No. 3498

NATIONAL ASSEMBLY

CONSTITUTION OF 4 OCTOBER 1958

TWELFTH LEGISLATURE

Recorded at the Presidency of the National Assembly
6 December 2006

No. 101

SENATE

2006 – 2007 ORDINARY SESSION

Annex to the minutes
of the sitting of 6 December 2006

PARLIAMENTARY OFFICE FOR SCIENCE AND TECHNOLOGY ASSESSMENT

REPORT

on

RESEARCH ON THE OPERATION OF HUMAN CELLS

By Mr Alain CLAEYS,
Member of Parliament

Tabled with the Bureau
of the National Assembly
by Mr Claude BIRRAUX,

First Vice-President of the Office

Tabled with the Bureau of the Senate
by Mr Henri REVOL,

President of the Office

Composition of the Parliamentary Office for Science and Technology Assessment

President
Mr Henri REVOL

First Vice-President
Mr Claude BIRRAUX

Vice-Presidents

Mr Claude GATIGNOL, deputy
Mr Pierre LASBORDES, deputy
Mr Jean-Yves LE DÉAUT, deputy
Mr Jean-Claude ÉTIENNE, senator
Mr Pierre LAFFITTE, senator
Mr Claude SAUNIER, senator

Deputies

Mr Jean BARDET
Mr Christian BATAILLE
Mr Claude BIRRAUX
Mr Jean-Pierre BRARD
Mr Christian CABAL
Mr Alain CLAEYS
Mr Pierre COHEN
Mr Francis DELATTRE
Mr Jean-Marie DEMANGE
Mr Jean DIONIS DU SÉJOUR
Mr Jean-Pierre DOOR
Mr Pierre-Louis FAGNIEZ
Mr Claude GATIGNOL
Mr Louis GUÉDON
Mr Christian KERT
Mr Pierre LASBORDES
Mr Jean-Yves LE DÉAUT
Mr Pierre-André PÉRISSOL

Senators

Mr Philippe ARNAUD
Mr Paul BLANC
Mrs Marie-Christine BLANDIN
Mrs Brigitte BOUT
Mr Marcel-Pierre CLÉACH
Mr Roland COURTEAU
MrJean-Claude ÉTIENNE
Mr Christian GAUDIN
Mr Pierre LAFFITTE
Mr Serge LAGAUCHE
Mr Jean-François LE GRAND
Mrs Catherine PROCACCIA
Mr Daniel RAOUL
Mr Ivan RENAR
Mr Henri REVOL
Mr Claude SAUNIER
Mr Bruno SIDO
Mr Alain VASSELLE

SUMMARY

Introduction

Biotechnologies are often presented as the third phase of the technological revolution of the post-war years after the development of nuclear power in the 1950s and 1960s and that of new information technologies in the 1970s and 1980s.

Biotechnologies arose with the great genetics adventure which culminated with the deciphering of the genome, mainly that of mankind. Genome deciphering has helped to begin to understand the structure of living beings, without however leading to an understanding of the operation of life and even less to its mastery.

This knowledge will come perhaps when we know the exact operation of cells, the areas confined by a membrane which obey the laws of physics and chemistry and which are common to all living beings.

Cells were the subject of a genuine rediscovery at the time of the birth of Dolly, the first mammal cloned from adult cells. Since that relatively recent date, barely a decade ago, the interest for cell biology has not weakened.

The work by Mr James Thomson, who managed to create the first human embryonic stem cell lines in 1998 was to give a new impetus to cell biology. Since then it really has been at the heart of current events with its advances, failures, scandals, controversies, hopes and also fears.

This field is highly controversial for we realise the extent to which it can transform our lives.

On the one hand, there are the hoped for benefits: new diagnosis methods and new therapies. On the other hand, there are the new threats with the possibilities of the re-emergence of eugenics.

The debate on embryonic stem cells has reactivated the debate on the embryo which is presented as the main ethical problem and as a fatal obstacle to the use of embryonic stem cells. I will not address this issue in this report as I feel it is first and foremost a matter for everyone to decide in his heart and soul.

As I already stated in December 2003, during the examination in second reading of the bill on bioethics, **the protection of mankind is central to bioethics legislation**. The latter must be confronted with the realities of research and emerging knowledge. It must be placed at the service of a living society and living research.

In order to respect the dignity of human persons, bioethics legislation absolutely must reconcile three principles:

- Freedom of thought, in other words freedom of the researcher who must know what limits society intends to set for his activity;

- The rights of the sick and of the handicapped to have their sufferances lessened and their hopes for a cure raised, which requires research and experimentation;

- Respect for the human person and body.

These principles apply all the more to stem cells as they are the basic elements of our life.

Two ethical issues will be addressed for they are at the heart of the debates: the issue of ovocyte donation for research, and marketing. I wish to add scientific fraud, even if it is a marginal problem. It must be fought as it can make citizens lose confidence in science.

This report devoted to the operation of living cells will focus on the issue of adult and embryonic stem cells.

I have made this choice for I wanted to expose with the greatest clarity, openly and without any preconceptions, the real situation in this field which is too often the subject of overly flattering or overly critical papers. Another reason for this choice is to prepare parliamentary work which, at the latest in 2009, as laid down in the bioethics Act of 2004, must again address the issue of embryo research and decide whether nuclear transposition[1] can be authorised in France.

It is indeed a matter of 'nuclear transposition' for I have banned from this report the expression 'therapeutic cloning' that is employed in a facile manner and also fallaciously.

It is a misleading expression.

For its opponents, the accent is placed on the word *'cloning'* and this technique is likened to human reproductive cloning which nobody in his right mind defends.

For its supporters, the accent is placed on *'therapeutic'* and can have us believe that we are on the brink of using this technique to cure, in particular, terrible diseases that are still unfortunately incurable. Nobody in fact knows at

[1] Translator's note: 'Transposition nucléaire', otherwise widely known as 'nuclear transfer'.

present whether this technique will be used one day and, if it is, will it help obtain what can theoretically be hoped for.

I have made this overview of the stem cells field by enrolling the help of a steering group whose composition is given in an annex to this report. May its members be thanked.

I also wish to express my gratitude to all the people who accepted my request to hear them in the public hearing. The account of the hearing appears towards the end of this report. I felt this method was one of the most effective, in addition to the rapporteur, to inform public opinion of the main challenges of this field.

Contrary to custom, the account of the public hearing was published before the rapporteur's conclusions came out. That was my wish as, at the time, we were in the middle of what has been dubbed the 'Hwang affair'. It was important to let the voices of researchers be heard at a time when one of them was beginning to be highly suspected of having seriously infringed scientific deontology.

I was in Korea, after having gone to Japan, when the 'Hwang affair' broke out. The disappointment of Koreans when they heard of the fraud became very clear to me. My desire to take stock of this matter as exactly as possible also led me to the United States, Great Britain, Brussels, and Munich, to the European Patents Office. They were action packed and enthralling trips.

In the first two parts of this report, I review what has been dubbed the 'genomic revolution' and give a rapid presentation of cells, the basic element of life. In the third part, I then address the issues of stems cells by presenting them first of all with their potential applications. I underscore the need to pursue research, in the fourth part, by taking stock of the present organisation of research in France and various other countries, before insisting, in the fifth part, on the challenges to be faced in this field.

First part:
Where does the 'genomic revolution' stand?

The pioneering description of the double helix structure of deoxyribonucleic acid (DNA) in 1953 by James Watson and Edward Crick raised the veil on the physico-chemical nature of the gene.

This discovery heralded the start of considerable research and the mapping of a certain number of genomes, among which those of the mouse, cow, pig, rice and also thale cress (*Arabidopsis thaliana*).

Such mapping has allowed the precise establishment of correlations between the presence of a gene in a specific form, and an hereditary disorder or an interesting biological or agronomic property. This knowledge allows the rapid and precise selection of individuals bearing the form of the gene responsible for the sought biological property. Vegetal and animal selection programmes based on the use of these genetic markers are therefore now used on a large scale. This has led to the notorious genetically modified organisms (GMOs).

At the same time, the beginning of the 1990s saw the commencement of the great adventure of the deciphering of the human genome which was to be concluded in 2003. As it advanced, great enthusiasm overcame the scientific and media world for what has been called the 'genomic revolution'.

This 'genomic revolution' appeared highly promising but the promises have not materialised.

A – The great promises of the 'genomic revolution'

The 'genomic revolution' has been built on the hypothesis that the gene is the basis of life, which has led to the development of a certain number of prospects banking entirely on genes.

1 – The gene as the basis of life

This hypothesis developed following the work in the United States at the end of the 1930s and beginning of the 1940s, when the 'one gene - one enzyme[2]' equation was posited.

The discovery of the double DNA helix gave new significance to this hypothesis. It can indeed be understood as the establishment of a direct correspondence between a gene nucleotide sequence and a protein amino acid sequence. The sequence of nitrogen bases along the molecule act as genetic code, transmitting information from generation to generation unchanged. The gene then switches from a conceptual entity to a material entity.

Put simply: DNA is the molecule which not only conceals the 'secrets' of life but also executes its own encrypted instructions.

From that time on, the DNA of a cell was seen as the genetic programme, like the original language. DNA bases were likened to letters, genes then becoming words. With these words, text, in other words the genetic sequence, is then formed. The DNA 'book of life' metaphor was then created. It encountered great success and has been used in copycat style, especially by the media.

A reductionist vision of biology therefore developed which was very influential during the development of the human genome deciphering programme. DNA was assigned a central and almost exclusive role in the operation of organisms and this fuelled the prospects banking entirely on genes.

2 – Prospects banking entirely on genes

These prospects, which then attracted attention, resided in the hopes of curing by introducing one or several genes into the body.

Many genes in question in many disorders have been discovered. This has been the case, in particular, with diabetes, some cardiovascular diseases, breast cancer, Duchenne myopathy or mucoviscidosis… This entirely real and substantial progress in knowledge on the mechanisms of a certain number of disorders was immediately accompanied by the idea of 'correcting' these dysfunctionings by gene therapy.

Gene therapy is the operation consisting in introducing a functional gene into the cells of an organism for preventive, curative or diagnostic purposes. The Act of 28 May 1996 defined gene therapy products as 'biological products with a therapeutic effect aimed at transferring genetic material so as to obtain *in vivo*, the

[2] An enzyme is a protein.

expression of one or several genes of interest, in a target cell, for a therapeutic, diagnostic, or marking purpose'. The introduced gene(s) can either replace the function of a defective gene or control the synthesis in the organism of a therapeutic protein. Among the indications of gene therapy, mention could be made, in addition to monogenic diseases like mucoviscidosis, of many acquired disorders like cancers, Alzheimer's disease, and atherosclerosis…

Two approaches to gene therapy can be distinguished: **germ gene therapy and somatic gene therapy**. The latter affects only the treated individual whereas the former, by modifying germ cells (spermatozoons, ovocytes) produces a permanent effect on all the descendants of the treated organism. For obvious ethical reasons, it is limited to animals.

The idea of introducing one or more genes into an organism for therapeutic purposes appeared all the more appealing as it helped to avoid the difficulties and delays in developing conventional treatments. The latter, as noted by Mr Bertrand Jordan[3], indeed generally imply a detailed understanding of the disorder, then the discovery of agonists or antagonists acting on the key elements of the regulations affected by the disease. The introduced gene(s) were considered as drugs, as clearly evidenced by the 'DNA drug' expression then in vogue.

Genome deciphering programmes then mobilised large-scale means with, in particular, the use of high-performance and very sophisticated data processing techniques. It is to be noted that private funding, especially in young start-ups, was very high.

The promises of therapeutic applications were, already, highly publicised. As recalled by Mr Bertrand Jordan in the quoted article, in 1995 the brochure presenting the American gene therapy programme was entitled 'From Maps to Medicine'. In France, it was the Telethon which, for the first time, brought gene therapy out of the shadow of laboratories and into the public realm.

The prospects of the sector's turnover were in unison with the hopes: accordingly, in 1994, the turnover was estimated at twenty billion dollars for the year 2006…

Scientific journals were equally bullish: *La Recherche* bore the headline in 1985: 'Traitement des maladies génétiques : le compte à rebours' ('Treatment of genetic diseases: the countdown'); *Science* published in 1990 an article entitled: 'Thérapie génique : le but en vue' ('Gene therapy: the goal in sight').

It must be admitted that the enthusiasm then brought about by the deciphering of the genome has remained completely out of proportion with the modesty of the benefits derived from it by patients. For instance the HIV genome

[3] In *Médecine/ Sciences* no.5 volume 22 May 2006.

was sequenced in 1985 but no solution to combat it has been developed over the past twenty years.

From this point of view, the promises of the 'genomic revolution' have not yet been delivered.

B – Promises have not yet been delivered

These promises have not been delivered as genetics has focussed on identifying genomes and on describing the network of molecular interactions, without making any headway with understanding how an organism operates. There is still an abyss between what was hoped and what has currently been achieved. This should not be forgotten when we address the issue of embryonic stem cells.

The functions of genes for instance have still not been elucidated, and a certain number of difficulties have hindered the development of gene therapy. These obstacles make it necessary in fact to go beyond the gene, towards the study of the cell.

1 – Gene functions have not been elucidated

In my previous reports presented to the Office[4], I had already largely addressed this issue.

I will simply recall that, in the great majority of cases, genes merely allow the production of the elementary components of the living being which, by combining in complex networks, create the characteristics of these organisms. Each gene has an elementary function used by the organism to accomplish many complex and different functions, each complex function resulting from the participation of hundreds or thousands of genes.

Reductionism, consisting in making the complex structures of living organisms depend on a few genes, should be abandoned. It has, for instance, been progressively discovered that the same genes are to be found in different species with different functions. The same gene can be found in the same organism, with different roles, depending on the type of cell and stage of development.

Genetics must therefore take account of the intracellular environment of genes, in other words not only of other genes, but also of proteins and other molecules. The activity of genes as a whole is to be considered as an integrated

---

4 'La brevetabilité du vivant' ('Patentability of living organisms') (2001).
'Les conséquences des modes d'appropriation du vivant sur les plans juridique, économique et éthique' ('The economic, legal, and ethical consequences of the methods used to appropriate living organisms') (2004).

activity in close relationship with their environment, as the DNA sequence does not suffice to explain the diversity of cells and organisms.

This new approach has led to an important new concept: epigenetics.

2 – Concept of epigenetics

The term 'epigenetics' coined by the British geneticist Conrad Waddington at the beginning of the 1940s, literally means 'outside customary or conventional genetics'.

Epigenetics formalised heredity using two concepts: the phenotype, the appearance and all the inherited individual characteristics; and the genotype, all of the units of heredity, genes.

Molecular biology had explained in an apparently satisfactory manner the issue of the transmission of characters by designating the DNA molecule as the only and unique bearer of heredity. But a contradiction remained: how can it be explained that all organisms or all cells having inherited the same chromosomes or genes do not necessarily present the same phenotype?

A certain number of explanations can be advanced, one of which is the existence of epigenetic differences, in other words differences at the level of the genome mode of expression.

In effect, DNA is not present in the form of bare molecules in the cell. It is combined with proteins called histones and forms a complex substance, chromatin. Any chemical change in DNA or histones alters the structure of chromatin without modifying the DNA nucleotide sequence.

Epigenetic variation is therefore a modulation of the expression of genes or of groups of genes which, unlike mutation, does not involve a modification in the structure of DNA.

Epigenetic variation also exists in plants and is studied under the name of paramutation. It is characteristed by its property of being not only stable during the development of an organism at the somatic level but also of being transmitted to descendants during crossing and over several generations at the germ level, with distributions different from those predicted by Mendel's laws.

These modifications are still quite ill-known and depend on the environment of the genome in a wide sense. The important thing, as mentioned by Mr Michel Morange[5], is that these epigenetic mechanisms concern cell

[5] In *Médecine/Sciences* no. 4 volume 21 April 2005, page 368.

differentiation and embryonic development: this epigenetic regulation is kept in a stable manner during cell division, mitosis.

However, we must not pass from 'banking entirely on genes' to 'banking entirely on epigenetics' for, as emphasised by this author, *'the gene can be deconstructed ad lib'* but it must not be forgotten *'that the structures and functions of living beings are based on the properties of complex macromolecules',* organisms having created a sophisticated and precise mechanism to reproduce their primary structure. He therefore considers that *'the idea of a genetic programme was an unwarranted extension of this mechanism of reproduction of macromolecular components to the entire organism: the genetic programme notion no longer exists today except in the form of a vague metaphor'*.

Without rejecting all the achievements of genomics, it must therefore be gone beyond to integrate in it all the possible epigenetic variations which are going to come from its environment in the wide sense. This will be important as regards the culture of cell lines where, in particular, the conditions of their culture can be decisive.

This broadening of prospects is all the more necessary in the face of the difficulties of gene therapy.

3 – Difficulties of gene therapy

The popular interest for gene therapy has come up against its complexity for it has become more of a general principle than a precise technique. In effect the methods used have become extremely diverse.

The methods differ depending, for instance, on whether the aim is to obtain the production of an active protein replacing a lacking or inactive protein for hereditary disorders or to combat diseases like cancer or AIDS. The techniques for transporting the gene into cells are also highly varied and may be linked with other strategies, especially vaccinal, which further complicates the process.

Roughly speaking, several types of difficulties are encountered:

- Difficulties in targeting diseased cells and risks of the organism rejecting gene therapy products;

- Difficulty in elaborating viral vectors which may well attack a multitude of target cells;

- Problem of the efficacy of non-viral vectors, such as liposomes, which must be employed in such quantities that toxicity problems may arise;

- Difficulty in obtaining the correct regulation of the gene which may well integrate into an inappropriate chromosomic region;

- Financial obstacles due to the sheer volume of investments necessary for research, for the production of vectors and for patient care establishments.

In July 2006[6], there were 1192 ongoing gene therapy trials worldwide with the following aims:

. Treatment of cancers: 797 (66.9%)
. Vascular diseases: 106 (8.9%)
. Monogenic diseases: 102 (8.6%)
. Infectious diseases: 78 (6.5%)
. Genetic marking: 50 (4.2%)
. Healthy volunteers: 19 (1.6%)
. Other: 40 (33 %)

The progress of these 1192 ongoing trials, in July 2006, clearly shows the still largely fledgling nature of gene therapy:

. Phase I: 743 (62.3%)
. Phase I/II: 242 (20.3%)
. Phase II: 169 (14.2%)
. Phase II/III: 12 (1%)
. Phase III: 26 (2.2%)

According to Mr Bertrand Jordan[7], the technical problems *'have been worsened by the haste with which we have sometimes proceeded owing to the competition between teams and (above all) between companies in a hurry to stake their place in a promising market.'*

Mr Bertrand Jordan feels however that 'it should nevertheless not be concluded that gene therapy is today in a blind alley.' He quotes a certain number of areas of progress, especially the new possibilities of transferring a gene so that it integrates into a pre-defined place of the genome, and the use of micro RNAs.

It is also necessary and essential **to bear in mind the success of the gene therapy implemented by Mr Alain Fischer and Mrs Marina Cavazzana-Calvo regarding the severe combined immunodeficiency syndrome (SCID-X1)**. Owing to this serious immune deficit, affected children were forced to live in a sterile shelters ('bubble babies') to avoid exposing their immature immune system to environmental germs. **The introduced gene helped the immune system of these children to develop and re-established its normal operation. Admittedly, three leukemias and one death are to be deplored but twenty or so children**

[6] Source: http://www.wiley.co.uk/genmed/clinical/.
[7] In the article quoted *supra*.

are living a normal life thanks to this treatment. For other disorders, such as haemophilia and mucoviscidosis, the trials have come up against immune difficulties and have not been successes.

