficially desired as a person in his own r ight, the clone would be a substitute for a phantasmagorical yearning to which he would be totally alien . In no circumstances should biomedical competence be put at the service of such ravings; that way lies scientific and ethical perversion, support given to dreams of magical practices and constructions which outrage human dignity.

Procreative obstinacy attaining absurdity.

Reproductive cloning of human beings is also advocated in some quarters as an acceptable medical application to compensate for insuperable male or female sterility due to the total absence of gamete production (see partB, paragraph I.c). Cloning of an adult cell of a sterile man or woman, possibly using an oocyte contributed by a partner, is presented as a procreation substitut e. In some cases, the couple could well invoke a parental project as French law requires them to do, by offering to use a woman's oocyte to activate a man's cell

nucleus.

But it is important to be aware of the fact that in all such cases, sterility would not be compensated by some new method of procreation. Instead, impossible procreation, i.e. impossibility of giving birth through sexual channels, will be replaced by asexual reproduction, with all previously mentioned consequences. In particular, it mus t be remembered that a child produced in this way will in fact be the twin of the mother or the father, with all the parent's genetic traits, including for that matter possible genome defects which may be the cause of the original sterility. The instrumenta l nature of this child of fantasy is as patent as his complete genetic predetermination . The desire to have children at any cost can in no way justify such actions which transgress the limits of what could be termed procreative obstinacy, reach beyond sexual reproduction and thereby, beyond human nature.

* * *

There is therefore not a single conceivable variation of reproductive cloning of human beings, be it cloning of an adult or of an embryo, which is safe from an accumulation of intractable objections. For all of these reasons, it can only provoke vehement, categorical, and absolute ethical condemnation. Such a practice, which imperils radically the autonomy and dignity of the human person, would be a grave moral regression in the history of civilisat ion. One might well consider whether the concept of degrading violation of the human condition , of which reproductive cloning is a clear example, should not be legally qualified with a view to an universal ban.

III - Legal considerations

The above scie ntific data provide a definition of cloning. *To clone is to produce a population of individuals possessing within the nuclei of their cells a set of identical genes.*

We also learn from the same source that clone populations can be obtained through various methods, spontaneously or experimentally. An embryo made up of a few cells can be split into two or more sections in order to develop clonal embryos; cell nuclei fr om the same embryo which has been allowed to develop for a few days, can be transferr ed to oocytes which have been previously enucleated ; and it is possible to transfer to a recipient oocyte, the nucleus of a cell from an adult organism, and it may be from the same female organism or from another, male or female. It appears that it may be possible to apply such techniques to humans although it is not possible to predict how difficult this might be.

As has been emphasised in the Ethical Considerations above, the National Consultative Ethics Committee proposes that there should be abso lute opposition to such procedures being applied to humans, thus enabling production of an embryo using a somatic or an embryonic cell and its development culminating in the birth of a child. This is described as the birth of a child by reproductive clon ing of a human being.

It is clear that bioethical laws adopted in 1994 do not refer specifically to cloning as defined above. They were not drafted in a situation where experiments such as Dolly could be conceived of for humans. In particular, the pr ospects of asexual reproduction of the species, leading to the birth of a human being who would not be the result of the fusion of gametes, male and female, were not mentioned.

However, studies and research leading to formal legislation all indicate that they referred to the same boundaries which form the conclusions now reached by the National Consultative Ethics Committee.

The CCNE considers that research to establish the possibility of reproductive cloning of a human being, and *a fortiori* , developmenta l assistance after scission of an embryo or

fusion of cells, according to procedures known as cloning, of a viable human being is prohibited by bioethical laws on several counts.

1 - Research on human beings with the purpose of making possible the production of a population with an identical set of genes is contrary to articles added to the *Code Civil* (Civil Code) as a result of the adoption of the law dated 29th July 1994 which was one of the bioethical laws voted at the time.

Article 16-4

No one i s permitted to violate the integrity of the human species.

Any eugenic practice with a view to organising a selection of persons is prohibited. Without prejudice to research for the prevention and treatment of genetic diseases, no modification can be made to genetic traits with the purpose of modifying the desce nt of a person.