Gene therapy techniques must not however be abandoned but improved by going beyond what some authors have called the 'gene paradigm', in other words the explanation of all life's mechanism by genetics.

Mr Jean-Claude Ameisen[8] has made this link between genetics and cell biology in a very enlightening manner:

'An essential dimension of the complexity of living beings arises from the fact that cells and bodies can use their genes in highly different manners and that, with an identical genome, different potentialities are going to open up in different environments. All the cells of our body, apart from a very few rare exceptions, possess throughout our life exactly the same genes. Their capacity to become and remain stem cells, or to transform into one of the two hundred families of differentiated cells of our body, is due to the fact that each cell does not use its genes in the same manner. The interactions, partly haphazard, which each cell establishes with its neighbours lead to more or less reversible changes in the accessibility of some of their genes, and therefore different manners of use of these genes. In other terms, the external environment of the cell will influence the elaboration of its internal environment, which itself will influence in turn the possibilities the cell has with its external environment. This underscores the ambiguity of the widespread notion of a 'genetic programme'. ***Genes do not determine the future: they give cells a certain number of constraints and potentialities – a field of possible outcomes – and what actually happens will depend on the specific history of the interaction of the cell with its environment'*** [9].

It is therefore necessary to go beyond the level of the gene and study the cell.

4 – Beyond the gene: towards study of the cell

I feel that the present limits of functional genomics as well as the increasing interest in stem cells testify to major renewed interest in cell biology.

We are indeed witnessing a genuine revival of issues in which society is taking an increasing interest, such as reproduction and development, old age, and the operation of the brain. Current events are also showing that issues considered as solved are resurfacing like, for instance, questions related to the

[8] At the pulic hearing of 22 November 2005.
[9] I put the sentence in bold

study of infectious agents. The latter have been greatly neglected owing to the existence of antibiotics and this remark is even clearer in the face of the new threats, like the persistence of avian influenza or the development of epidemics like chikungunya.

Therefore a certain number of notions have become very topical again. For instance, matters related to the organism's defence and what is called, using a very ancient term, 'virulence', remain largely unknown. Virulence indeed covers very little known mechanisms like, for instance, the penetration of pathogenic agents into the organism's cells.

All these matters, reproduction, ageing, cognition, and the balance between man and microbes are of course not recent, but it must indeed be acknowledged that they have been somewhat marginalised by genetic engineering and genomics.

It will certainly be necessary to return to the study of complex living beings and the operation of the cell in its various dimensions.

Second part:
the cell is the elementary unit of life

In this second part, the organisation of the living cell and its operation will be outlined.

A – Organisation of the living cell

The cell is the basic unit of living beings. Any organism, from the simplest to the most developed, is composed of cells, from a single one to several billion in a very coordinated set. Cells give organisms their capacities, whether first of all keeping them alive and allowing them to reproduce or, turning to animals, allowing them to move thanks to their deformation possibilities.

We will address the organisation of the living cell and its operation.

The invention of the microscope, at the end of the XVIIth century, was to pave the way for the exploration of the structure of living organisms on a scale invisible to the bare eye. The observation of plant tissues allowed cell organisation to be discerned for the first time.

It was then necessary to wait for the beginning of the XIXth century and the development of microscope optics for the accumulation of observations made among animals and plants to form the basis of a unifying theory: cell theory. This theory was expressed in 1839 by the German physiologist, Theodor Schwann, according to whom any living being is formed of cells and only of cells. This theory was established definitively by Rudolf Virchow's famous axiom in 1858: '*Omnis cellula e cellula*': any cell derives from another cell.

Cells are minute compartments that exist among all living beings, animals or plants.

Cell organisation moreover determines two major families of living beings: procaryotes and eucaryotes.

Procaryotes were probably the first living beings on Earth. They are unicellular organisms characterised by the absence of a real nucleus. Their present-

day descendants are bacteria of which two different categories are known: archeobacteria and eubacteria.

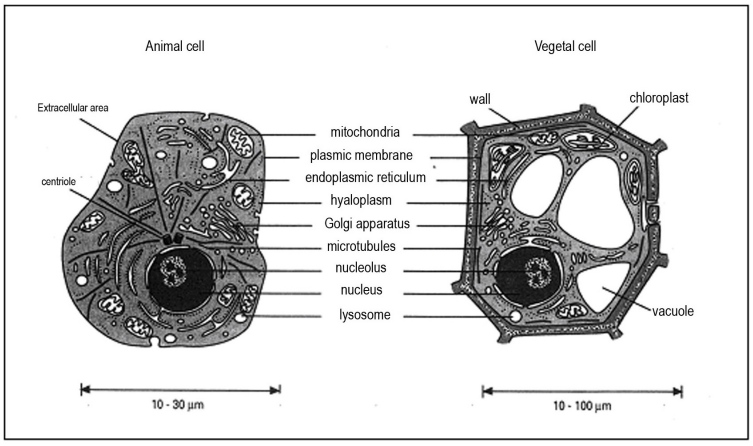
Archeobacteria are abundant in nature today and populate very inhospitable environments: very salty waters, thermal sources with a temperature exceeding 70°C, highly acid waters.

Eubacteria are far more common and comprise, inter alia, Gram-positive bacteria, spirochetes, myxobacteria, cyanobacteria, etc.

Eucaryotes are organisms whose cell(s) are composed of a genuine nucleus delimited by a nuclear membrane, several chromosomes, a nucleolus and intracytoplasmic organelles with a complex structure.

Eucaryotes comprise pluricellular species (animals, plants, mushrooms) and unicellular species (protists: paramecia, unicellular algae, baker's yeast, etc.).

Eucaryote cells, although possessing considerable similarities, present differences in animals and plants as shown by the following diagram:



The cell is the basic unit of all living organisms. A human being possesses more than a hundred thousand billion of which there are approximately two hundred different types. Cells feed, produce energy, exchange information with their surroundings, multiply and die after a certain length of time.

As seen in the previous diagram, animal and plant cells present a certain number of differences which we will address successively.

➥ Animal cells

These generally appear as small bags of a dimension from 10 to 30 µm[10]. However some of them can reach large sizes. This is the case, for example, with nerve cells whose prolongations can exceed a metre in length, or with eggs composed of a single cell.

Cells are delimited by a membrane and have a nucleus at their heart. The nucleus is a small flexible sac containing deoxyribonucleic acid (DNA), the bearer of genetic material and which controls all cell activity. Cells are isolated from the outside by a plasma membrane that allows some substances to pass and stops the passage of others.

Other internal membrane systems, forming the cytoplasm, delimit compartments, or intracellular organelles, each having a specialised role:

- Mitochondria, which supply the necessary energy for cells to operate. Their number, from a few to several tens of thousands, depends on the intensity of cell activity, a muscle cell, for instance, having a very large number;

- The endoplasmic reticulum, which plays an important role in the processes of secretion, the synthesis of proteins, of steroids and of lipids, and in the intracytoplasmic transport of various substances;

- The Golgi apparatus, composed of vesicles and cisternae, which plays an important role in cell metabolism by ensuring the glycosylation of proteins, and the concentration of substances elaborated by the endoplasmic reticulum and their transformation into secretion products;

- Lysosomes degrading and recycling cell structures;

- The nucleus, which is the vital centre of the cell. It comprises the nucleolus and chromosomes. The nucleolus is a homogeneous and dense spherical little body. It bears the chromosomes, each of which is composed of a very long molecule of DNA that bears genes, molecules, proteins, and ribonucleic acid (RNA).

At any given time, chromosomes can in fact be seen in only a very small number of cells. They exist in this very specific form only during the phase immediately preceding cell division. In all the other phases, the content of chromosomes appears diffuse in the nucleus. It is then called chromatine;

- The hyaloplasm, a gel forming the fundamental cytoplasm and supporting the nucleus and cytoplasmic organelles. It is the seat of synthesis and degradation of the various molecules necessary for the cell;

[10] A micrometre (or micron), symbol: µm, is equal to one millionth of a meter.

- The centriole, an organelle playing an important role during mitosis, normal cell division leading to two cells similar to the mother cell;

- Microtubules, hollow cylinders formed by linear polymers which are the essential components of the cytoskeleton[11]. They are involved in many cell functions such as cell division, intracellular traffic or the growth of neurons.

➥ Vegetal cells

Vegetal cells present specific characteristics compared with animal cells.

For instance their plasma membrane is doubled outside by a cellulose wall produced by the cell. They possess large cavities, vacuoles, which are dilatations of the endoplasmic reticulum and where the vacuolar liquid is to be found. They possess specific organelles, plastids, delimited by a double membrane.

Among chlorophyllic plants, chloroplasts capture light energy and are the seat of photosynthesis.

B – Operation of the cell

Cell activity consists in movements, exchanges and transformations of:

- Matter, to feed and grow;

- Information, to know about the external environment and communicate with other cells;

- Energy, to stay alive.

In the cell cytoplasm there is therefore a genuine 'biological factory' with many 'workshops', organelles, devoted to different tasks.

We will rapidly outline the operation of cell metabolism as well as that of cell division.

➥ Operation of cell metabolism

Organelles carry out a certain number of biochemical reactions which, considered as a whole, constitute cell metabolism.

This takes place, roughly speaking, as follows.

[11] The cytoskeleton is the network of filaments serving as a skeleton for cells.

Nutriments enter the cell, either by active transport through specialised channels if small molecules are concerned, or by membrane invagination for larger bodies. Elements that have entered the cell are digested in bodies rich in enzymes, especially lysosomes. Degradation into increasingly smaller size molecules continues in the cytoplasm by means of a set of reactions such as glycolysis[12] and fermentation. These reactions lead to the transfer of part of the chemical energy of glucose into the cell's main energy vector which is one of the cell's most important substances: adenosine triphosphate (ATP). This transfer of energy continues and is amplified in the mitochondria by cell respiration which produces the greatest part of adenosine triphosphate.

The energy and small molecules produced during the degradation processes are the departure point of the assembly reactions of the cell's specific macromolecules, in accordance with instructions given by its genetic material. All of this activity is organised in a finely regulated complex network in order to meet the cell's needs and changes in its environment

➥ Cell division

Cell multiplication is a vital necessity for it allows organisms to grow and ensures their maintenance by replacing cells that die. Cell multiplication must ensure the transfer of DNA from mother cell to daughter cells.

Cell division, called mitosis, begins by an accumulation of cell proteins. Then the complete replication of DNA takes place. This is carried out by local separation of the two strands of the double helix and an enzyme, DNA polymerase, copies each of the two complementary strands.

At the end of this operation, the cell contains a double quantity of DNA. Chromatin then condenses massively to form chromosomes. The nucleus membrane disappears and the cytoskeleton takes up the chromosomes. The cytoskeleton is deformed in such a way that the content of the mother cell is shared exactly between the two daughter cells. Each of these therefore inherits a complete set of chromosomes which then condense to give chromatin again in a nucleus reformed until the next division.

These events are accompanied, as a rule, only by very rare changes in the structure of DNA and that of homologous chromosomes. Therefore daughter cells keep identical genetic material to that of the mother cell. This mechanism allows all the cells of the same individual to have the same DNA content. The only exceptions are sexual cells and some immune system cells, lymphocytes, which produce molecules capable of recognising foreign substances.

[12] Glycolosis is the breakdown of glucose.

The cell is living matter (it is born, lives and dies) and is a place of exchanges and interactions with the external environment. It therefore appears as a central unit of the living world.

In their great majority, human cells are differentiated, in other words capable of fulfilling a precise mission: red globules transporting oxygen in the blood, intestinal cells absorbing nutriments, etc. Another characteristic of differentiated cells is that they do not divide.

However, every second, more than twenty million cells in our body divide to keep the number of cells constant by replacing those that disappear by ageing or injury. The sole maintenance of the number of red globules requires two million cell divisions per second.

Cells which divide are stem cells. They represent a major challenge of biology.

Third part:
stem cells represent a major challenge of biology

The interest taken in stem cells can be traced back to the beginning of the last century. As early as 1920, the existence of precursor cells at the origin of all blood cells was suggested in the chicken.

The precise concept emerged during the 1950s when the principle of the renewal of blood cells was determined. Blood cells have a short life, a human red globule lives only 120 days, and they must be replaced throughout our lifetime. Renewal is ensured by cells residing in the bone marrow. These are capable of self-renewal. At the same time, by asymmetrical division, they produce cohorts of rapidly proliferating cells which enter differentiation pathways leading them to produce all the variety of blood cells in the circulation.

A stem cell is a cell which can self-renew indefinitely, often throughout the life of the organism, by cell division while keeping at the same time its specific properties and the possibility of giving birth to more specialised daughter cells.

In normal conditions or following a suitable signal, stem cells give birth (differentiate) to the various types of cells forming the organism. They can develop into mature cells having specialised functions such as heart, skin or nerve cells.

All pluricellular organisms possess stem cells. The concept of the stem cell is used rather with regard to animals but plant meristems are also made of them.

Stem cells can be distinguished in terms of their differentiation capacities or their origin: adult stem cells and embryonic stem cells.

A – Distinction of stem cells in terms of their differentiation capacity

Several types of stem cells can be distinguished depending on their differentiation capacity, in other words depending on the appearance and progressive development of distinct properties or characteristics in cells which till then were equivalent or, at least, appeared so. This involves a qualitative change in phenotype, for instance the appearance of new membrane proteins, due to the activation of the expression of a given gene.

The four types of stem cells distinguished are totipotent, pluripotent, multipotent and unipotent stem cells.

1 – Totipotent stem cells

These result from the first divisions of the fertilised egg until the fouth day (morula of 2 to 8 cells). They are the only ones that can lead to the formation of a complete individual. As such they have the capacity of inducing the formation of all human tissues, including those of the germ line.

2 – Pluripotent stem cells

These result from the internal cell mass of the blastocyst, at the stage of 40 cells. They cannot produce an entire organism but can differentiate into cells of the three embryonic germ layers (mesoderm, endoderm, ectoderm).

3 – Multipotent stem cells

Present in the adult organism, they give rise to several types of differentiated cells but which keep their capacity to self-renew. They can give birth to several types of cells, but are already engaged in a given direction. For instance the hematopoietic cells of mammals give rise to red globules, T or B lymphocytes, and macrophages, but not muscle cells.

4 – Unipotent stem cells

These can produce only one cell type such as skin, liver, intestinal mucous cells, etc.

Distinction in terms of their origin leads to referring to adult stem cells and embryonic stem cells.

B – Adult stem cells

While adult stem cells certainly exist, it is difficult to identify and characterise them. While the question of the plasticity of adult stem cells is debated, three specific categories of stem cells are beginning to be well known.

1 – Existence of adult stem cells[13]

Adult stem cells present at least two characteristics:

- They can supply identical copies to themselves for long periods;

- They can give birth to mature cells having morphological characteristics and specialised functions.

At present their origin is not known. Researchers have proposed the hypothesis that they represent foetal cells that have remained undifferentiated.

Adult stem cells are, according to a certain number of opinions, rare: between 1 out of 10,000 and 1 out of 15,000 in the bone marrow and only 1 out of 100,000 in the blood[14]. It should be mentioned that Mr Daniel Louvard[15] strongly disagreed with this rarity, feeling that in fact this was not known and that 'for some tissues, it's untrue'.

Adult stem cells have been identified in many human and animal tissues.

They are located either in tissues with a rapid renewal or in tissues with a slower renewal.

In three tissues with a rapid renewal, stem cells operate permanently:

- Epidermis: renewal of skin and hair system cells every 30 days;

- Intestine: production of 10^8 cells per day;

- Bone marrow: production of 10^{12} cells per day.

In quiescent tissues[16] stem cells are present but their location is less precise and their functions less well defined. Two types can thus be distinguished, in muscle and in the liver. In the brain, stem cells have been located in two places.

Stem cells are also thought to be present in dental pulp, the cornea and the retina. The stem cells present in the pancreas are also thought to be capable of producing Langerhans islet cells which synthesise insulin.

---

[13] The term 'adult ' is inappropriate as these cells can be found in a variety of tissues, equally well in the foetus, child or adult. As emphasised by Mrs Marina Cavazzana-Calvo, on 22 November 2005, there is no notion of an adult individual but of differentiated tissue. **The term 'adult' in fact means that these cells are already differentiated.** It would undoubtedly be more correct to use the term 'non embryonic ' but the term 'adult' is currently used. This report will therefore continue to use it.

[14] According to the report by the National Institutes of Health, 'Stem Cells: Scientific Progress and Future Research Directions'.

[15] On 22 November 2005.

[16] A quiescent tissue is a tissue that does not self-renew.

This last result still appears controversial and illustrates a major difficulty: how can adult stem cells be identified and characterised?

2 – Difficulty in identifying and characterising adult stem cells

Adult stem cells are difficult to characterise for they do not appear to bear any specific marker.

As emphasised by Mrs Laure Coulombel[17], **acquiring proof that a cell is a stem cell requires characterising its progeny, *in vitro and/or in vivo*. It is therefore a matter of indirect and retrospective identification**.

For that purpose two requirements must be met.

The first is to place this cell in conditions permitting the expression of all its proliferation and differentiation capacities. This leads to difficulties bearing in mind the difference, specificity and incompatibilities of the environments necessary for each differentiation pathway.

The second requirement is to analyse cells individually by the manipulation of single cells or the follow-up of a marker of clonality. This clonal analysis is imposed by the heterogeneity of basic tissues and by the fact that it is impossible to purify stem cells to homogeneity, for a phenotype is not the faithful reflection of a function.

Mrs Laure Coulombel emphasised in this study that if these constraints are not met - and that is rarely the case - it is impossible to define with any certainty the potential of cells analysed. She therefore feels that prudence is required in the conclusions granting a cell stem-cell status.

Mrs Laure Coulombel reiterated this advice of prudence at the public hearing of 22 November 2005.

One of the main difficulties is therefore identifying 'genuine' stem cells, in other words those which have not yet started to enter a differentiation pathway. For we still do not know the factors controlling the 'stem' character, those that would guarantee that these cells keep their properties.

It is felt that several signalling pathways are probably involved, some being induced by the stimulation of receptors located at the surface of cells, while others involve the intervention of growth factors. The expression of all the genes of a stem cell has been studied in the hope of identifying those controlling the 'stem' character. For instance, the expression profiles of embryonic stem cell genes, of hematopoietic stem cells and of neural stem cells have been compared. It appears

[17] In *Médecine/Sciences* no. 7 vol. 19 June-July 2003.

that, to date, it has not been possible to determine the specific genetic fingerprint of the 'stem' character of these cells. Apparently we still do not even know whether this absence of any result reflects technical difficulties that are still not or only ill-mastered, or intrinsic differences between cell types.

Other difficulties remain.

For instance it is still unknown how a stem cell keeps its quiescence or its low-level replication or begins to proliferate and differentiate.

It is currently believed that stem cells are controlled by the combined activity of many factors creating a genuine signalling network, the latter being able to change with time and place. These signals can also have dissimilar effects on different types of stem cells. But it is not known how a stem cell integrates all these signals and how all of the signalling networks control its molecular operation.

As mentioned in another chapter of this report, these difficulties have their importance regarding therapeutic applications, insofar as differentiation must be perfectly controlled.

Knowledge of the characteristics of adult stem cells is therefore well and truly imperfect.

Mr Daniel Louvard[18] emphasised in this respect that 'the number of adult stem cells that have been characterised today can be counted on the fingers of one hand or perhaps two.' Characterised stem cells are ones 'in which markers have been identified allowing them to be sorted and allowing their origin and their properties to be identified.'

The issue of the plasticity of adult stem cells is also debated.

3 – Plasticity of adult stem cells

Now that the difficulty of this issue has been defined and observed, mention will be made of the scientific arguments making it a controversial phenomenon.

a – Definition and difficulty of the issue

The plasticity of adult stem cells is the phenomenon according to which a transplanted adult stem cell can give rise to differentiated cells of other tissues. It is the possible capacity of a cell type of a specific tissue line from one of the three embryonic germ layers (endoderm, mesoderm, ectoderm) to differentiate into the

[18] On 22 Novvember 2005.

cells of the other two. For instance this would be the possibility of neural stem cells to transform into blood stem cells or of blood stem cells into muscle cells, etc.

As stated by Mrs Laure Coulombel[19], this possibility would be a *'transgression of the dogmas according to which a stem cell located in a given tissue gives rise only to the specialised cells of that tissue and cannot adopt in its progeny the fate of two different embryonic germ layers.'* In scientific texts another term is also used, 'transdifferentiation'.

In short, **the plasticitiy phenomenon is possible only under certain conditions**:

. The transplanted cells must survive after the transplant;

. They must then migrate towards the lesion;

. They must give the cell type that is to be replaced and this type only so that they do not cause tumours;

. Lastly, the cells which differentiate from transplanted cells must integrate into the damaged tissue so that the damaged organ returns to its normal operation.

Over the past few years, the controversy over this issue has not ceased. Researchers are engaging in an extremely intense, not to say occasionally passionate, debate on this subject.

b – A highly controversial phenomenon

I will present the main elements of this controversy without of course being able to settle the matter.

In 1999, an article in the American journal *Science* related the observation of adult stem cells from the mouse brain that had induced the production of functional blood cells when they were injected intraveinously into an irradiated mouse. As irradiation has the effect of killing some cell populations, and especially hematopoietic stem cells, the reconstitution of the blood capital could be ascribed only to the action of new cells.

This was the first time that the *in vivo* entry of adult stem cells into a differentiation pathway (blood cells), which could not be predicted by their origin (the brain), was reported.

A certain plasticity would therefore exist for some adult stem cells: the stem cells of the bone marrow, muscle, skin, adipose tissue and some neural stem cells.

[19] *Médecine/Sciences* no. 6-7 volume 19 June-July 2003.

Two hypotheses have been advanced to explain this phenomenon: the existence of an embryonic stem cell which would be preserved at adult age in all tissues and the existence of a transdifferentiation phenomenon.

It should however be noted that several attempts to reproduce these results have failed.

On the basis of this article, several scientific reports therefore suggested that adult bone marrow stem cells can undergo a transformation phenomenon into completely different types of cells such as, for example, heart muscle cells or brain cells.

To my knowledge, no objectively verifiable and renewable experimental result has yet recorded this phenomenon.

At the public hearing of 22 November 2005, a controversy therefore arose between Mrs Marina Cavazzana-Calvo who feels *'that it can be said without too much fear of being wrong that there is no plasticity* [of adult stem cells]*'* and Mr Daniel Louvard who believes *'that this question cannot be answered as we have not been able to study it.'*

Another controversy regarding adult stem cells that may possibly give rise to cells of the three embryonic germ lines has arisen in recent years.

This controversy arose when, in 2002, a team of researchers from the University of Minnesota led by Mrs Catherine Verfaillie gave a description of bone marrow stem cells, called MAPCs (Multipotent adult progenitor cells).

According to this study, these cells would have the power to differentiate *in vitro* and *in vivo* into all the types of cells forming the tissues and organs of the body from which they have been taken. This team demonstrated that MAPCs could create endoderm, mesoderm and ectoderm lines. Chimeric embryos were obtained, some constituted of 40% of foreign cells distributed in all the tissues, thereby leading it to be believed that these cells were functional. No tumour formation was observed and a very high development potential was observed without ageing signs having been seen. This discovery was hailed at the time as marking a decisive step.

But, since then, enthusiasm has fallen off.

In effect, apart from the fact that these cells are thought to be extremely rare – there are apparently less than 2,000 in a mouse – they have not been identified *in vivo*. Since then, it has not been possible to reproduce the original experiments, which was confirmed by Mr Jacques Hatzfeld[20], who emphasised that *'all the work carried out on MAPCs are currently completely unreproducible.'*

[20] On 22 November 2005.

Mr Daniel Louvard has moreover acknowledged that *'in an adult tissue, we know that there are stem cells which derive from the various embryonic germ layers. It has not been possible to explore exactly, outside the tissue in which they exist, or the organ in which they exist, whether they recapitulate or not all of the properties of the germ layer cells from which they derive'.*

Lastly mention should be made of the work on cell fusion by Messrs. Douglas Melton and Kevin Eggan of the Harvard University Stem Cell Institute. We will refer in more detail to this work in the part of this report on nuclear transposition.

A certain number of adult stem cells are now well known.

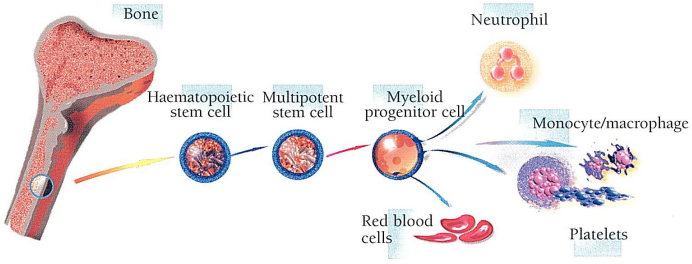
4 – A few well known adult stem cells

We will refer to hematopoietic stem cells, mesenchymal stem cells and umbilical cord blood stem cells.

a – Hematopoietic stem cells

These are probably the currently best known adult stem cells.

They mainly derive from the bone marrow and give rise to the blood cells necessary for the daily renewal of blood and combating infections as shown in the following diagram:



Source: *UNESCO Courier 2004*
Special issue 'Human cloning'

In comparison with other adult stem cells from other tissues, hematopoietic stem cells are easy to obtain either from the bone marrow or from peripheral blood.

These stem cells have been studied for a very long time and are the first ones to have been used with success in various therapies.

On the other hand, the potential of these stem cells to produce cells other than blood cells has become a subject of major debate. In particular it has not yet been precisely determined if they can be used to restore tissues and ogans other than blood and the immune system, even if announcements have been regularly made to this effect.

Mrs Laure Coulombel therefore felt that transdifferentiation, which would be conducive to a hematopoietic stem cell being capable of making something else than hematopoietic cells, has not currently been experimentally proven, by noting that *'with a single cell in the mouse, nothing else is produced than hematopoietic stem cells.'*

On the other hand, she observed that some derivatives of hematopoietic stem cells can fuse in a diseased tissue with a diseased cell and then grant it the capacity to become 'normal' again. She emphasised that we were faced here with a different case: somatic nuclear reprogramming. She also drew attention to the fact that it was possible to sometimes observe the expression of some markers of other hematopoietic stem cells but that it could be a matter of a culture artefact.

b – Mesenchymal stem cells

Mesenchymal stem cells are another category of adult stem cells that are beginning to be well known.

These cells were isolated in the 1960s from animal bone marrow. They therefore have the same origin as hematopoietic stem cells.

Mesenchymal stem cells possess many interesting properties from the therapeutic viewpoint. For instance they produce many hematopoietic growth factors and a factor allowing hematopoietic cells to become established in the marrow. They are barely immunogenic[21] and even tend to inhibit many immune reactions. Lastly, they possess plastic properties allowing them to differentiate into many cell types and give in the laboratory chondrocytes[22], myoblasts[23], adipocytes[24] and even neural cells.

[21] Is said of a substance that can provoke a reaction or an immune response.
[22] Chondrocytes are the cells forming cartilage.
[23] Myoblasts are precursor cells of adult muscle cells.
[24] Adipocytes are adipose cells containing lipids. They are the cells that store energy as fat.

The techniques of their isolation in cultures are now well established and, although there are not many of them, they can be multiplied in quite large quantities *in vitro*. They can therefore be kept and propagated for long periods of time in the laboratory without losing their qualities.

These characteristics make them good candidates for cell therapy use.

c – Umbilical cord blood stem cells

Umbilical cord blood stem cells made the headlines in summer 2006 with the information given by the British press according to which a certain number of sportsmen had stocked their child's umbilical cord blood. The blood would have been taken not only to treat their child one day but also to treat their own cartilage or ligament problems.

This interest for the capacities of hematopoietic umbilical blood cells is nothing new. In effect, the world first umbilical blood graft was performed by Mrs Eliane Gluckman at the Hospital Saint Louis in Paris in 1988, on a little boy affected by a hereditary blood disease. Since then, approximately 6,000 cord blood grafts have been performed worldwide.

The primary interest of this blood is that it is particularly rich in hematopoietic stem cells believed to be present only in bone marrow.

But it has other advantages over bone marrow:

- Its collection does not present any special difficulties insofar as the blood is taken when the umbilical cord is cut. There are no constraints and no risk for mother or child;

- It can be frozen for distant use after collection;

- The cells have higher proliferation and expansion capacities than those of bone marrow or of the peripheral blood of an adult;

- The cells are immature. They must therefore cause a lesser rejection reaction of the graft on the part of the receiver's organism owing to the fact that the immune characteristics of stem cells and the antibodies of newborns are not yet fully developed;

- The resources can be considered as unlimited, particularly when compared with the difficulties of a bone marrow harvest which requires a general anesthesia of the donor.

The use of cord blood is today a well mastered technique, very useful in particular in treating certain serious blood diseases like acute leukemias. But its

therapeutic use still comes up against the small size of the grafts, insufficient to treat adults.

Since the 1990s, most developed countries have started to set up public umbilical cord blood banks. There are presently fifty or so public umbilical cord blood banks worldwide.

The banks presently set up keep this blood for mainly allogeneic uses, even if the possibility of an autologous use exists in favour of the donor child.

But in recent years private companies have been created, especially in the United States and Great Britain, offering the possibility of freezing, against remuneration, the cord blood of newborns with a view to future use should the need arise.

Advertisements and the premature announcements by a certain number of publications of the possibility of curing by this means a large number of disorders play on parents' distress. They insist for instance on the future possibilities of the transdifferentiation of hematopoietic stem cells to treat, one day, diabetes, Parkinson's or Alzheimer's disease, or to repair a damaged heart…, all goals which remain speculative.

After having the issue of the storage of cord blood (umbilical or placentary) brought before it by the health director-general in 2002, the National Consultative Ethics Committee, in its opinion of 12 December 2002, emphasised inter alia the three major dangers of the autologous storage of placentary blood:

'1) The most serious danger is for society insofar as the setting up of such banks opposes the solidarity principle without which no society whatever can survive;

2) Such banks give rise to utopian ideas and disguise a mercantile goal under the pretext of helping children;

3) They call justice and equity into question. If reasonable indications existed, the proposal should become systematic and organised under public responsibility; here the cost intervenes and the large scale notion […].'

In conclusion, the National Consultative Ethics Committee favoured public storage for grafts but opposed private storage for personal reasons. It also invited the public authorities to promote major development of public cord blood banks rather than support the setting up of private banks.

I approve this position which is still fully justified today.

However, worldwide today there is a very great disproportion between the number of private blood cord banks (more than a hundred thirty) and public banks

(fifty or so). Private banks are expanding rapidly in the United States, Great Britain, Belgium, Germany, and Asia.

In the face of this trend, France must develop public blood cord banks through the Biomedicine Agency. France must also warn international organisations about the development of private banks. The National Consultative Ethics Committee's recommendation to develop public blood cord banks should therefore be reactivated. This will be a recommendation of this report.

Adult stem cells are currently the subject of major debate insofar, in particular, as they are compared with embryonic stem cells.

C – Embryonic stem cells

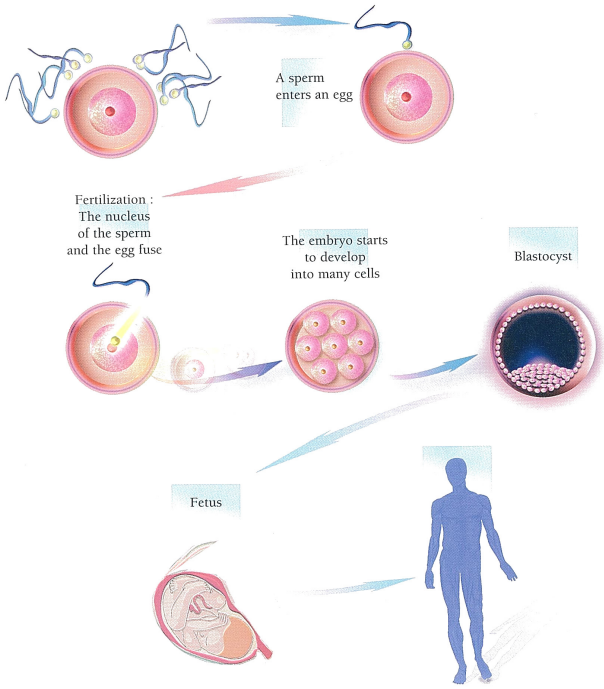
After presenting embryonic stem cells, I will mention their characteristics, their derivation and the problems of their culture.

1 – Presentation of embryonic stem cells

The fertilised ovocyte, the zygote, which is monocellular, enters into a series of divisions.

Embryonic stem cells are the cells resulting from the first divisions of the zygote. They are termed totipotent, in other words they are capable of recreating an entire organism if isolated. Very soon this property is lost but the cells of the early embryo remain capable of giving rise to any of the organism's cells.

Four or five days after fertilisation, these pluripotent embryonic cells undergo a first specialisation. The five-day embryo is then called the blastocyst. It is a small hollow sphere in which a small pile stands out, the preimplantation embryo, composed of an internal cell mass and an external cell mass. This cycle takes place as follows:



Source: *UNESCO Courier 2004*
Special issue 'Human cloning'

The cells constituting the external cell mass will form, with cells from the mother during gestation, the placenta.

Cells from the internal cell mass begin the formation of germ tissue and of the three somatic germ layers from which the organic tissues of the future individual derive. The external germ layer, or ectoderm, will give rise to the skin, neurons, eyes and ears. The middle germ layer, or mesoderm, will give rise to the bone marrow, muscles, blood and blood vessels. Lastly, the internal germ layer, or endoderm, will give rise, for its part, to the pancreas, liver, thyroid gland, lungs and bladder.

When cells enter these differentiation pathways, they lose their pluripotency.

The discovery of human embryonic stem cells is recent since it was in 1981 that, simultaneously in the United States and in Great Britain, two researchers

demonstrated that the cells of the preimplantation embryo of mice placed in culture in specific conditions began to divide and propagated indefinitely without differentiating, 'frozen' at this early stage of embryogenesis.

These researchers realised that, even after the formation, in culture, of many generations, these embryonic stem cells 'remembered' the reason why they were programmed. They therefore kept the capacity to differentiate into any specialised cell type in the organism. In effect, if such cells were reintroduced into a blastocyst, they would colonise it and their decendants would be found in all the tissues of the newborn mouse.

As murine cells differ in many points from their human counterparts, it was not before 1998 that human embryonic cells were isolated from human blastocysts by Mr James Thomson et al. from the University of Wisconsin.

2 – Characteristics of embryonic stem cells

They have three main characteristics distinguishing them from other types of stem cells:

- They express factors making them pluripotent;

- They are unspecialised cells that self-renew during many cell divisions. A population proliferating for several months in the laboratory can therefore be counted in millions. An important challenge for research is to understand why a population of stem cells remains unspecialised and continues to proliferate;

- They can give rise, in certain conditions, to specialised cells.

It appears[25] that these cells could possess immune privilege. In effect, they express only a few histocompatibility antigenes and are not targeted by T lymphocytes. They could secrete a local immunosuppressor factor and induce a tolerance phenomenon. Lastly, they could possess immunological neutrality and powers of adaptation to the environment of the host tissue.

3 – Derivation of embryonic stem cells

The source of embryonic stem cells is therefore a blastocyst which can be obtained from:

- So-called 'spare' embryos collected at the time of an attempt at *in vitro* fertilisation (IVF) , the characteristics of which are incompatible with freezing. The present embryonic stem cell lines were isolated from the blastocysts of spare

[25] Michel Pucéat 'Les cellules souches embryonnaires. Du développement myocardique à la médecine régénératrice ' ('Embryonic Stem Cells. From Myocardial Development to Regenerative Medicine') in *Médecine Sciences* no.12, volume 21, December 2005.

embryos left over from IVF. The yield varies between 35 and 50%, i.e. one line for two or three blastocysts;

- Embryos from a preimplantation diagnosis;

- Frozen embryos no longer required for fertility treatment;

- Embryos created by nuclear transposition. This will be studied in the following chapter.

4 – Embryonic stem cell culture issues

Three issues arise: culture media, control over cell differentiation and genomic instability.

a – Culture media

Since 1998, human embryonic stem cell lines have been grown on a substrate containing foetal calf serum and a layer of nourishing cells, mice embryo fibroblasts. These fibroblasts were irradiated to prevent them from dividing while remaining capable of secreting the necessary growth factors. Such culture conditions obviously represented a potential danger of contamination by murine viruses or bovine-derived prions.

Progress has been recorded from this viewpoint. In effect, the team of Mr James Thomson of the *WiCell Research Institute*, in association with the University of Wisconsin, developed last year a new culture medium devoid of any animal content. However, while the two lines created by this team from spare embryos left over from IVF survived for more than seven months, they presented chromosome abnormalities. It could not be determined whether these abnormalities were related or not to use of the new nutrient support.

Mrs Jane Lebkowski told me that new lines of embryonic stem cells have been derived in the laboratories of the company Geron without ever having been exposed to animal products.

b – Control over cell differentiation

In order to specifically orient embryonic stem cells towards defined tissue lines, it is necessary to have factors controlling cell differentiation *in vitro*.

At present, when embryonic stem cells are separated from nourishing cells and placed in a liquid culture medium, they tend to group in aggregates called 'embryonic bodies' within which differentiation takes place anarchically and very haphazardly. Reinjection of these embryonic bodies into immunodeficient mice often leads consequently to the formation of benign tumours (teratomas).

c – Genomic instability

In a recent article[26], a certain number of researchers demonstrated that genetic anomalies appear in human embryonic cell lines cultivated *in vitro* over an extended period.

They showed that major changes took place: losses or amplification of some parts of DNA, mutations of mitochondrial DNA, modification of the expression of genes. The authors noted that the impact is not yet known of genetic mutations on stem cell behaviour or on their capacity to differentiate. It appears that cells which accumulate modifications of their DNA, whether genetic or epigenetic in origin, acquire an advantage as regards duplication, over cells not affected by these phenomena. The reasons for this situation remain unknown.

The authors emphasised that out of the 22 authorised stem cell lines entitling to federal funding in the United States, 10 are affected by these mutations. This genetic instability phenomenon of stem cell line cultures was confirmed to me by all my interlocutors.