For the differentiation process to be re-initiated, there must be either transformation of an embryo resulting from sexual reproduction, or else cells must be altered to enable th eir fusion. One of them, female of necessity, is deprived of its nucleus to serve as a recipient cell. The other is left only with a nucleus which is transferred and its genetic heritage is replicated. All of these modifications are undertaken with the aim of modifying the descent of a person. How can it be argued that these articles could not apply because the result of the procedure possesses the same genetic heritage as the original embryo, or as the nucleus donor cell ? It has indeed been necessar y to remove the nucleus of the recipient cell, whose genetic nature has been modified so that it can be used and with the result that it can no longer transmit its genetic heritage.

Furthermore, this is a modification of the genetic nature of a living being if it becomes possible for it to reproduce without fusion of gametes. Since the human species was established by sexual reproduction, to so fundamentally modify the mode of transm ission of the genome would mar the integrity of the species.

Since the aim is to obtain a new being, identical to either the embryo or the nucleus donating adult, this is a eugenic practice aiming at selection of persons and is therefore prohibited. It is also open to penal sanction, by virtue of article 511-1 of the *Code Pénal* . The only exception to this set of rules is pre-implantation diagnosis.

To the above should be added considerations regarding the ban on conceiving in vitro human embryos for research and experiment. This activity is punishable, one should note, according to article 511-18 of the *Code Pénal* , with seven years of detention and a fine of 700000 French Francs. All operations leading to reproductive cloning include renewed cell division and differentiation and also re-implantation, gestation, and finally a birth. Without any shadow of doubt, a h uman embryo is involved and in a way it is a fortunate circumstance that French legislation does not define an embryo more precisely. No judge, it is felt, could exonerate from this stern sentence an imprudent scientist o n the basis of theoretical arguments to the effect that a being resulting in vitro from fusion of the cells concerned, and who is potentially capable of birth like any other human being, is not an embryo. The text, without any extrapolation required, ap plies to research on in vitro embryo-splitting.

These prohibitions regarding the aims of possible research on human beings, are strongly supported by the *Conseil Constitutionnel* which took the following decisions about the bioethical laws dated 27th July 1 994 : *these laws set out a corpus of principles including primacy of the human person, respect of the human being from the beginning of life, that the human body is unalienable, that its integrity and the principle of non-patrimony must be respected as must also be the integrity of the human species ; that the principles stated above aim to ensure respect of the constitutional principle to safeguard the dignity of the human person.*

They entirely suffice to steer clear of the dangers presently perceive d in research projects.

The foregoing analysis leads to the conclusion that as far as is known at present, there is no need to modify the relevant articles of the Civil Code to ensure conformity with the CCNE's proposals in the name of ethics.

2 - An examination of the second law dated 29th July, 1994, which modified the *Code de la Santé Publique* (Code of Public Health) and ruled on donation and use of products of the human body and on medically assisted procreation, also reveals legal obstacles to cloni ng. As far as is known, cloning in its present form requires a medically assisted procedure which can hardly be said to have been authorised by legislation.

There could not be quite obviously an anticipation of recent discoveries which lead to considering the possibility of reproduction by cloning. The law uses the word procreation which brings to mind engendering and suggests sexual reproduction. The law governed and limited no more than assistance for this form of reproduction of the species, by a ssisted fusion of gametes and within the framework of a parental project. Thus, articles introduced in the appropriate sections of the code of public health define the techniques which are regulated with no mention, for good reason, of any other techniqu e than those which can constitute an embryo by sexual reproduction. This interpretation of the expression medically assisted procreation is exactly the one physicians have in mind when they take care to offer their patients only the re-establishment o f a natural process to remedy a state of infertility.

If another form of reproduction of human population were possible, it does not necessarily follow that it would be authorised by the law we are discussing. It would involve in all cases assistance ranging from the in vitro procedure up to implantation an d the birth of a child. The French law took care to give a particularly broad definition - broader than legislation in other countries - to the practices it regulated.