Embryonic stem cells therefore present, like adult stem cells, a great number of difficulties.

But these two categories of stem cells appear to possess a great number of qualities and their potential applications are currently being examined.

D – Potential applications of stem cells

The most immediate idea is that stem cells will help develop treatments, cell therapy, for very many diseases. However, before addressing cell therapy, a few wrong ideas should be insisted on. Lastly, we will consider the issue of nuclear transposition.

1 – A few wrong ideas

In recent years we have witnessed the development of a certain number of wrong ideas: immediate curing of diseases thanks to stem cells; research must have **short term** therapeutic prospects; opposition between adult stem cells and embryonic stem cells; and the tumorigenicity of human embryonic stem cells.

[26] *Nature Genetics,* October 2005.

a – Immediate curing of diseases thanks to stem cells

This idea has developed considerably in recent years and the events in Korea caused it to be significantly amplified.

A certain number of media, fortunately isolated, played a major role in this affair. They not merely suggested but affirmed that it was extremely soon going to be possible to be cured of terrible diseases today incurable like Parkinson's and Alzheimer's disease. The aim, as one of my interlocutors told me, was to 'give hope!'

Fortunately a certain number of journalists are aware of this situation. For instance, Mr Jean-Yves Nau[27] notes that *'[…] scientific publications on the creation of mammals by the cloning technique have always received high coverage in the media. This gave their authors renown and an aura making many of their peers jealous. A race for fame arose which led to repeated out-of-control deeds on the part of researchers and also of the media […]'.*

But, in the process, is a thought given to the situation of persons suffering from these disorders and who are enticed to believe they can escape the consequence of these terrible diseases?

Is a thought given to their close relatives and their distress in seeing a loved one suffer a terrible ordeal? Unfortunately, it appears that the need to make big, attactive front page headlines has got the better of intellectual honesty.

As I stated at the public hearing of 22 November 2005, I feel it is a scandal to say that today's research on embryonic stem cells will represent tomorrow's therapeutic applications. I sincerely hope that this research will indeed lead one day to major therapeutic applications but, today, intellectual honesty, forces me to say that is not at all the case yet.

All the scientists heard on 22 November 2005 unanimously emphasised this viewpoint.

Of course it is not for me to criticise the media which have a genuine role to play in disseminating scientific culture, thereby taking part in the necessary training of citizens in subjects which, it should be acknowledged, are very difficult to understand. They do so, in a great number of cases, with relevance and great strictness. Journalists, especially generalist press ones, rely on articles that have appeared in scientific publications. They naturally don't have the possibility of checking the authenticity and exactness of these articles.

---

[27] In 'L'affaire Hwang ou les ravages de la course à l'audience', ('The Hwang Affair or the Ravages of the Race to Arouse Interest') *Le Monde* 14 January 2006.

It is all the less in my intentions to make journalists bear responsibility for this situation as there are a certain number of members of the scientific community whose attitude has been highly questionable to say the least. This has been the case for instance with certain very well known professors of medicine, non specialists of the field, who, to promote their books, expressed judgments allowing it to be believed that a cure for these terrible diseases was imminent.

A certain number of researchers have also made imprudent, or insufficiently qualified, remarks on the possibilities opened up by stem cells – both adult and embryonic – as regards therapies. This imprudence is due to the competition between scientists to accede to fame on which their funding in fact depends.

Out of honesty, it is also certainly necessary to call politicians into question. For want of time, they cannot devote all the necessary attention to precisely following up all the extremely rapidly evolving work in this field. On every announcement in this field, they would need to have the necessary hindsight allowing them to distinguish proven facts from phony announcements.

Mr Marc Peschanski[28] summarised the duty of researchers with reference to embryonic stem cells, by emphasising that *'here there is […]* ***something which is high-risk and which cannot be promised today. All that we can promise is that we will work [to] reach a therapy'.***

b – Research must have short term therapeutic prospects

I feel this is a very sensitive field which, unfortunately, has been enshrined in legislation.

In effect, Article 25 of Act no. 2004-800 of 6 August 2004 on bioethics sets forth that *'research can be authorised on the embyro and embryonic cells when it is likely to allow major therapeutic progress […]'.*

I fought against this provision at the time of the second reading debate of the bill. This provision is indeed tantamount to denying the need for fundamental research. Having a therapeutic prospect will be mandatory to start research in this field. I unfortunately did not manage to convince, at the time, either the rapporteur, the minister, or a majority of my colleagues.

This way of proceeding can be potentially extremely dangerous. It could force scientists to justify applications for funding for their activities. This may have strengthened the out-of-control deeds that have just been mentioned with respect to the hypothetical imminent possibilities of curing thanks to stem cells. I will make

[28] On 22 November 2005.

proposals in the fourth part of this report on the policy which to my mind should be followed in France.

If we return twenty years back, the prospect of 'major therapeutic progress' has never been imposed to authorise gene therapy research. If that had been the case, it can be believed that nobody would have started work in this field.

Generalising this attitude would dissuade researchers from any fundamental research work, confining them solely to utilitarian type work. We would run the risk of begetting a system where no fundamental research protocol would be possible.

Mr Hervé Chneiweiss[29] has summarised this situation best:

'[…] a utilitarian approach is prevailing which arose with genomics and large-scale biology, when our American colleagues launched in 1969 the great human genome programme as the new ambition after man had walked on the Moon. They did not sell it as knowledge of the human genome but as a new frontier to cure cancer. ***From then on there was a kind of snowballing which meant that, in any scientific article, authors have begun or finished by justifying their work by a pathology[30].*** *There is also a game with respect to the various public representations, the media or politicians, to try and justify the underlying idea crossing through all political parties that pure scientific knowledge is something noble but which is not worth [a] fight vis-à-vis moral beliefs deeply rooted in the history of a country. It has sometimes appeared easier to some to defend utilitarian positions […]'.*

At first reading, the National Assembly had adopted the authorisation of research on the embryo and embryonic cells for 'a medical purpose', which was entirely different. It is therefore necessary to return to this text and delete the terms contained in the Act of 2004.

This will be a recommendation of this report which will propose the revision of Article 25 of Act 2004-800 of 6 August 2004 on bioethics.

The notion of fundamental research absolutely must be rehabilitated for it is the prerequisite for the progress of knowledge.

c – Opposition between adult stem cells and embryonic stem cells

As can be seen in the report of the public hearing of 22 November 2005, the debate on the respective merits of the two types of stem cells certainly was lively.

[29] On 22 November 2005.
[30] I put the sentence in bold.

The specialists of adult stem cells apparently sometimes feel a certain uneasiness about embryonic stem cells being presented as having all the advantages. They have the impression that the qualities of adult stem cells are neglected.

Embryonic stem cells do sometime enjoy greater attention on the part of a certain number of media bearing in mind, in particular, their greater novelty. It is also fair to emphasise that these cells had enjoyed, at the time, all the effervescence that had progressively developed around the 'achievements' by Mr Hwang Woo-suk's Korean team.

This dissymmetry which is felt to be to the detriment of adult stem cells is in fact merely an illusion, for research funds are massively in their favour. This is the case in France where Mr Christian Bréchot[31] stated for instance that Inserm's funds were in their immense majority devoted to adult stem cells, at end 2005, owing to the legislation. The situation is similar in Japan where Mr Norio Nakatsuji emphasised that the effort on adult stem cells is ten times greater, regarding their funds and researchers, than on embryonic stem cells.

I have shown that the uncertainties of these two types of stem cells remain very high. Neither of these two categories is therefore to be given greater importance.

This was also stated by a certain number of participants at the public hearings day.

For instance Mr Philippe Ménasché noted that *'in the state of ignorance in which we find ourselves […] there is no sense in opposing adult cells and embryonic cells. The two pathways must be explored parallely […], it is not impossible that the two types of cells will finally find their place in different pathologies. To give an example, it is known today that if we want to replace a heart cell, it is unlikely, in the present state of knowledge, that this can be achieved with adult cells. Embryonic cells are apparently capable of this. In contrast, if the aim is simply to get cells that can secrete insulin, i.e. Langerhans islets, adult cells taken from subjects in an irreversible coma do the job fine. […]* ***The opposition that sometimes exists between adult cells and embryonic cells is meaningless clinically***[32]*. Both types of cells must be explored, which means that the embryonic cell pathway must not be closed […]'.*

Going further, Mr Jacques Hatzfeld emphasised the complementary character of the work on embryonic and adult stem cells within the framework of the European Genostem project on adult stem cells: *'It's thanks to embryonic stem cells that I [can] find the markers of adult stem cells, not by starting downstream,*

[31] On 22 November 2005.
[32] I put the sentence in bold.

like we did previously, but by starting upstream, by deriving, from embryonic stem cells, mesenchymal stem cells, which allows me to have a quantity of them and enables me to study all the most primitive markers. ***If we do not work on embryonic stem cells, we will never understand adult stem cells'.***

Mrs Laure Coulombel, for her part, insisted on the fact that it is essential not to oppose the two types of cells for two reasons:

- It is probable that molecular mechanisms governing the amplification of embryonic stem cells are similar to those of adult stem cells, especially those governing their diversification;

- Embryonic stem cells allow an accessibility in terms of their number that would be impossible to obtain with adult stem cells, except regarding hematopoietic stem cells.

I am however worried about the turn taken sometimes in France by this debate on the various types of stem cells.

I feel that the two sides are always more or less about to be at loggerheads, in an excessively adamant manner, on the respective merits of these two types of cells. I quite understand that researchers working on adult stem cells are irritated by the fact that embryonic stem cells are sometimes presented as the alpha and omega of cell research and that they alone make the headlines.

I am entirely convinced that the specialists of embryonic stem cells and those of adult stem cells are all working to find treatments that will relieve suffering human beings.

I will therefore follow, to apply it to adult stem cells *and* to embryonic stem cells, the opinion of Mr Claude Huriet[33] who writes[34]: *'[…] the danger must be emphasised, in any scientific process, of an overly manichean attitude. […] It is necessary[…] to put an end to quarrels in which, too often, ideological presuppositions prevail over the scientific process'.*

I therefore feel that it is essential not to oppose the two categories of stem cells.

d – Tumorigenicity of embryonic stem cells

This issue has been debated for a certain number of years. It was addressed at the public hearing of 22 November 2005.

Mr Daniel Aberdam noted that to demonstrate that an embryonic stem cell is pluripotent, these cells are injected into an immunodeficient mouse, i.e. whose

[33] Honorary senator, member of the UNESCO International Bioethics Commitee, President of Institut Curie.
[34] In *Le Figaro* 6 August 2005.

immune system has been destroyed. He mentioned that teratocarcinomas are then obtained but only because it is a matter of an immunodeficient mouse and its immune system cannot rid itself of them.

He emphasised that it is *'clearly established that when embryonic stem cells are differentiated, these tumours no longer appear. […] If it is managed to purify differentiated cells from embryonic stem cells, all the published, unpublished or commented experiments show that no tumour appears'*.

Mr Philippe Ménasché agreed with these remarks by noting that *'from the moment that cells are correctly pre-differentiated, not the slightest tumour has ever been observed.'*

Difficulties nevertheless remain from this viewpoint, for it appears that the extent to which these cells are to be differentiated is not exactly known.

2 – Cell therapy

Cell therapy is defined by the texts as the administration to a patient of biological products with therapeutic effects made from preparations of live human or animal cells with a preventive or curative aim in mind.

As written by Mr Axel Kahn[35] cell therapy can fit into 'the age-old dream of medicine' to repair part by part the defective or worn out elements of the human machine.

It was the first organ grafts performed some fifty years ago which paved the way for the possibility of regenerative medicine. Organ grafts are today performed with success in a certain number of fields thanks to the improvement of surgical methods and the development of effective immunosuppressive drugs. However a major limiting factor is the insufficient number of transplants with respect to demand. While xenografts could attract attention, they imply major difficulties owing to the immunological problems posed and the risks of transmission to man of animal retroviruses.

This situation explains the interest taken in cell therapy which is based on the use of live cells taken either from the patient to be treated or from a donor.

Depending on the degree of cell transformation, cell therapy can be likened firstly to a mere graft of cells taken from a donor and administered to a recipient. It may also require more elaborated techniques insofar as the cells administered may have undergone a complex process of storage, selection and transformation which grants them new properties. These modifications can go as far as modifying their

[35] In *Médecine Sciences* no. 4 volume 18, April 2002.

genetic heritage, thereby making these cells a product combining cell therapy and gene therapy.

Cell therapy applications already exist while other research pathways are opening up. An approach can be envisaged combining gene therapy and cell therapy.

a – Already existing applications of cell therapy

Cell therapy applications currently concern the regeneration of blood cells and of skin cells by the use of adult stem cells. Prospects of the therapeutic use of embryonic stem cells will be examined in the following part of this report on nuclear transposition.

➥ Regeneration of blood cells

Blood cell regeneration was initially achieved by bone marrow stem cells, but other techniques have now begun to be applied.

. Bone marrow stem cells

These were the first known stem cells and they were grafted to man from the end of the 1950s. This graft treats autoimmune diseases[36], immune deficits, leukemias and also a certain number of solid cancers. In order to avoid reactions against transplants, autografts are performed whenever possible. Insofar as these cells do not enable the total number of blood cells to be restored, there is the prospect of combining them with mesenchymal stem cells which offer the necessary micro-environment for good activity of hematopoietic cells.

Bone marrow stem cells can also differentiate into bones and cartilage allowing the repair of bone or cartilage lesions.

. Other techniques

Since the past ten years or so, umbilical cord blood has been used to regenerate blood cells. This technique has already been mentioned previously.

➥ Regeneration of skin stem cells

This is performed conventionally by using keratinocytes, but another technique has just been employed experimentally.

. Use of keratinocytes

[36] An autoimmune disease is a disease during which immune reactions develop within an organism against some its own antigens.

The skin regenerates entirely every three weeks approximately thanks to the action of keratinocytes in the epidermis. They are produced in its deepest layer, multiply and migrate little by little to the skin surface.

For more than twenty years, they have been currently cultivated with a view to transplanting skin, especially to the severely burnt. Merely a few centimetres of healthy skin have to be taken from the patient before culturing it on a nourishing layer of dermis cells, fibroblasts. A few weeks suffice to obtain a large surface of epidermis that is autografted.

. A new experimental technique

In March 2006, a skin burn by irradiation was successfully treated in France by an autologous graft of bone marrow stem cells. This was the first application of a treatment hitherto implemented only in animals.

The patient's own mesenchymal stem cells were isolated, collected and cultivated in the laboratory with growth factors.

➥ Compliance with certain conditions

However the success of cell therapies using adult stem cells requires, save in the case of an autograft, the donors and recipients to have genomes as similar as possible. At the very least they must have the same tissue groups to avoid graft rejections.

As with any heterologous graft, immunosupressive treatments help diminish the recipient's immune defences. This facilitates the graft but the person treated then becomes very sensitive to infections.

b – Opening of other research pathways

Mention will be made of the work carried out by the use of foetal neuronal cells, the treatment of heart disorders and the treatment of neuronal disorders.

➥ Use of foetal neuronal cells

Two examples of cell therapy using foetal neuronal cells have recently attracted attention: treatment of Huntington's chorea and treatment of Batten's disease.

. Treatment of Huntington's chorea

A team of French researchers directed by Mrs Anne–Catherine Bachoud-Lévi and Mr Marc Peschanski published in March 2006 the first experimental results of their research on the treatment of Huntington's disease by the intracerebral graft of foetal neuronal cells.

Huntington's disease or chorea is an incurable hereditary disease leading to neuronal degeneration affecting the motor and cognitive functions. It ends up in dementia. These psychiatric manifestations of the disease are accompanied by neurological disorders leading to incoherent and abnormal movements and balance disorders.

After the development of an experimental model in a monkey, a trial was performed on five patients in whose brains foetal neuronal cells were transplanted. The results of this experimentation, six years after its commencement, have shown, for part of the sample, remissions in motor symptoms and intellectual disorders for four or five years. On the other hand, in other cerebral regions, the transplant did not stop the progression of the characteristic disorders of the disease.

As Mr Marc Peschanski told me, it is not a curative treatment strictly speaking but an attenuation of symptoms. He emphasised that it would be possible to graft only fifty patients a year at most at present and that it would therefore be necessary to use embryonic stem cells instead. This type of trial must be pursued at European level.

. Treatment of Batten's disease

The lysosomal disease or Batten's disease is a rare neurodegenerative disease affecting approximately 2,000 children worldwide. It combines the syndromes of Alzheimer's and Parkinson's disease, epilepsy, schizophrenia and autism.

The American company *StemCells* obtained on 20 October 2005 the agreement of the Food and Drug Administration (FDA) to begin a phase 1 safety and primary efficacy trial, by using foetal neuronal stem cells.

As recalled by Mrs Ketty Schwartz[37], the first goal of this company has been to establish the feasibility of this regenerative therapy using foetal cells. After conducting *in vivo* tests on murine models of the pathology, a process was developed to purify to a very high degree foetal neuronal cells. It was documented that they repopulated the target tissue. Lower than 10%, this repopulation was weak, yet considered sufficient to produce a functional improvement.

Mrs Ketty Schwartz considered that the possibility of an immunological reaction against allogeneic neuronal cells is relatively weak, probably in the short term, no doubt because of the specific confinement of the nervous system. No teratoma was detected in more than three thousand animals which were treated for periods of up to more than sixty weeks. Validation of this approach should lead this company to develop it in more frequent neurodegenerative diseases, like Parkinson's or Alzheimer's disease, medular traumatisms, or multiple sclerosis. Mrs

[37] On 22 November 2005.

Ketty Schwartz felt that it was a very important step for the therapeutic use of stem cells.

➥ Treatment of heart disorders

Heart disorders, and especially cardiac insufficiency after the occurrence of an infarct, have been the subject of attempted treatments by the use of stem cells. The aim is to get the areas of the myocard affected by the infarct to recover a certain contractility by administering contractile stem cells to them.

These cells could be bone marrow stem cells which, in certain conditions, would be capable of producing cardiomyocytes.

Mr Philippe Ménasché et al. made the choice of transplanting skeleton muscle cells. A small fragment of the patient's thigh muscle was removed and placed in culture to obtain several hundred million muscle cells. These were then injected into multiple places of the non-contractile scar of the infarct during a conventional coronary bypass operation. Following the operation, some areas of the myocard which received this autograft recovered a certain contractility.

➥ Treatment of neuronal disorders

In 1998, the existence of brain stem cells capable of producing new neurons was demonstrated for the first time.

In 2003, Mr Pierre-Marie Lledo et al. of the Institut Pasteur/CNRS showed that immature neurons were to be found in the deep part of the brain around the lateral ventricles. In 2004, this team discovered that these immature neurons could migrate towards the front part of the brain, at the level of the olfactory bulb epithelium. They were attracted there by a molecule secreted by the latter. This could therefore allow these immature neurons to transform into adult neurons capable of establishing new connections. It had therefore perhaps become possible to get these neurons to head towards damaged parts of the brain in order to possibly participate in their repair.

But the first experiments in this respect in the mouse and the monkey have shown that major difficulties still remain. These did not however prevent a British team, very recently, from transplanting olfactory epithelium-derived neuron precursors into patients.

Cell therapy and gene therapy approaches can also be combined.

c – Combining cell therapy and gene therapy approaches

Gene therapy can be implemented either, as we have seen, by direct gene transfer or by the use of live cells as vectors of genes of interest.