The new article L. 152-1 of the Co de of Public Health reads as follows :

Medically assisted procreationmeans clinical and biological practices allowing in vitro conception, embryo transfer and artificial insemination, as well as any technique with equivalent effect which enables procreation to take place outside the natural process.

The law continues by specifying situations in which such techniques are admissible and article L. 152-2 limits their use to a couple's parental project. Article L. 152-3 further states that *An embryo ca n only be conceived in vitro within the framework and according to the objectives of medically assisted procreation as defined in article L. 152-2. It must not be conceived with gametes which do not emanate from at least one member of the couple.*

Authorisation concerning what is allowable within the definition of article L. 125-1 is therefore very limiting. Outside the bounds of this authorisation, practitioners may not advocate a method with equivalent effect culminating in a birth which is not a natur al process. It must be remembered on this point that the law did not state that what is not forbidden is therefore authorised. The principle is quite the contrary, according to article L. 665-10 of the Code of Public Health : *The disposal and use of elements and products of the human body are governed by the rules set out in chapter II of title 1 of the first volume of the Civil Code and by the rules set out under the present heading.* Referral is to the guiding principles on research analysed above.

Are also found in the Code of Public Health, stipulations restricting further Article L. 152-8 : *In vitro conception of human embryos for the purpose of study, research, or experiment, is prohibited. Any experiment on the embryo is prohibited*

It would be hardly conceivable, without actual duplicity as regards the law, to allow the continuation of research which follows scission of an embryo or the activation of a process

of differentiation in vitro after fusion of cells, whereas any research w hatsoeve r using an embryo which is the result of the fusion of gametes is banned. On this occasion again, the impossibility of defining an embryo is of help since it makes it possible to encompass the process leading to a birth by reproductive cloning.

Work accomplished before enactment, in particular the report from the *Conseil d'Etat* entitled : From Ethics to Law *(De l'éthique au droit)* categorically classified research with the aim of modifying artificially the human genome which is passed on to descendant s, and research aiming to achieve an entire gestation in vitro, or parthenogenesis, cloning, or the production of chimeras, as totally prohibited whatever the circumstances. The Lenoir report also stated that *certain medical practices and research are or will be of a nature that endangers the continuity of the human species and the identity of man. This would be the case of creation of human clones...* To negate all these arguments, it would be necessary to state that the process which would precede im plantation in a cloning operation is unrelated to an embryonic process. This is not easy to defend.

Consequently, existing stipulations of the Code of Public Health should be sufficient deterrent to any tentative offer, in response to appeals for a child, of one or other of the techniques which ongoing experiments with animals lead us to reflect upon. They make clear that research which would be required to apply such techniques to mankind is illegal. Government and public opinion should therefore harbou r no fears on this point.

3 - The Committee considers that debate on the subject of recent scientific discoveries has served to confirm the soundness of principles enacted in France in 1994. Whilst expressing firmly a basic concept, namely the protection of human dignity which led to a ban on procedures which could modify a person's descent, on a more technical matter legislation provided a status for medically assisted procreation. The CCNE is unanimous in thinking that an analysis of the situation create d by the Dolly experiment does not motivate a renewed examination of principles involved.

The law, as it stands now, and supported by its examination by the *Conseil Constitutionnel,* condemns reproductive cloning of a human being. There is no need for new legislation except for purposes of clarification. The CCNE considered whether the ban needed to be further elucidated.

As a first step, the Committee agreed that it would be useful to complement in this way stipulations appearing in the Code of Public Health. This text, as stated above, regulates medically assisted procreation and clearly makes no reference to totally different techniques which could lead to the reproduction of a human being by cloning. No properly informed person could conclude ther eby that such practices are permitted. But to dispel any doubt, one could simply declare that none of the stipulations in the Code of Public Health regulating medically assisted procreation and the status of the embryo can be interpreted to mean that repr od uctive cloning is permissible. If clarification is considered useful, which the CCNE believes, if only to make it plain that medically assisted procreation must remain separate from subjects presently debated, then in order to do so there is no need to w ait until the end of the five year period before revision.

On similar lines, the ban could be elucidated by adding a sentence to the end of article 16-4 of the Civil Code as follows : Are and remain prohibited, in particular, practices aiming to reproduc e human beings by cloning. As can be observed, this wording is an interpretation and an illustration by means of an example, of the principle already stated in the existing text.