In this paragraph we will address the use of live cells as the vector of genes of interest[38].

This pathway is relatively more complex than direct gene transfer. It can be divided into three steps:

· The cells of the patient or from other origins are first isolated and multiplied in the laboratory;

· The gene of interest is then introduced into these cells.

Genes can be introduced into cells by using two methods: transfection or transduction.

Transfection uses physical or chemical methods. Small molecules, like, in particular, liposomes, are employed to facilitate entry into cells of the DNA coding the gene of interest. Brief electric shocks can facilitate this entry. However it is difficult to control the destination of DNA. In most cases it disappears after a few days or a few weeks. In still rare cases, it integrates the host's DNA haphazardly.

Transduction uses viral vectors for DNA transfer. Per se, viruses introduce DNA or RNA[39] very effectively into cells. Genetically modified viruses can be used to introduce almost any genetic information. In most cases the genetic information introduced by a viral vector integrates the host cell's genome in a stable manner.

· Cells modified this way are introduced into the patient's organism.

A still difficult to control problem in this respect is the risk of an uncontrolled introduction into the host's genome, which can cause disorders leading either to malign tumours or genetic dysfunctioning.

If the cells introduced are not autologous, the patient's immune system may reject them.

This technique presents a certain number of advantages. Among these, mention can be made of the facility and precision of the *in vitro* rather than *in vivo* modification and the ease in multiplying cells, owing to the fact that they continue to divide in laboratory conditions.

The disadvantages result from the fact that an additional biological complexity is introduced owing to the live nature of these cells. In addition, the isolation of specific cells requires not only knowing their biological markers but

[38] According to the National Institutes of Health 'Regenerative Medicine' 2006.

[39] RNA (ribonucleic acid) is the macromolecule formed by the polymerisation of many nucleotides of which the sugar is ribose. It is present in the cytoplasm, mitochondria and also in the cell nucleus, and mediates the synthesis of proteins.

also the conditions in which they will remain alive *in vitro* and continue to divide. Unfortunately the specific biological markers of a large number of cell types are not known and cannot, as we have seen, be kept *in vitro* for long periods without mutating.

These achievements and advances are therefore highly encouraging.

But as emphasised by Mr Philippe Ménasché[40] *'[...] it should be said [...] that in the field of cell therapy clinical trials, the experience to date is very limited except for that of marrow grafts which have existed for a long time. Whether it is a matter of the brain, pancreas, or heart, few patients have today benefited from cell therapy, and* ***to be honest it should be stated that we are incapable today of saying whether the efficacy of cell therapy will be limited, very high or nil.*** *Nobody can know, even if a certain number of signs are encouraging. [...]. The first trials to have been performed are phase 1 trials testing feasibility, tolerance and not really efficacy. We are now going to enter the clinical trials phase designed to demonstrate efficacy, which remains to be demonstrated.* ***We must therefore remain prudent, especially with regard to patients, and not give rise to unfounded hopes'***[41]***.***

3 – Nuclear transposition

On 5 July 1996, the announcement by the researchers of the Roslin Institute in Edinburgh of the birth of the lamb Dolly, the first mammal cloned from adult cells, shook the news headlines. This event has considerably accelerated the development of cell biology... as well as controversies.

It is first necessary to present animal cloning, outline the nuclear transposition technique in man and take stock of its development. The prospects of this technique will then be addressed before mentioning the attempts to obtain embryonic stem cells without destroying the blastocyst. Lastly, it will be insisted on the need not to confuse nuclear transposition with reproductive cloning.

a – Animal cloning

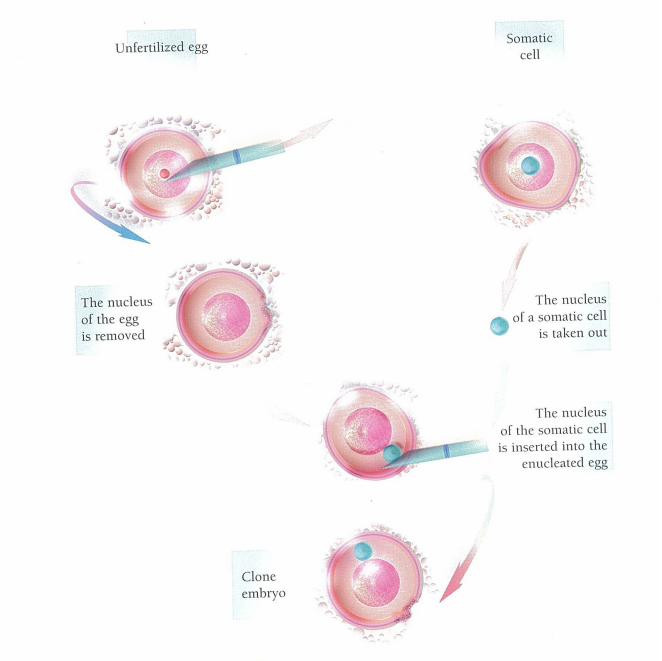
The beginnings of animal cloning date back to 1952 with the work by the American biologists Robert Briggs and Thomas King.

Before that date, we knew about natural cloning phenomena in some forms of invertebrates. But the cloning of invertebrates by human intervention appeared far more complex. Robert Briggs and Thomas King began their work on frogs by using 'somatic cell nucleus transfer'. This method had been theorised in a quite

[40] On 22 November 2005.
[41] I put the sentences in bold.

rudimentary manner in the 1930s by the German embryologist Hans Spemann, on the basis of his experiments on salamanders.

Animal cloning by nuclear transposition takes place as follows:



Source: *UNESCO Courier 2004*
Special issue 'Human cloning'

This method requires removing the nucleus of a somatic cell[42]. The nucleus is then inserted in an enucleated cell from an unfertilised ovum. The transplanted nucleus then begins to divide like in a normal cell.

By transferring embryo cell nuclei into enucleated eggs, Robert Briggs and Thomas King succeeded in obtaining tadpoles. But difficulties appeared when transfers were made using nuclei from more advanced cells. It then appeared that genes from cells at a more advanced stage of differentiation changed irreversibly and could not be reactivated. The cloning of an adult animal from one of its somatic cells therefore appeared impossible.

[42] In other words any cell of an organism, excluding reproductive cells.

However, at the beginning of the 1970s, the British biologist John Gurdon succeeded in cloning a tadpole from a somatic cell. However the application of this method to mammals appeared necessarily more difficult than with amphibians. First it is necessary to have mammal ovocytes, which are not very numerous and which must be obtained by invasive methods. Then the cloned embryos must be transferred into a 'substitute' mother's uterus to reach gestation.

Given all these difficulties, it was thought that the cloning of mammals would remain a remote possibility for a long time.

Therefore the birth of Dolly, using a modernised version of the techniques of Robert Briggs and Thomas King and John Gurdon, was a considerable event, opening up prospects of new medical techniques. It should however be recalled that it had been necessary to perform 277 nuclear transpositions for a viable foetus to reach the end of gestation and survive after birth.

This event was also the source of an unprecedented ethical upheaval.

The cloning of many mammal species has led, since then, to many viable births of porcines, ovines, bovines, cats, rodents, equids and rabbits. A dog was also created for the first time in April 2005 by Mr Hwang Woo-suk's Korean team.

The main aim of this research and these achievements is to master the genetic engineering of animals. The commercial interest is to have similar animals, especially to produce food (meat, milk) of constant quality. Other prospects are mentioned, like the production of products of pharmaceutical interest in cow or goat milk.

These results naturally received very high media coverage but we are apparently still far from perfect mastery of this technique in mammals.

First, it should be noted that such a clone might not be a perfect clone. In effect, the ovocyte in which the somatic cell is inserted possesses mitochondria containing a very small coding DNA for a few proteins thus conveyed to the embryo. But it is a subject of discussion between scientists, some considering that this contribution is entirely marginal and inconsequential.

The cloned embryos success rate is still very low. Mr Bertrand Jordan, for instance, stated[43] that '*in the mouse, it is generally necessary to treat a hundred or so ova to obtain a single clone, i.e. a 1% yield. The figure is comparable in cows, and also in sheep and goats. The pig appears more difficult to clone, with values of 0.1% to 0.2%'*.

The success rate does not appear to have improved. Indeed, to create the already mentioned dog, the Korean team collected on average 12 ovocytes from

[43] In 'Les marchands de clones' ('Clone Merchants') Seuil 2003.

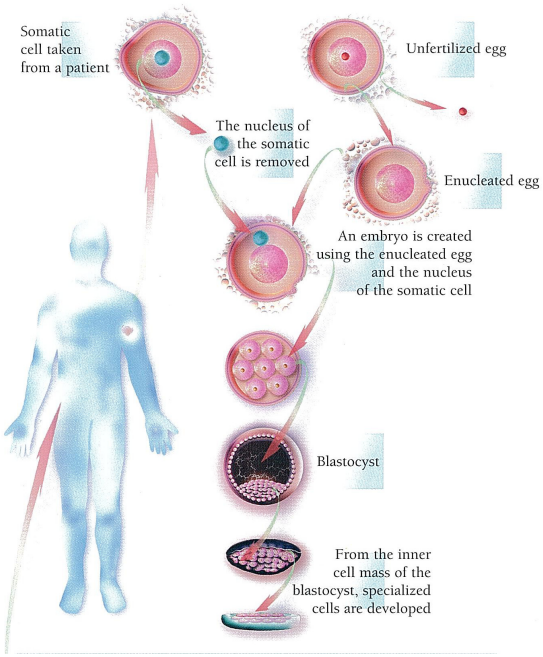
123 females to create nearly 1,500 embryos. 1,095 of these were transferred into the 123 females. Three commencements of gestation were recorded and two led to a birth, one of the pups having died from pneumonia after twenty-two days. So the success rate is particularly low.

Lastly, the ongoing debate between scientists should be mentioned on the issue of the state of health of cloned animals which apparently present anomalies in some cases. Knowledge of the mechanism of animal cloning from somatic cells is therefore still patchy.

b – Technique of nuclear transposition in man and its prospects

The aim of nuclear transposition is to obtain, by derivation, embryonic stem cell lines.

Nuclear transposition in man takes place according to the following diagram



Source: *UNESCO Courier 2004*
Special issue 'Human cloning'

The nuclear transposition process comprises three steps. Nuclear DNA must first be removed from the ovocyte by taking care not to damage it insofar as possible. An enucleated ovocyte and a somatic cell must then be fused. The

ovocyte must normally give the signal allowing the reprogramming of the somatic cell DNA. Last, the group of cells must be isolated from the internal mass of the blastocyst and grown on culture substrates.

Everyone still remembers the tremendous scandal caused by the falsification of data by Mr Hwang Woo-suk's team which claimed to have created human embryos and derived embryonic stem cell lines by this technique.

Presently, only the team of Mrs Alison Murdoch and Mr Miodrag Stojkovic, of the University of Newcastle upon Tyne, in the United Kingdom, has succeeded in creating a human blastocyst. But no embryonic stem cell line could be derived from it. This creation was documented in a publication[44] which has not been disputed.

According to an Article in *Science*[45], the teams engaged or having the intention of engaging in the creation of human embryonic stem cells by nuclear transposition are as follows:

Great Britain: apart from Mrs Alison Murdoch's team, Mr Ian Wilmut, now at the University of Edinburgh, has received an authorisation to perform human nuclear transposition experiments. But he does not have any ovocytes. According to him, a new British team from King's College was about to apply for authorisation to perform human nuclear transposition.

United States: three teams are reported to have the intention of engaging in this work, at the Harvard Stem Cell Institute, at the University of California, San Francisco (UCSF), and at the Memorial Sloan-Kettering Cancer Center in New-York.

In Europe, Mr Miodrag Stojkovic has left the University of Newcastle and set up in Spain where the legislation is expected to evolve in this respect.

Last, said article states that a team from the Institute of Biological Sciences in Shanghaï had applied for authorisations to perform work on human nuclear transposition.

c – Prospects of this technique

The creation of embryonic stem cell lines by nuclear transposition could have four fields of application: possibility of better knowledge of human diseases, better understanding of embryogenesis mechanisms, elaboration of new research instruments, and cell therapy.

---

[44] In *Reproductive Biomedicine Online* volume 11 no. 2 August 2005.
[45] Gretchen Vogel 'Picking up the Pieces after Hwang' *Science* volume 312 no.5773 28 April 2006.

➥ Possibility of better knowledge of human diseases

Many of my interlocutors emphasised that work on animal stem cells, and among them, on mice cells, was very important for fundamental aspects of biology and embryology. This work, for instance, allows the construction of human disease models. But they also noted that rats and mice are different from humans and that, even if the phenomena are similar, there are major differences.

The rat's nervous system is, for example, far less complicated than a human being's and the results obtained with such a model cannot in any case be directly extrapolated to humans. Similarly, a cancer can, for instance, be induced in mice, but that affecting human beings is not the same.

Obtaining diseased human material and follow-up, at cell level, of the development of a disease are very difficult. Embryonic stem cells would be very useful from this viewpoint.

It would indeed be possible to produce embryonic cells from which differentiated cells could be developed characterising various pathological states. As these cells develop very rapidly, it could thus be possible to follow, in fast-forward mode, the development of disorders. Fully-fledged disease models would thus be created in the laboratory. Parkinsonian embryonic stem cells or diabetic pancreatic stem cells could be created.

➥ Better understanding of embryogenesis mechanisms

I feel that research work on nuclear transposition should also lead to a better understanding of embryogenesis mechanisms.

In effect, when the nucleus becomes positioned in the cytoplasm of an ovum, some genes are then reduced to silence while others enter into action. Similarly, when the embryo becomes a blastocyst, errors can occur and stop this growth.

These crucial steps are also those of the development of a future child. Studies on nuclear transposition should therefore enable us to better understand, and therefore, better foresee all the problems leading to spontaneous abortions and miscarriages.

➥ Elaboration of new research instruments

Human stem cells could constitute an extremely useful instrument to test new drugs.

As recalled by Mr Marc Peschanski[46], drugs and cosmetics are today tested on models more or less remote from the human situation, and it is difficult to test all the effects of molecules on all the tissues of the human organism. Thanks to the very large variety of tissues and cells which develop in embryonic stem cell cultures, we have here a system reproducing a large part of the complex interactions between the organism's tissues and cells.

This instrument would undoubtedly be extremely useful to test, using high-density screening, the thousands of molecules kept in particular by large pharmaceutical companies in their combinatorial libraries. New drug candidates could thus be found and their efficacy and toxicity tested.

This is one of the strategic action lines of the new Institut des cellules souches pour le traitement des maladies monogéniques, I-Stem (Stem Cells Institute for the Treatment of Mongenic Diseases), located in Evry and mainly supported by AFM, Inserm and Généthon.

This approach would help reduce the number of tests necessary in animals whose physiology is different from man's. This would help decrease the development costs of new molecules. New targets in human cells could also be identified on which to act for therapeutic purposes.

➥ Cell therapy

Cell therapy would involve the use of embryonic stem cells derived by nuclear transposition, instead of and in the place of adult stem cells which have already been mentioned.

Two pathways open up in this field: transplantation of allogeneic cells and that of autologous cells.

· Transplantation of allogeneic embryonic cells

The transplantation of allogeneic stem cells leads to problems of immune rejection as with a conventional graft. Immunosuppressive drugs then need to be used, with all their possible undesirable effects.

Mrs Anne McLaren considers that it will not be envisageable to create stem cell lines for each patient. She therefore feels that research must be conducted on the antigenic properties of stem cells. To her mind, rejection is due to the presence of small proteins on the cell membrane.

The creation of embryonic stem cell banks could be envisaged which would be used to treat patients. The problem would then arise, as with the present organ

[46] On 22 November 2005.

banks, of compatibility with receivers. Great Britain has just set up a national stem cell bank under the aegis of the Medical Research Council.

· Transplantation of autologous embryonic stem cells

These stem cells will be produced by nuclear transposition from the somatic cells of the patient to be treated. They will therefore possess the same genome and will therefore not be subject to the immunological rejection triggered by xenografts.

These uses are based on a certain number of experiments performed, in particular, on mice. Various studies have shown that cardiomyocytes developed from murine embryonic stem cells are capable of colonising damaged heart tissue. Results concerning rats treated by the injection of such stem cells and which have regained mobility were presented to me by Messrs. Jeffray Rothstein and Douglas Kerr.

Many uses have been proposed for the employment of this type of cells.

They could for instance be used in all degenerative diseases in the repair of lesions, or in the reconstitution of damaged organs: Parkinson's disease, diabetes, traumatic injury of the spinal cord, Purkinje cell degeneration, Duchenne de Boulogne muscular dystrophy, and myocardial infarction. Alzheimer's disease, according to Mr William Lensch, would not be concerned by this type of treatment insofar as its causes are still unknown.

It should however be emphasised that these indications are only possibilities which remain today completely uncertain. From this viewpoint, the case can be quoted of type 1 diabetes. While embryonic stem cells can presently be differentiated into insulin-secreting pancreatic cells, these function very poorly without us knowing why.

I feel that these treatments are even further off in the future as no clinical trial, even in phase 1, is currently ongoing.

Mr Marc Peschanski however confirmed to me that Geron was going to perform this type of trials. They are expected to consist in the injection of embryonic stem cells into the spinal cord to obtain oligodendrocytes for the remyelinisation of nerve fibres, which we are presently incapable of obtaining another way. These trials were to take place at end 2005 but have had to be postponed. They should begin either at end 2006 or the beginning of 2007.

However, as the number of trials is increasing, difficulties are beginning to appear.

For instance, in a very recent publication[47], American researchers reported an attempt to treat Parksinson's disease with embryonic stem cell grafts. Transformed embryonic stem cells capable of producing dopamine were injected into Parkinsonian rats. The behaviour of the treated rats improved significantly with respect to the untreated group of animals. But their autopsy demonstrated that while transformed embryonic stem cells indeed developed, piles of undifferentiated cells, in other words potentially cancerous, were discovered.

Another difficulty arises from the fact that after a certain length of time the number of dopamine-secreting neurons apparently decreases. This study concludes that it is essential to work only with completely differentiated cells. Cell therapy with embryonic stem cells is far from perfected and we do not know when it will be so, if that is possible one day.

Nuclear transposition leads to the creation of a blastocyst, 'precursor' of an embryo, from which cells are extracted. Attempts have been made to obtain human embryonic stem cells without having to destroy the blastocyst.

d – Attempts to obtain human embryonic stem cells without having to destroy the blastocyst.

These attempts can be grouped firstly around the 'altered embryo' and cell fusion techniques before mentioning the two most recent attempts in this field.

➥ The 'altered embryo' technique

Various attempts have been made to create embryonic stem cell lines without being led to destroy an embryo.

The first technique was developed, using mice, by the team of Mr Robert Lanza from the American company Advanced Cell Technology in 2005.

Using the preimplantation diagnosis method, a cell was taken from a mouse embryo at a stage when it had eight. Embryonic stem cell lines could be produced from this cell. The original embryo, in which there remained seven cells, was implanted in the uterus of a mouse and, according to the statements by this team, pursued its growth normally till its term.

The second attempt was that by Mr William Hurlbut who proposed an 'altered nuclear transfer' technique.

---

[47] *Nature Medicine,* 22 October 2006 'Functional engraftment of human ES cell–derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes'.