As to whether such an addition is appropriate, opinions within the CCNE differ.

In favour of adding to the existing text, the following arguments were put forward. The ban on reproductive cloning would be expressed in the most formal manner by inclusion in fundamental legal assertions on the subject of the protection of the hu man body and the

dignity of the human person. By adopting legislation on this point, our country would be expressing forcefully and in clearly understandable terms a position which it would like to see shared abroad. If the legislative authorities inter vene to provide an indisputable interpretation of such fundamental rules, such action will serve as an example and a model.

But in an opposing argument, expressed no less forcefully, it was argued that it would weaken principles so excellently stated in a rticle 16-4 if were added any explicit and specific prohibition. Scientists have in particular underlined that it would be conceivable, even at the present time, to mention other disquieting or reprehensible prospects and that to state safeguarding princi ples, in the long run can only be detrimental if they are continuously added to as and when various aberrations suggested by new discoveries come to mind. This particularly important article of the Civil Code could be overburdened with a long list of bans a nd forfeit its positive universal scope. A society which has agreed on a most solemn assertion of principles safeguarding human dignity has nothing to gain by periodically reopening a Pandora's box of the more bizarre scientific applications.

The task of arbitrating this discussion which the CCNE hopes it has clearly represented, will fall to policy makers.

The legal concept which has just been formulated, i.e.that are and remain prohibited, in particular, practices aiming to reproduce human beings by cloning, can in any case serve as the keystone for positions defended by France internationally.

The real issue in the immediate future is to see to it that the strict position adopted by French law which recent events reinforce, influences measures which will without doubt be taken internationally. This should be feasible, since many countries share the same preoccupations and no existing international instrument threatens the positions which have just been described.

The World Health Organisation publi shed a declaration on 11th March 1997 according to which *the use of cloning for the replication of human individuals is ethically unacceptable as it would violate some of the basic principles which govern medically assisted procreation. These include respect for the dignity of the human being and protection of the security of human genetic material.*

A Convention of the Council of Europe on Human Rights and Biomedicine has just been signed in Oviedo by 21 states. It contains, as does French law, the s olemn statement that human beings must be protected in their dignity, and it adds, in their identity. It guarantees to all without discrimination respect of their integrity and other fundamental rights and freedoms with regard to the application of biolo gy and medicine. It could therefore be thought that it is inspired by the same principles as French law and should be interpreted as meaning to ban reproduction of human beings by cloning. There is, however, an ambiguity because it gives a partial list of f orbidden practices, in particular on the subject of the human genome. Although sexing is mentioned in this context, cloning is not. Absence from the list could lend itself to debate and all the more so since it is also said elsewhere that research activit ies shall be carried out freely, subject to the provisions of the present Convention and other legal provisions ensuring the protection of the human beings being observed. It therefore seems essential that an addition should be made in some appropriate fo rm to complete this international instrument with a view to prohibiting reproductive cloning.

The European Parliament has requested that common rules should be adopted throughout the European Union. In this case it will be necessary to make sure that inevitable compromise and hazier language as a result of negotiation on particularly difficult sub jects do not complicate the legal situation. It should be noted that such texts once their conditions of application are obtained, supersede national legislation wh ich is a serious safeguard.

To illustrate the problem, it is worth referring to the present situation in the United

Kingdom, which is the country where the most spectacular form of cloning an animal took place. A report of the Science and Technology Committee of the House of Commons, published 18th March 1997, shows that a debate is about to take place, of the same kind as has been the case in France, on whether to complement legislation in force at the moment. The Human Fertilisation and Embryology act 1 990, bans in section 3(3)(d) replacing the nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo, or subsequent development of an embryo. Legal opinions given to Parliament conclude that should the case arise, an extensive definition of an embryo would be adopted which should cover the Dolly case. But the Commission is of the opinion that definition of the embryo is not legally suffici ently safe, and recommends a review and extension of this definition, and to expressly ban intentional creation by artificial means of two or more individuals whose cell nuclei had identical DNA. The conclusion of this report is therefore to introduce into legislation a prohibition of cloning as defined above. But this is still in the for m of a Parliamentary Commission report and one can easily imagine the subtlety of discussion which will be needed depending on the context in various countries.

In conclusion, the Committee considers that the development of practices aiming to make identic al reproductions of a human being and research which could achieve such purposes, should be opposed in every possible fashion. There is ample reason in view of the present situation why our country should take initiatives on the international scene which are necessary for that point of view to prevail. The stake is human rights and dignity inasmuch as those principles are universal. That is why an appeal to global conscience must be made at the highest possible level and very probably, an initiative in fa vo ur of a resolution by the General Assembly of the United Nations to proscribe reproduction of human beings by cloning would illustrate the universal nature of the condemnation that appears necessary. A French initiative in that direction could find suppo rt in the firm principles agreed by legislation in 1994 and on the quality of the discussion which served as preparation for present developments.

Conclusion

The National Consultative Ethics Committee, since its creation, has considered on numerous occa sions new problems arising out of scientific and medical progress as it applies to the beginning of life. The question put to the Committee by the President of the French Republic leads that reflection a further step forward. Were humanity to replace pr ocreation by cloning technology, a momentous break with the past and a serious threat to human dignity would be made.

In the act of procreation, a man and a woman contribute jointly to engendering a person whose characteristics cannot be foreseen and cann ot be equated to those of the genitors, thus furthering the recognition and protection of that person's singularity and autonomy; these are two essential elements of the human condition and dignity.

If reproduction of human beings by cloning became a technical possibility, it is to be feared that its use would be demanded by those who claim it responds to so-called clinical indications, to the fantasy of immortality, or the desire for genetic perpetu ation at any cost by those who cannot procreate.

An atte mpt at identical reproduction of human beings whose genome would no longer be the result of the lottery of heredity and instead depend on another's will, would seriously endanger essential original indetermination as well as other fundamental traits o f a person. Furthermore, a person so created would become means in the service of an alien end. Such an undertaking must be proscribed once for all.

French law passed on 29th July 1994 reforming the Civil Code and the Code of Public

Health, does not expl icitly mention the cloning of human beings, but there is every indication that the legislative body intended to ban it.

Indeed, article 16-4 of the Civil Code appears to prohibit any practice which aims to modify the descent of a person. That is what cloning would do.

As for article L. 152-1 of the Code of Public Health, it states that an embryo can only be conceived within the framework.../...of medically assisted procreation, which would seem to exclude absolutely a non procreative method su ch as asexual reproduction.

It is for the decision of the legislative body to consider whether more explicit language should be used to ban the use of methods aiming to make identical reproductions of humans . A revision of normative texts concerned could be required.

For its part, the CCNE reaffirms the fundamental distinction which must be drawn between non reproductive cloning of human cells which cannot themselves engender human beings - a customary and long established practice for the purpose of res earch and biomedical analysis - and reproductive cloning to bring about the birth of a child.

The use of such reproductive cloning techniques for the purpose of engendering humans imperils to such an extent the human condition and dignity that global collaboration becomes essential so that all the nations of the world find means to save themselves from this danger. As on so many occasions throughout history, France might well sponsor a major initiative in various international fora to uphold Human Rights.

Notes

1. Eukaryotes : organisms made up of cells with a nucleus containing genetic material

2. **Procreation in a couple in which the woman has a mitochondrial disorder.** Certain diseases, not exceptionally, are due to mitochondrial genome alteration. Such affections can be extremely severe and give rise, in particular to muscular, neurological, and metabolic disorders or sometimes to blood diseases. They are inherited on ly in the maternal line, potentially to all their offspring. To be certain that children are n ot affected, the only solution so far is adoption or oocyte donation. The desire on the part of both spouses to achieve biological filiation could be satisfied by nuclear transfer of the couple's embryo, obtained by in vitro fertilisation of the mother's oocytes by the father's sperm, into a enucleated oocyte donated by a healthy woman. Another possibility would be to transfer before fertilisation the maternal oocyte's nucleus into the donor woman's oocyte.