The 'altered nuclear transfer' concept is based on the inactivation of a gene essential for the development of the trophoblast, which prevents the formation of the foeto-maternal barrier. This technique therefore produces blastocysts incapable of becoming implanted in the uterine wall, while leaving the internal cell masses intact.

The third method is that which has been developed by Messrs. Rudolf Jaenisch and Alexander Meissner. It consisted in creating a mouse clone embryo incapable of becoming implanted in the uterus by transferring the previously altered DNA of an adult cell into an enucleated ovocyte. The embryo obtained this way is not viable but allows embryonic stem cell lines to be grown. This approach could not however be applied to man.

Lastly, another attempt was made recently, in August 2006, again by Mr Robert Lanza's team at Advanced Cell Technology. The method described in the scientific journal *Nature* consists in extracting one cell out of the eight or ten of a three-day embryo. Embryonic stem cells are obtained after a series of manipulations. According to the publication, the embryo was not destroyed, whereas, to date, it was impossible to extract these cells without destroying the embryo. We will return back to this case.

On the basis of the good faith of this article in *Nature*, the general press conveyed this information, insisting on the fact that embryonic stem cells had been created without destroying an embryo. However this announcement was in fact misleading. Embryos were well and truly destroyed during this experiment.

➥ Cell fusion

This technique was developed and published in August 2005 by the team of Messrs. Chad Cowan, Douglas Melton and Kevin Eggan, from the Harvard Stem Cell Institute.

These researchers managed to fuse somatic cells, skin cells, with embryonic stem cells. They thus obtained tetraploid hybrid cells containing twice as many chromosomes as normal. They demonstrated that this cell fusion led to a form of deprogramming of the skin cell genome. Part of the skin cells returned to their embryonic stage by expressing the genes characteristic of embryonic stem cells.

Scientists had known for several years that embryonic stem cells could fuse with somatic cells to produce hybrids similar to stem cells. By genetically analysing hybrid cell lines, the contribution of this team has been to demonstrate that they presented the same genetic expression profile as normal embryonic stem cells and were very different from the original skin cells.

The major difficult of this technique is that the cells obtained comprise 92 92 chromosomes instead of 46. They naturally could not be used as such, especially for therapeutic purposes.

All these attempts are in fact specific to the American context which forbids public funding of research involving destruction of the embryo.

➥ Recent attempts in this field

We refer here to the work by a Japanese team and that by Mr Miodrag Stojkovic.

· Work by the Japanese team

A Japanese team directed by Messrs. Kazutoshi Takahashi and Shinya Yamanaka of the University of Kyoto announced, at end August 2006, that they had managed to induce, thanks to the introduction of four transcription factors, in mice fibroblast cultures, a pluripotent character resembling that of stem cells. Injected together, these four factors proved to be capable of transforming adult stem cells into cells that could differentiate into dissimilar tissues.

The pluripotent character of these cells was in particular confirmed by the formation of teratomas. The origin of these induced pluripotent cells also remains to be determined insofar as they could come from the few rare multipotent stem cells existing in fibroblast cultures.

It should however be noted that two of the four transcription factors are oncogenes, of which one is central in the genesis of tumours in man.

· Work by Mr Miodrag Stojkovic's team

According to a work published on 21 September 2006, researchers studied 161 embryos donated with parental consent by an *in vitro* fertilisation clinic. Thirteen of these embryos reached the stage of 16 or 24 cells before stopping. The researchers managed to extract an embryonic stem cell line from just one of these dead embryos.

According to Mr Miodrag Stojkovic, the aim of this research was to demonstrate that these embryos could supply an additional source of cells to those supplied by healthy embryos, rather than nurture competition between them.

A certain number of specialists have expressed their fears over this type of research on account of the possibility of undetected abnormalities on stem cells from dead embryos.

All these attempts are interesting and could have future applications: no research pathway is to be neglected. However, we may well wonder, with Mr

Hervé Chneiweiss[48], if this type of technical artefact is needed so as not to face the issue of nuclear transposition.

Nuclear transposition must not be envisaged without due consideration. A certain number of questions must be taken into account, especially ethical ones, but also others such as its possible repercussions on social protection systems. We will refer to these issues in the last chapter of this report on ethical challenges.

I feel that the controversy surrounding nuclear transposition has arisen with such intensity in our societies because it close to the issue of reproductive cloning whereas it is in fact entirely different.

e – Nuclear transposition is entirely different from reproductive cloning.

Reproductive cloning is the operation consisting in: creating an embryo bearing the same genetic information, save for the mitochondrial DNA, as the progenitor; implanting this embryo in a uterus to trigger a pregnancy and; lastly, giving birth to a human being. This is the transposal to the human being of the process that led to the birth of Dolly.

I very strongly and absolutely condemn reproductive cloning.

Reproductive cloning is forbidden in France by Article 21 of Act no. 2004-800 of 6 August 2004 on bioethics.

This article is drafted as follows: '*Any intervention is forbidden that aims at leading to the birth of a child genetically identical to another living or deceased person.'*

This practice is punished by thirty years' criminal imprisonment and a fine of 7,500,000 euros by Article 28 of said Act.

I approve these provisions without any reservations.

I wish to recall that the National Consultative Ethics Committee (CCNE) considered in the conclusion to its opinion no. 54 'Answer to the President of the Republic on the subject of reproductive cloning' of 22 April 1977, that *'replacement of procreation in the human species by a reproduction method using cloning techniques would constitute, biologically, symbolically and philosophically, a considerable disruption gravely jeopardising the dignity of the human person'.*

A certain number of international texts forbid reproductive cloning.

The 29th UNESCO Conference adopted in 1997, six months after the birth of Dolly, the Universal Declaration on the Human Genome and Human Rights

[48] On 22 November 2005.

which the United Nations took up in 1998. This Declaration sets forth in its Article 11 that 'practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted'.

In April 1997, the European Council promulgated the 'Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine' more frequently dubbed the 'Oviedo Convention'.

This and the problem it can pose will be examined in the chapter on the organisation of research in France.

On 8 March 2005, the United Nations General Assembly had to take a stand on a Declaration Banning Human Cloning.

This Declaration resulted from a Franco-German initiative adopted at the 78th Franco-German summit on bioethics that took place in Nantes on 23 November 2001.

On this occasion, France and Germany launched a proposal to ban human reproductive cloning within the framework of the United Nations General Assembly. This initiative was largely approved and a special committee of this organisation was then tasked with studying the possibility of elaborating an international convention on the banning of human reproductive cloning.

But the meaning of the original Franco-German initiative was diverted by a certain number of countries.

In effect, a paragraph of this text is drafted as follows: '[…] The Member States are invited to ban all forms of human cloning insofar as they are deemed incompatible with human dignity and the protection of human life […] '. This wording therefore led this Declaration not only to condemn human reproductive cloning but also to condemn nuclear transposition by adopting this voluntarily ambiguous position on the defence of human life.

Finally, this Declaration, without any binding legal value, was adopted by 84 votes against 34 and 37 abstentions. All the delegations condemned human reproductive cloning unequivocally, while a large number defended nuclear transposition.

France voted against this text. At the time, this vote appeared somewhat paradoxical to me. France indeed voted in New York against a resolution to ban nuclear transposition, whereas the provisions of the Act of 2004 maintained the principle of its ban.

I wish to recall, as I did so during the debate in second reading of the bill revising the 'bioethics' legislation, that **nuclear transposition is entirely different from reproductive cloning.**

There is no ambiguity: the sole aim of nuclear transposition is to create one or several embryonic stem cell lines and not to give birth to a human being. Nuclear transposition admittedly shares transfer of the nucleus with reproductive cloning, but **it differs from it** by the fact that the embryo obtained *in vitro* is not reimplanted in the uterus.

I deeply regret the confusion that has been fostered far too long between the two terms by the overly widespread use of the expression 'therapeutic cloning'.

This debate between nuclear transposition and reproductive cloning is in a way a victim of the acceleration of the acquisition of knowledge. In effect, before the birth of Dolly, nobody thought about condemning human reproductive cloning, quite simply because it was felt that this was, if not impossible, at least perfectly unthinkable scientifically! It was a subject left to science fiction authors.

The turns taken by the 'Hwang affair' appeared to bring us closer to its achievement but also demonstrated the difficulties in achieving it.

Admittedly, and this is abundantly emphasised by the opponents of this technique, the first steps of the processes leading to nuclear transposition and to reproductive cloning are common.

Mr Alain Fischer developed[49] an argumentation in response to this lumping together of the two techniques, which I adopt unrestrictedly:

'[The]*argument consists in saying that this technique is potentially dangerous for, alongside the possible benefits of a scientific or medical nature, it may be used for reproductive cloning. This argument can be debated for I feel that from the scientific viewpoint, there are today known notions as regards imprint problems which mean that it is far from obvious. Even if this argument was accepted, I feel that it is unreasonable to put it forward.* ***Per se, a scientific development is neutral: it is neither positive, nor negative. It is then necessary to regulate so as to promote socially 'useful' development, while avoiding a development which society rightly does not want*** [50] *[...] '.*

On the same day, Mrs Anne Fagot-Largeault similarly affirmed that 'the nuclear transfer or transposition technique is per se morally neutral. Everything depends on how it is employed'.

[49] On 22 November 2005.
[50] I put the sentences in bold.

It could be noted, in line with these opinions, that there are many techniques that can be diverted from a 'socially useful' use. I am thinking especially of nuclear energy which, as everyone knows, can be used destructively or entirely pacifically. And yet the same phenomena are implemented.

Fourth part:
Research absolutely must be pursued

This research must be pursued in many fields, and we will mention the present frameworks of its organisation in France, before turning to the European Union and each of its States. Stem cell research has a planetary dimension with two major poles of activity: the United States and Asia where the Republic of Korea occupied a special place till the end of 2005.

A – Need to pursue research

This research must be pursued in many fields and needs time. Time viewed by the media is diametrically opposed to long research time.

Cell therapy is still only in its early days but one day it will perhaps become reality. If it is to develop tomorrow, each type of stem cell, adult and embryonic, will have its usefulness depending on the type of disorder to be treated.

Many countries have started a major research effort. France cannot remain outside this research field lest it lose its best life sciences researchers.

There is also a risk, as Mrs Alison Murdoch reminded me, that the researchers of countries banning nuclear transposition will expatriate themselves to those authorising it.

From this point of view, this movement has no doubt already started, within the United States first, especially towards California. This is also the case for a certain number of American researchers, towards countries like Great Britain, Singapore or Israel. This movement is still very weak, especially after the revelation of the Korean failure in this field. But it could gain strength if major results were to be obtained in future years.

1 – Pursuit of research in many fields

a – Main pathways to be explored

It is difficult to draw up an exhaustive list of the scientific fields which must be explored, but, however, much remains to be done in terms of fundamental research.

Taking the risk of giving a few examples of fields to be studied, mention can be made of:

- Stem cell isolation (how to recognise them);
- Their characterisation and purification;
- Their growth;
- Their differentiation, which is a major issue;
- Their operation in their environment;
- Their autologous or heterologous insertion in a receiving organism;
- Their operation in this new environment …

b – Possible links between stem cells and cancer

Cancerous disorders[51] result from a series of genetic accidents that occur in steps. Anomalies accumulate on genes regulating the vital processes of the cell: division, differentiation, repair, apoptosis[52].

Loss of control over cell division is one of the main characteristics of cancerous cells. As stated by Mr Daniel Louvard and Mrs Sylvie Robine[53], 'the cancerogenesis process can effectively be summarised as a successive loss of the properties of cells which even forget the specialised 'work' for which they were programmed. *Tumoral cells thus return to a relatively undifferentiated state. In a way they take the opposite course to that of stem cells which differentiate as they divide. The study of this 'inverted mirror' can therefore help improve the comprehension of cancerogenesis'.*

At the public hearing of 22 November 2005, Mr Daniel Louvard mentioned the issue of the relations between stem cells and cancer.

---

[51] CNRS – Institut Curie – Press communique of 15 June 2005 'Cancer colo-rectal : le gène Notch ; nouvel acteur du développement intestinal' ('Colorectal cancer: the Notch gene playing a key role in intestinal development') .

[52] Apoptosis fits into an active process of cell self-destruction (suicide) by cell fragmentation, the resulting fragments being eliminated by phagocytosis.

[53] In *Le Monde* 18 June 2005.

He recalled that the concept of cancerous stem cells, whose existence had been postulated as early as the end of the XIXth century and which had received renewed interest in the 1930s, was again being studied presently.

The idea that cancerous cells possess the same properties as stem cells has indeed been acknowledged for several years. But it is only recently that techniques, especially markers, have been developed to identify the presence of stem cells in tumours. Thus, in 1997, cancerous stem cells were identified in certain types of leukemias.

Mr Daniel Louvard emphasised that the issue is currently being re-examined of knowing whether the perenniality and growth of a tumour could not be ascribed to a minority subpopulation of cells currently called 'tumoral stem cells'. He noted that this is what they are called without knowing in reality if they are really stem cells or cells derived from 'progenitor cells' which would 'themselves be derived from stem cells'.

However, some certainties are beginning to be established. It is known for instance, especially for brain or breast cancers, how to isolate and purify the subpopulations in question. Mr Daniel Louvard emphasised the minority nature of these populations by stating that to induce an experimental tumour in a mouse, it was sufficient to inject a few tens or less than ten of so of these cells.

In addition, he drew attention to the fact that tumours cannot be eradicated today, even after treatments have appeared to be effective. We are therefore in an impasse *'simply because we got the wrong target, because we kill cells that proliferate and differentiate and because we do not effectively kill the 1 to 2% of tumoral cells populating a tumour'.*

In their research activity, the teams of Messrs. Daniel Louvard and Spyros Artavanis-Tsakonas recorded in 2005 a major success by managing to develop a model that should help study more precisely the involvement of 'progenitor cells' and intestinal villi stem cells in the development of colorectal cancers.

This research appears very interesting and long-term cultures of tumorigenic cells having the properties of stem cells could offer an *in vitro* model to study the cells initiating the various forms of cancer. Eventually, this could help form instruments allowing the development of specific drugs and therapeutic strategies to eradicate the cancerous stem cells of tumours.

This research should be given the necessary time and should not have to adopt a rhythm prejudicial to its conduct. Time viewed by the media is diametrically opposed to long research time.

2 – Time viewed by the media and long research time

The public is presently wavering between fascination and mistrust as regards science.

Fascination, for everyone knows that the present lifestyle of the greatest part of the population of a developed country depends mainly on scientific progress, especially as regards health.

Mistrust also, especially in the health field, insofar as the major recent crises concerned this field, and underlying concern still exists.

However, despite this mistrust, our fellow citizens remain very interested by scientific facts because science provides knowledge often necessary to understand issues affecting their political, economic, social and cultural future. Scientific culture is therefore a major challenge for our society. Its dissemination involves various instruments including generalist media.

This is the journalistic mediation stage following on directly from the production of information in specialised scientific journals which cannot reach the general public. It is the journalist's job to be an intermediary between the production of knowledge and its reception by the public. This stage is the most visible insofar as it materialises by the presence or absence of scientific subjects in newspaper columns, and in radio or television programmes.

I am convinced that generalist media are a favourable means of disseminating scientific knowledge and that they play a major role in this field. However the relations between science and the media are sometimes difficult because their respective 'times' can differ greatly.

Science per se is barely adapted to the requirements of the mass media:

- First it has a complex content. The media must simplify this content which forces them to erase a large number of difficulties at the risk of distorting the initial information. Science needs time, explanation, and a reasoned discourse: it substantiates results by lengthy demonstrations, and by rational and complex explanations. Modern media, especially television, require rapidity, and often 'show' science without explaining it.

- Science produces few spectacular facts: it evolves slowly by successive discoveries that are often technical and not immediately applicable. Facts alone count and a new result must first be reproduced before being considered as acquired. The press tends to want to announce a miracle remedy whereas science can offer only uncertain promises and the advances it announces must previously have been confirmed.

- **Science produces few 'media' personalities as it is mainly based on collective work. The media however are rather inclined to prefer highly colourful personalities who know how to 'spin a story'.**

- **Science produces doubt and is open to criticism: researchers know that their results can be invalidated by others. The media often tend to neglect these doubts to present more appealing results**.

The great danger of this situation is that of turning science into a show, which could bring media pressure to bear on researchers. This of course does not easily mesh with the necessary serenity of the scientific process. Researchers must not be forced to abandon their questioning spirit and confuse their real results with those they would like to obtain.

It will undoubtedly always be impossible to get science and media 'times' to coincide perfectly, especially at a time when competition is getting stiffer between media and new competitors are arriving on the Internet. But I feel it is necessary to advocate a better match between science and the media, so that the latter do not lose their credibility in this field.

It should be noted that there is increasing competition between world scientific journals, as shown by various recent affairs.

B – Present organisation of research in France

We will first mention the problem posed by the Oviedo Convention, before examining the provisions of Act no. 2004-800 of 6 August 2004 on bioethics and the decree of 6 February 2006. It will then be necessary to take stock of research activity in France in the field of adult and embryonic stem cells.

1 – Problem posed by Article 18 of the European Council Convention on Human Rights and Biomedicine, known as the Oviedo Convention

a – Text of Article 18 of the Oviedo Convention

Article 18 of this Convention is drafted as follows:

"1 – Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.

2 – The creation of human embryos for research purposes is prohibited.'

The Additional Protocol of 12 January 1998 to this Convention states in its Article 1 'Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited."

France has not yet ratified either the Convention or its additional protocol.

b – Problem posed

The first paragraph of Article 18 does not pose any specific difficulty, emphasising only the need for the law to ensure adequate protection of the embryo when research on embryos *in vitro* is allowed.

On the other hand, the second paragraph, as underscored by the 'Explanatory Report'[54] of this Convention, *'prohibits the creation of human embryos for research purposes'.*

I feel this provision is not sufficiently clear insofar as it could ban nuclear transposition. This point should be clarified before France possibly ratifies this Convention.

The provision of Article 1 of the Additional Protocol prohibiting human cloning must also be clarified. The Netherlands, for instance has clarified this point in a note of 29 April 1998 by declaring that it interpreted the term 'human being' as referring exclusively to a born human individual.

It is therefore entirely desirable that this provision should also be debated in France and, if applicable, interpreted in the same way as in the Netherlands. This will be a recommendation of this report.

2 – Article 25 of Act no. 2004 – 800 of 6 August 2004 on bioethics

This Article 25, of which the text is annexed to this report, provides that, in addition to the ban on reproductive cloning:

'the in vitro conception of an embryo or the creation of a human embryo by cloning for research purposes is banned;
A human embryo cannot be conceived or created by cloning, or used for commercial or industrial purposes;
Any creation of a human embryo by cloning for therapeutic purposes is also banned'.

Article 28 of the Act, which was supported by the bill rapporteur at second reading, sets forth that non-compliance with any of these three provisions shall be punished by seven years' imprisonment and a fine of 100,000 euros.

[54] Available at http://conventions.coe.int/Treaty/fr/Reports.

It also sets forth the principle of the ban on research on the embryo, along with the possibility of derogations, and lays down the intervention of the Biomedicine Agency created by Article 2 of the Act. Delay in implementing this Act have made it necessary to introduce a transitory regime.

a – Principle of the ban on research on the embryo, along with the possibility of derogations

Research on the embryo is banned, but possibilities of derogations are provided for.

Research on the embryo and embryonic cells can be authorised by derogation for a period limited to five years if:

- It is likely to allow major therapeutic progress;

- Provided it cannot be pursued by an alternative method of comparable efficacy, in the present state of scientific knowledge.

Unlike the 1994 legislation, which formally banned any research on the human embryo, the 2004 Act sets forth, by way of derogation, for a five year period, the possibility of conducting research on human embryos and embryonic stem cells.

The criticism I made of the notion of 'major therapeutic progress' on 9 December 2003, at the National Assembly, at the second reading of the bill, still remains valid.

In effect, this notion can be interpreted strictly and it then restricts considerably the scope of the possible authorisation, bearing in mind the scale of the fundamental knowledge remaining to be acquired in this field. On the contrary, if a broad interpretation of this provision is adopted, it is then barely possible to discriminate between research that can be authorised and other research.

I feel these provisions are still highly tinged with hypocrisy as we do not know if it is finally a matter of allowing or refusing research on the embryo. I feel this maintains a certain cloudiness around this matter, likely to discourage and demotivate researchers.

The second necessary condition to authorise research on the embryo is also highly criticisable, leaving too much room to interpretation. If it is shown, at the time of the appraisal, that in practice this restriction was not finally applied, that would automatically weaken the authority of the law.

According to the law, this research can be performed 'only on embryos conceived *in vitro* in the framework of medically assisted procreation, and which

are no longer required for fertility treatment purposes' after written consent of the donor couple.

It should also be emphasised that it is now possible, after agreement of the Biomedicine Agency, to derive lines from embryos discarded after PGD insofar as they have therefore become spare. This is a positive application of the law which will allow researchers to have abnormal cell lines. These, as we have already mentioned, will be very precious in studying the evolution of many diseases.

b – Procedures for this research: intervention of the Biomedicine Agency

This type of research cannot be undertaken unless its protocol has been authorised by the Biomedicine Agency created by the bioethics Act.

The Biomedicine Agency can authorise this research only on the basis of its scientific relevance, the manner of its implementation with regard to ethical principles, and its interest for public health.

This Agency must also previously authorise imports of embryonic stem cells or foetal tissues as well as their export. An authorisation is also required from it to store these products.

The ministers of health and research can appeal against the Agency's decisions. They can ban or suspend the execution of a protocol if its scientific relevance is not established or if ethical principles are not respected. They can also ask the Agency for a new examination of a protocol it has refused.

The Act laid down in the last paragraph of Article 25 that a decree would fix the conditions for the authorisation and implementation of research on human embryos. Pending the publication of this decree, Article 37 provided for a transitory regime.

Delay in implementing the Act made it necessary to introduce a transitory regime which lasted until 6 February 2006, i.e. eighteen months.

c – Delay in implementing the Act: the transitory regime

The provisions of Article 37 of the 2004 Act were therefore applied.

These set forth that authorisations, which are issued by the Biomedicine Agency (use for study and research purposes, storage, import and export), are transitionally to be issued jointly by the ministers for research and health after obtaining the opinion of an *ad hoc* committee. Its members, scientific experts and non scientific members, were appointed by the order of 28 October 2004, and its first meeting took place on 25 November 2005.

From September 2004 to February 2006, 40 authorisations were issued by the competent ministers, thus allowing ten or so teams to start research.

At the public hearing of 22 November 2005, a certain number of researchers present regretted the length of time to obtain an authorisation and the lack of flexibility of the procedures.

The length of time to obtain an authorisation was around approximately four months. This seems reasonable bearing in mind the newness of the procedures and compared with the situation in Great Britain where this period of time was approximately six months according to Mrs Alison Murdoch and Mr M Ian Wilmut. The lack of flexibility of procedures must have been real, but the Biomedicine Agency took account of this experience.

This committee therefore had to examine dossiers on the basis of the criteria set by the legislation. It is interesting to examine how, according to the *ad hoc* committee's report, the criteria regarding 'major therapeutic progress' and 'absence of an alternative method of comparable efficacy' were respectively envisaged.

➥ Criterion regarding 'major therapeutic progress'

The activity report notes in this respect:

"The committee considers that the therapeutic purpose is not limited to research on therapeutic applications and that fundamental research as the prerequisite for therapeutic applications is included in this purpose. It therefore feels that research whose therapeutic applications are remote can be considered as likely to allow major therapeutic progress insofar as it constitutes a prerequisite for projects with more direct therapeutic applications.

The committee however requires applicants, even if no result can be expected in the short term, to specify the therapeutic applications to which their project could lead […]".

The committee therefore refused an authorisation for a dossier referring merely to cosmetology research.

It can be seen that the committee was thus obliged to have an extensive conception of 'major therapeutic progress' to be able to authorise applications. As I noted in December 2003, this makes these words of the legislation inoperative. They should therefore be deleted.

➥ Criterion regarding the 'absence of an alternative method of comparable efficacy'

The committee considers from this viewpoint:

'The committee examines the information supplied by the team on the alternative methods based, in particular, on the use of adult stem cells. It takes pains, in particular, to check if research has already been undertaken on animal embryonic stem cells but does not require this research to have already produced conclusive results on animals. The absence of results on animal cells does not lead it to refuse research being undertaken on human embryonic stem cells […]'.

Here again the committee is obliged to apply the provisions of the legislation very broadly. These provisions should not be kept either.

We will see at the end of this chapter that I propose to replace these provisions, which have not proved their efficacy, by those provided for by the text voted at first reading by the National Assembly in January 2002.

By allowing ten or so teams to start research on stem cell lines of foreign origin, the *ad hoc* committee has played a very positive role in the commencement of research in France on embryonic stem cells. All of those heard at the public hearing's day acknowledged this.

However, I feel that this delay in the implementation of the Act has been entirely excessive and extremely prejudicial to researchers and the organisation of research in France.

3 – Decree no. 2006-21 of 6 February 2006 on research on the embryo and on embryonic cells and modifying the public health code[55]

The first paragraph of this decree attempts to clarify ' major therapeutic progress '. It is drafted as follows:

"Are in particular likely to allow major therapeutic progress, according to Article L. 2151-5, embryo and embryonic cell research pursuing a therapeutic goal for the treatment of particularly serious or incurable diseases, as well as the treatment of embryo or foetal disorders."

It can be seen that the therapeutic prospect is the goal, which gives quiet a broad scope to research and should not hinder it. This is therefore closely akin to the *ad hoc* committee's appreciation of this point.

This decree therefore allows researchers to create and work on human embryonic stem cell lines from spare embryos conceived *in vitro* in the framework of medically assisted procreation in the French territory, and on imported cell lines created in the same conditions.

Three types of research are authorised, using:

[55] The text of this decree is appended.

· Spare embryos that are no longer required for fertility treatment purposes. The parents must give written consent for the donation of the embryo for research, without remuneration. This consent, once given, must be reaffirmed after a three-month reflection period;

· Embryos in a condition unsuitable for reimplantation or for storage for a future pregnancy, provided the parents give their authorisation;

· Embryos carrying an abnormality screened for in preimplantation diagnosis, provided the parents give their authorisation.

The decree specifies the procedures for authorising research on the human embryo and on embryonic stem cells.

These authorisations are now issued by the Biomedicine Agency.

4 – The Biomedicine Agency

Created by Article 2 of Act no. 2004-800, the Biomedicine Agency is a public administrative establishment under State control (ministry of health). It has taken over from the Etablissement français des greffes (French transplantation agency), and therefore deals with the four fields of graft harvesting and transplantation, embryology, procreation and genetics.

The Biomedicine Agency intervenes as regards the authorisation of research, external exchanges, traceability, and the follow-up and monitoring of research.

a – Authorisation of research

It examines and authorises the research protocols proposed by French scientific teams.

Having completed a standard dossier, applicants send in their application to the Agency in accordance with a schedule of transmission periods fixed by the director general. In 2006, for instance, these periods were as follows: 1 March - 30 March; 15 May - 15 June; 1 October – 30 October.

If the dossier is admissible, the director general must take his decision within four months of the end of the transmission period in question. Any request for additional information prolongs the time period.

Each research project is assessed by two scientific experts appointed by the Agency's director general. A debate then takes place within the college of experts.

The project is then studied by two rapporteurs, members of the Agency's orientation council, who present it to this body.

The orientation council gives its opinion.

This council brings together scientific and medical experts, human sciences experts, representatives of associations and of various institutions, and parliamentarians. It makes sure the Agency's action is coherent, and ensures compliance with the regulatory and ethical principles applying to these activities.

The director general then takes his decision which is communicated to the ministers for health and research.

If the Agency takes a negative decision, the ministers may ask it to reconsider the protocol. Should a positive decision be taken, the ministers may cancel or suspend the protocol if its scientific relevance is not established or if ethical principles are not respected.

b – Authorisation of external exchanges

Any organisation wishing to import foetal tissues or embryonic cells must obtain a research or storage authorisation. It must ensure that these tissues or cells have been obtained in compliance with ethical principles as stated in the bioethics Act and, especially with the consent of the parents and without remuneration.

The Agency is also empowered to authorise exports of these tissues and cells.

c – Traceability

The Agency holds a national register of embryos and human embryonic cells, the information being transmitted by the bodies authorised to create or import such lines. These bodies must also hold a register of the biological equipment held. Identification systems ensure traceability of embryos and the cells derived from them, while assuring anonymity for the persons donating embryos.

d – Follow-up of research

After the protocol has been approved, the person responsible for the research must send the Agency an annual progress report on the work and a final report at the end of the authorisation. If the protocol is modified while research is being conducted, such modifications must be submitted to the Agency which considers them according to the same process as the initial application.

e – Monitoring of research

The Agency can perform inspections with its personnel. Mrs Carine Camby told me for instance that an inspection is made within 18 months of an authorisation. Should legislative or regulatory provisions be breached, or if the

authorisation framework is not complied with, the research can be suspended for a maximum three-month period by the director general who accordingly informs the orientation council.

Admittedly it is too early to make an appraisal of these arrangements but I feel they are entirely satisfactory. The community of researchers also apparently expresses its satisfaction.

The Agency has already authorised 10 research projects on embryos.

5 – What is France's commitment as regards stem cells?

France's situation is characterised by a weakness of financial and human means, making public intervention necessary.

a – Weakness of human and financial means

➥ Human means

There is a very great contrast between the number of teams working on embryonic stem cells and on adult stem cells.

Indeed, while ten or so teams are working – or, for some of them, are going to work – on embryonic stem cells, several dozen teams are conducting research on adult stem cells. I mentioned some of these teams in the passage on adult stem cells.

However, while there is no difficulty in knowing about activities involving embryonic stem cells, because authorisation is necessary, the same does not apply to adult stem cells.

The exact number of teams involved in research on adult stem cells is apparently not at all known precisely. Research teams are recorded on the basis of the therapeutic purpose of their studies, for example neurological studies, rather than on that of the means employed, for instance cell therapy. It would however definitely be useful for a precise list to be made of all the activities undertaken in France on adult stem cells. This will be a recommendation of this report.

This disproportion of activity between embryonic and adult stem cells is entirely normal, given the fact that until the 2004 Act was voted, it was forbidden in France to work in the embryonic stem cells field. The present consequence is however a major lack of competences in this speciality which it was banned to exercise in France.

It will no doubt take quite a long time to set up a large number of teams competent in this field. One way of quite rapidly obtaining these competences

would be to get a certain number of post-docs currently in jobs abroad, and especially in the United States, to return to France.

During my trip to that country, I therefore met a large number of these French post-docs. Some told me of their desire to return to France but admitted they were concerned about finding not very favourable work conditions.

A few have nevertheless returned. Some have found entirely satisfactory work conditions, but the problem of their remuneration remains a major issue. They have often had to accept a considerable financial sacrifice.

➥ Financial means

The financial effort and very great activity of Inserm in this field are to be emphasised.

Mr Christian Bréchot indeed stated[56] that *'for several years, Inserm has committed significant sums in this field. […] Inserm spends for instance 15 million euros, in aggregate cost, for the units working in this sector'.* Until now, the very great majority of Inserm's expenditure was devoted to adult stem cells, given the legislation in force.

Apart from these sums, 'since 2001, Inserm has, with several partners, especially the Association Française contre les Myopathies (AFM – French Association against Myopathies), Juvenile Diabetes Research Foundation (JDRF), Vaincre la mucoviscidose (VLM – Overcoming Mucoviscidosis Association), and the Ministry of Research, etc., supported project programmes to the tune of 8 to 10 million euros in all, leading to nearly twenty-four research projects being submitted'.

As part of these activities conducted since 2001, Inserm has launched three invitations to tender for the creation and support of research projects and networks having therapeutic aims regarding adult stem cells:

- 2001 invitation to tender (AFM and Inserm): support for fifteen projects funded over two years: 1.22 million euros, including 300,000 euros per year provided by Inserm;

- 2002 invitation to tender (VLM, AFM, Ministry of Research, Inserm) : support for sixteen projects funded over eighteen months: 1.77 million euros, including 366,000 euros provided by Inserm;

- 2003 invitation to tender (Ministry of Research, AFM/JDRF, Inserm, 'adult stem cells research programme': thirteen projects funded for three years: 3.9 million euros, including 260,000 euros per year for three years provided by Inserm.

[56] On 22 November 2005.

The research fields mainly concerned by these invitations to tender are haematology, dermatology, cardiology, neurology and hepatology.

Lastly, Mr Christian Bréchot recalled the importance of European projects based on the use of stem cells, including the Genostem programme on mesenchymal stem cells, resulting from the 6th Framework Programme for Research and Development (FPRD), which has an appropriation of 8.7 million euros and a planned length of four years, from 2004 to 2008. This programme will be presented in the chapter on the organisation of research in the European Union.

Mr Michel Van der Rest stated[57] for his part that the 'stem cells' topic concerned approximately 10% of the research potential of the 'Living organisms' department at the Centre national de la recherche scientifique (CNRS – National Centre for Scientific Research). He added that the sums involved at CNRS probably represented approximately 7 million euros.

These are considerable sums but not commensurate with the challenge or the effort undertaken in this field by other countries like Great Britain.

b – Need for public intervention

All my French and foreign interlocutors particularly insisted on the need for public intervention in this research sector, insofar as, for reasons we will examine in the last part of this report, the investment of private companies in France is currently practically completely absent.

Public intervention is necessary for, as we have seen, stem cells are still a fundamental research field which must be developed to attract private investment in the future. Mr Philippe Pouletty therefore emphasised that *'if States do not make a very great funding effort for research on this type of innovation, private companies and investments will not be able to take over'.*

From this viewpoint, I feel that the present French policy is totally unsuitable insofar as no public funding is visibly assigned to this field.

For instance, no invitation to tender has been made by the new Agence nationale de research (ANR – National Research Agency) as regards stem cells, whether adult or embryonic. I was told that ANR programmes are organised on the basis of their therapeutic purpose and not on that of means. Stem cells may therefore be concerned by research on such or such a type of disease.

I feel that research on the topic of adult and embryonic stem cells must be **brought into the limelight**. **The State must indicate its priorities through the ANR's invitations to tender** which will thus exercise a leverage effect on the

[57] On 22 November 2005.

sector and could also lead to a grouping of teams in poles of excellence. These will be recommendations of this report.

The public effort is thus easily identifiable and must also be **perennial**, in proportion to this sector which implies long term research.

A certain number of structures that can serve as a model for these groupings in poles of excellence are beginning to exist. This is the case of the pole in Evry where Génopole and the young structure I-Stem are already located. I-Stem is the stem cells institute for the treatment of mongenic diseases, supported and funded by the AFM, Inserm, the University of Evry Val d'Essonne and Génopole. The Essonne General Council also participates in funding various pieces of equipment.

It does not however appear useful to physically bring together all teams working on stem cells. The aim would rather be to create a 'wall-less laboratory' structure bringing together public and private competences in the field of embryonic and adult stem cells so as to achieve cross-fertilisation of all the work. This type of structure would also have the very great advantage of avoiding a 'sprinkling' of public and private means, the latter being mainly of associative origin.

6 – Legislation on embryo research is to be changed and nuclear transposition legalised

a – Legislation on embryo research is to be changed

This legislation is to be changed by deleting the provisions of Article 25 of the Act of 6 August 2004 that are taken up in the drafting of the first four paragraphs of Article L 2151-5 of the public health code.

On the other hand, the provisions on the role of the Biomedicine Agency will be kept as it has been devised in a balanced manner and its operation has been satisfactory to date.

I propose that the deleted provisions be replaced by those of the first two paragraphs of Article 2151-3 of the public health code, in the drafting given by Article 19 of the bioethics bill voted at first reading by the National Assembly in January 2002 and whose text is appended. This will be a recommendation of this report.

The first paragraph of this text sets forth that 'research on the human embryo and embryonic cells is authorised which has a medical purpose, provided it cannot be pursued by an alternative method of comparable efficacy, in the present state of scientific knowledge'.

This text appears more balanced to me and free of the hypocrisy of the provisions adopted in 2004.

b – Nuclear transposition is to be authorised

I feel that this authorisation is now essential to allow France to remain a major scientific nation and to encourage a certain number of French post-docs to return. This will be a recommendation of this report.

This legislation must be preceded by a major public debate, which could be organised by the Biomedicine Agency.

This agency should be tasked by the future Act with a major role regarding the implementation of this new legislation which shall provide for strict monitoring of nuclear transposition.

These two legislative modifications should not wait until the end of the period laid down by the 2004 Act, i.e. 2009, but should start to be debated as of 2007, after the election dates. This will be a recommendation of this report.

I sincerely hope we take advantage of the pre-electoral period to debate these issues in a very broad democratic debate.

I am not hostile to nuclear transposition, apart from the issue represented by ovocyte donation. I feel it is necessary to authorise this technique, on the one hand, for fundamental research and, on the other hand, given the international context, to avoid France and Europe losing their footing in this essential field.

I feel that the situation has evolved since 2004 and that it is **probably possible** to reach a political agreement on the authorisation of this technique. I have thus seen with great interest that opponents to this measure in 2004 have publicly changed opinion. This makes me very pleased for this will strengthen the chances of French research in international competition.

But there is an absolute prerequisite: the ethical conditions of ovocyte donation are to be determined. I will address this issue in the last part of this report.

C – Organisation of research in the European Union

The European Union intervenes in research on stem cells through the Framework Programmes for Research and Development (FPRD).

Framework programmes are the main financial instruments of the intervention of the European Union regarding research and development in nearly

all scientific disciplines. A framework programme is proposed by the European Commission and adopted by the Council of Ministers and European Parliament in accordance with a codecision procedure.

Framework programmes have existed since 1984 and cover a five-year period beginning in the last year of the previous programme and ending in the first year of the following programme.

The present framework programme, the sixth, began in 2002 and is to end at the end of 2006. The seventh framework programme, for its part, is to begin on 1 January 2007 and finish in 2013, in other words an exceptional length of seven years.

1 – Sixth Framework Programme for Research and Development

Under FP6, the European Union has funded collaborative research projects on stem cells. These projects concern stem cells either as subjects of study in themselves, or as discovery means, or biological tools of broader projects. On the other hand, projects using stem cells as non-specific tools, for instance to create animal models, are not included in it insofar as they are used by all laboratories on a daily basis.

These research programmes are grouped under seven chapters[58] :

- Understanding - Fundamental knowledge relevant to human health
14 programmes, allocation: 107,893,900 euros

- Developing - Tools for new therapies and medicines
14 programmes, allocation: 83,278,920 euros

- Repairing – Preclinical and clinical studies for diseases and impairments
5 programmes, allocation: 18,057,200 euros

- Treating – Improvement of standard hematopoietic stem cell transplantation
3 programmes, allocation: 15,500,000 euros

- Building – Tissue engineering
14 programmes, allocation: 69,076,405 euros

- Testing – Alternatives to animals for toxicology tests
2 programmes, allocation: 11,359,754 euros

- Valuing – Ethical, legal and societal aspects

[58] Source: European Commission: 'Stem Cells. European research projects involving stem cells in the 6th Framework programme' 14 December 2005.

5 programmes, allocation: 4,834,514 euros

These research programmes concern adult stem cells.

FP6 has totally excluded from its funding research aimed at:

- The creation of human beings by reproductive cloning;

- Modification of the human genome which may be transmissible;

- The creation of human embryos for research purposes or for the purpose of creating embryonic stem cell lines, in other words nuclear transposition.

As regards human embryonic stem cells, European funding was reserved for projects concerning the derivation and use of cells from spare embryos that would have been destroyed and for which the parents had authorised donation for research.

But this type of stem cells was accepted only in specific cases as no invitation to tender concerned them directly and alone. Priority was therefore given in all circumstances to research on adult stem cells.

However, fourteen programmes comprising at least one research component involving human embryonic stem cells were nevertheless funded by this FPRD.

Only one of these programmes was entirely devoted to human embryonic stem cells. This is the ESTOOLS programme devoted to the characterisation of the 52 human embryonic stem cell lines. It has been allocated a 12 million euros budget and groups twenty participants from ten different countries.

Before addressing the 7th Framework Programme, it appears interesting to refer rapidly to the Genostem project, a major project coordinated by Inserm

The aim of Genostem is to develop research on adult stem cells to repair conjunctive tissue in inflammatory diseases. This programme has been allocated a budget of 8.752 million euros and groups 23 partners from 9 European countries and Israel.

Genostem has three goals:

· Fundamental research: phenotypic and genetic characterisation of mesenchymal stem cells, thanks to new tools developed in genomic and proteomic technological platforms;

· Pre-clinical trials in animals;

· Treatment of inflammatory diseases by the search for methods of delivering growth factors and allowing the regeneration of cartilage, tendons and bone.

A recent discovery is to be credited to this project. In effect, the Israeli team that is part of this project obtained, in the rat, the repair of a tendon damaged by the transplantation of modified mesenchymal cells. The next step of this research will be the performance of trials in a bigger animal.

The first appraisals of FP6 will be made in the months ahead at the time of the commencement of FP7.

FP7 has been difficult to elaborate in the field of embryonic stem cell research.

2 – Difficult elaboration of the seventh FPRD as regards embryonic stem cell research

The discussion prior to the elaboration of FP7 as regards stem cell research gave rise to certain difficulties. These result from the different approaches in Europe as regards embryonic stem cells, as we will see in detail in the following chapter, country by country.

In effect, some European countries are hostile to research on human embryonic stem cells. They either purely and simply ban it, like for instance Austria, or have a more ambiguous attitude, like Germany which bans their creation but authorises their import.

Throughout the preparation of FP7, opposition to Community funding of this research remained strong both at the Council of Ministers and the European Parliament. But changes have occurred in recent months.

For instance, on 15 June 2006, the European Parliament gave a decisive vote in this field in favour of the explicit possibility of FPRD support for this type of research in the Member States where it is authorised.

At the Council of Ministers, the new recently elected majority in Italy decided no longer to oppose Community support for this research. The major consequence was that countries wanting a ban of this research no longer had a blocking minority at the Council of Ministers.

On 24 July 2006, the EU Council of Ministers finally approved the funding of research on embryonic stem cells.

This agreement provides for the authorisation, under conditions, of the funding out of Community funds of research activities involving human embryonic stem cells.

This research will be highly framed. It will concern only projects using already existing embryonic stem cell lines and will be implemented only in Member States where it is authorised.

It was under these conditions that a compromise was obtained, although five of the Member States refused to sign the final text: Poland, Austria, Malta, Slovakia and Lithuania.

The European Parliament should be in a position to vote the text at its next session of 29-30 November 2006. The Council of Ministers, for its part, should be able to take its final decision on 5 December 2006. FP7 should therefore be adopted on that date as well as the specific programmes and participation rules. The first calls for proposals should be launched at the end of December or the beginning of January 2007.

Under the pressure of Germany, the ministers added a Commission statement whereby it commits not to present, before the Committee of Member States which must give its agreement on a case per case basis, research programmes involving the destruction of human embryos, including the harvesting of stem cells. Only projects on already established line will be funded.

This situation is likely to considerably jeopardise European research by encouraging researchers to head to places where they are authorised to work and can find considerable funding. This is likely to even further accentuate the diversity of situations of EU countries.

D – Diversity of the situation in EU countries

We will briefly present the situation in the various EU countries as regards human embryonic stem cells, adult stem cells not raising any specific problems.

1 – Austria

The main Acts on embryonic stem cells are the Act on genetic techniques and the Act on medically assisted procreation.

The first text, dating back to 1994 and amended in 1998, addresses genetic analyses on man, gene therapies and genetically modified organisms. The second, dating back to 1992 and amended in 2001 and 2004, is devoted to artificial insemination and embryo transfer.

According to the latter Act, cells capable of developing, in other words fertilised ovocytes and embryonic stem cells deriving from them, can be used only

for medically assisted procreation. Their therapeutic use and research on them are banned. Nuclear transposition is therefore also banned. This text also prohibits any intervention on germ cells.

Austria refused to sign the European Council Convention on Human Rights and Biomedicine (Oviedo Convention) and its additional protocol, considering that Austrian regulations were more strict and more explicit.

2 – Belgium

Research on embryos and embryonic stem cells is governed by the Act of 11 May 2003.

According to Article 3 of this Act, research on human embryos *in vitro* is authorised, if in particular:

- It has a therapeutic purpose or is aimed at the advancement of knowledge on fertility, sterility, organ or tissue grafts, and the prevention or treatment of diseases;

- It is based on the most recent scientific knowledge and meets the requirements of a correct scientific research methodology;

- It is performed in an approved laboratory;

- It is conducted on an embryo during the first fourteen days of development, excluding the frozen period;

- There is no alternative method of comparable efficacy.

Article 4 of this Act authorises nuclear transposition by banning the creation of an embryo *in vitro* for research purposes except if the aim of the research cannot be reached by research on spare embryos.

It is interesting to note that the second paragraph of this Article 4 tries to settle the ovocyte donation issue by setting forth that 'the stimulation of ova is authorised if the woman concerned is of age, gives her agreement in writing, and if this stimulation is scientifically justified'.

Lastly, Article 6 of this Act bans reproductive cloning.

According to the scientific department at the French embassy, research on embryonic stem cells does not appear to be a subject of political debate.

3 – Cyprus

There is currently no specific legislation in this field in this country.

4 – Czech Republic

The Act of 12 May 2006 lays down that human embryos cannot be created to pursue research (ban on nuclear transposition). On the other hand, research can be performed on spare embryos, whether Czech or imported, from assisted procreation.

This Act authorises the creation of new embryonic stem cell lines. Research can be performed only on nationally created lines or ones imported from countries complying with the laws and regulations of the Czech Republic or on spare embryos from assisted procreation. This research can be pursued only if it leads to the development of diagnosis and therapeutic progress, once conventional animal experimentation resources have been exhausted.

At the University of Masaryk in Brno, the Faculty of Medicine biology department groups fifty or so persons working on human embryonic and adult stem cells and on animal stem cells.

5 – Germany

a – Legislation

The Act on protection of the embryo of 13 December 1990 entered into force on 1 January 1991 and bans in particular:

· The creation of human embryos for research;

· Any use of human embryos for purposes other than their storage;

· Gene transfer into human germ cells;

· The extraction of totipotent cells from a human embryo, for instance for research or diagnosis;

· Cloning;

· The creation of chimeras and hybrid beings from animals or humans […].

The Act of 28 June 2002 however authorises German researchers to work on imported human embryonic stem cell lines provided they were established before 1 January 2002.

This date was set before the entry into force of the Act to prevent the import authorisation from encouraging the creation of spare embryos abroad. Only cells produced from spare embryos initially created for reproductive purposes and no longer required for fertility treatment purposes can be imported but without remuneration.

Lastly, the import of embryonic stem cells and the use of embryos must not infringe the regulations of the countries of origin of the cells and the German Act of 13 December 1990.

b – Research projects

Research projects must be examined and assessed by the Central Board for Stem Cell Research Ethics to determine if they meet the legal requirements and are justifiable from an ethical viewpoint.

In Germany, as in France, only research on human embryonic stem cells likely to allow major therapeutic progress and that cannot be conducted by an alternative method of comparable efficacy is authorised. Presently, 19 research projects using human embryonic stem cells are authorised.

Differences in legislation between France and Germany make Franco-German cooperation in this field very difficult. No such cooperation exists at present.

c – The debate in Germany

As seen, the German law is very restrictive. The regulation on the date of import of stem cells forms the crux of the debate.

Scientists criticise in particular the penalties risked by German researchers participating in international research projects on embryonic stem cells established after 1 January 2002.

From a scientific viewpoint, they consider that the quality of human embryonic stem cells available in Germany is deteriorating as time goes by.

The German government apparently does not want to modify the current state of legislation applicable, in particular regarding the last permitted date for the production of stem cells. It has been seen that a number of difficulties in the negotiation of FP7 were due to the German attitude in this field. A number of German scientists dread that their country will fall considerably behind in this field and therefore fear a brain drain.

6 – Denmark

The Danish Act of 1997 on medically assisted procreation was amended on 1 September 2003, thereby allowing research on human embryonic stem cells, in order only to acquire new knowledge to improve patient treatment possibilities.

Nuclear transposition is presently banned.

Embryonic stem cell lines can be created from spare embryos only for a research project approved by the Danish National Committee for Biomedical Ethics, and after the donating couple has consented.

7 – Estonia, Lithuania, Latvia

Research on human embryonic stem cells has not reached a significant level in these countries. The authorities of these countries have not yet legislated on this matter.

8 – Greece

The Act of 23 December 2002 authorises the use of spare embryos for therapeutic and research purposes, with the prior and informed consent of the persons concerned.

This Act explicitly bans nuclear transposition.

9 – Spain

Until 2003, the Act on assisted procreation banned the creation and use of healthy embryos for scientific research purposes.

The Act of 21 October 2003 authorised research using stem cells from spare frozen embryos no longer required for fertility treatment purposes.

This legislation was preceded by two initiatives undertaken in Andalusia and in the Autonomous Community of Valencia. In these two regions, several human embryonic stem cell lines were created from human embryos before this practice was legalised nationally.

With the return to power of the PSOE, these local initiatives have been incorporated in a stem cells decentralised national network.

In September 2006, the Spanish government announced it had prepared a bill authorising nuclear transposition, which will be submitted to the vote of the Spanish deputies.

10 – Finland

Finland is in a somewhat ambivalent situation. The law does not explicitly allow nuclear transposition, but it is accepted that as this technique is not explicitly banned, it is 'accepted' only as part of clinical research.

The 1999 research Act authorises the creation of human embryonic stem cell lines from spare embryos from *in* vitro fertilisation whose storage period, in theory three years, has expired. Consent of the two gamete donors is necessary before beginning any research, and prior approval of the Ethics Committee is essential.

Given these flexible regulations, research centres have developed in Finland in this field in Helsinki and in Tampere.

11 – Hungary

This country's legisalation dates back to the middle of the 1990s and is similar to that of Germany, in other words reproductive cloning is of course banned as well as nuclear transposition.

A certain number of research centres are active in the human embryonic stem cells field. The lines used are those listed in the NIH register and come from the United States, Great Britain and Singapore.

12 – Ireland

Ireland's constitution guarantees the right to life but does not give a legal definition of the 'non-born'.

This situation creates a legal vacuum for a certain number of questions and in particular research on human embryonic stem cells.

The Medical Council of Ireland, the body regulating the medical profession, has made ethical recommendations explicitly banning research and experiments on embryos. But the research and experiments concern only doctors and not researchers.

The cultural and scientific cooperation department of the French embassy noted that *'technically, Irish researchers could work on embryonic stem cells or stem cell lines, but it is difficult to know if they indeed do so; in any case, they do not publicly admit so'.*

13 – Italy

Reproductive cloning and experimentation on the embryo are banned. Clinical research and experimentation on the embryo are accepted only for therapeutic and diagnostic purposes, to guarantee its health and development, only if there are no alternative methods.

Nuclear transposition, as well as the production of embryonic stem cell lines from spare embryos from *in* vitro fertilisation, are banned by Act no. 40 of 19 February 2004.

Embryonic stem cell lines can however be isolated from foetuses from voluntary terminations of pregnancy.

This Act provides for the possibility of importing and working on embryonic stem cell lines produced before 2001. It is banned to use lines produced after that date.

Given this situation, only one group of researchers is working, at the University of Milan and in cooperation with foreign laboratories, on lines produced before July 2001.

On the other hand, ten or so public and private institutions are performing research on adult stem cells, no restriction affecting this field.

14 – Luxembourg

A bill is currently being debated in Luxembourg. According to this bill there will be no possibility of either creating human embryonic stem cell lines or importing them. There is only a low amount of activity as regards adult stem cells.

15 – Malta

There is no legislation in this field in Malta.

16 – The Netherlands

Research on spare embryos is authorised by the Act on the embryo of June 2002. On the other hand, it is banned to create embryos only for research purposes, the aim of the creation of embryos being to give birth to a living being.

Spare embryos can be used for research after necessarily obtaining the agreement of the parents having asked for a VTP.

Three institutions perform research on embryonic stem cells, whereas more than ten or so work on adult stem cells.

17 – Poland

The Polish law bans research on human embryonic stem cells (ban on growing and importing them), and also on nuclear transposition. As voluntary

terminations of pregnancy are banned, there is no possibility of research on spare embryos.

A few laboratories perform research on adult stem cells.

18 – Portugal

No legislation frames research on human embryonic stem cells. No provision gives researchers the possibility of creating human embryonic stem cell lines or importing such lines of cells.

The issue is presently being posed in this country regarding the fate of spare embryos from medically assisted procreation, which is not authorised in Portugal but has been practised for over twenty years in some private clinics.

19 – Sweden

Sweden very soon became aware of the interest and potential of human embryonic stem cells. The authorities of this country have always adopted very open positions on this matter, preferring ethical debate to the introduction of overly strict legislation.

a – Legislation

Sweden is one of the first European countries to have legislated on stem cell research: research on human fertilised ovocytes has indeed been authorised since 1991.

This legislation was introduced to limit research on human embryos to the improvement of *in vitro* fertilisation techniques. But it did not explicitly ban research on human embryonic stem cells, which could be performed to increase knowledge on embryonic development.

In 2001, the stem cell research framework was clarified by guidelines authorising the use of human embryos if there was no alternative to obtain corresponding results and if the project was deemed necessary to advance research on embryonic stem cells.

These guideline therefore laid down that:

· The human embryos used must either be unusable for *in vitro* fertilisation or spare following their legal storage period (five years) and following parental consent;

· The production of embryonic stem cells is limited to the 14 following days;

· Research activities on nuclear transposition are subject to the issue of a research licence by an ethics committee.

Nuclear transposition was not therefore banned but subject to the same ethical limitations as research on fertilised ovocytes.

The production of a human embryonic stem cell line must comply with the Act on human tissue banks which acknowledges the donor's right to refuse their use.

Research on stem cells obtained from spare embryos is authorised after obtaining the donors' consent.

The import of stem cell lines is authorised.

Swedish legislation is certainly one of the world's most advanced in this field and has allowed research to develop remarkably.

b – State of research

Research on human embryonic stem cells is mainly concentrated in the universities and higher education institutions:

· The University of Lund houses the Stem Cell and Cell Therapy Biology Centre bringing together more than 130 researchers;

· The Karolinska Institute is Sweden's biggest stem cell research centre. It was the first centre in Europe to be authorised to conduct research on human embryonic stem cells.

This institute has developed six human embryonic stem cell lines listed at the NIH.

· The Sahlgrenska Academy groups the health sciences activities of the University of Göteborg and the Chalmers University of Technology. It has two embryonic stem cell lines listed at the NIH.

Lastly, the private company Cellartis, located in Göteborg, is the world's biggest source of listed stem cells, maintaining thirty of them, but not all have been produced by it

Swedish research laboratories are in receipt of direct funds allocated by the universities or research institutes they are dependent on, and they also receive research grants assigned on a competitive basis. In addition they attract foreign funds, especially from the United States: NIH, Juvenile Diabetes Research Foundation (5.5 million euros in 2002), US Ministry of Defence (240,000 dollars in 2004).

Research on adult stem cells is free and is performed in the three previously mentioned university establishments.

Lastly, it is to be noted that Sweden is engaged in European cooperation (with Denmark, the United Kingdom, European programmes), and also with the United States, Asia and, especially India.

20 – Slovenia

In this country there is no national Act on embryonic stem cells but the Act on biomedically assisted fertilisation contains a certain number of provisions that can be applied to these cells.

For instance Article 38 of this Act stipulates that 'scientific research on early embryos (defined as the embryo developing outside the uterus during the first 14 days) created for the purpose of a biomedically assisted fertilisation is authorised exclusively with a view to protecting and improving human health' and 'only if research cannot be performed with comparable efficacy on non-human embryos or by other methods'.

The creation of embryos genetically identical to another human being is also explicitly banned by Article 33 of the Act, which excludes nuclear transposition.

There is no research on human embryonic stem cells in Slovenia, whereas there are a few activities in the adult stem cells field.

21 – Slovakia

In Slovakia, nuclear transposition and the creation of human embryonic stem cell lines are banned.

A few research activities are performed in the adult stem cells field in haematology and cardiology.

22 – United Kingdom

The United Kingdom has had a solid tradition of research on human embryology since the birth of Louise Brown, the first child born from *in vitro* fertilication, on 25 July 1978. It is also highly experienced in cloning, with the birth of Dolly in 1997. This country is today, with Sweden, one of the world's most advanced in this field.

The framework set in place in 1991 has allowed research to develop.

a – Research framework

In 1982, the British government commissioned a report from Mrs Mary Warnock on the issues raised by the new possibilities of creating human embryos outside the natural way, which was published in 1984.

This report concluded that the human embryo has a special status and that research on it should by undertaken only for want of other alternatives. But it also considered that an embryo of under 14 days was sufficiently different from a human being for it to be used for the benefit of the general wellbeing. This reference to 14 days is now currently accepted in international research circles.

In 1990, The Human Fertilisation and Embryology Act was voted to frame the practice of *in vitro* fertilisation and the creation, use and storage of embryos produced by this method.

This Act regulates the use of human embryos for research aimed at:

- Improving treatments against sterility;

- Increasing knowledge on the causes of congenital diseases and malformations and of spontaneous abortions;

- Developing better contraception techniques;

- Developing methods of detecting genetic or chromosomic abnormalities before implantation.

In 1991, the Human Fertilisation and Embryology Authority (HFEA) was created, the high authority tasked with regulating medically assisted procreation activities and embryology research. This authority is the only one empowered to issue research licences.

The HFEA is a public body placed under the authority of the Ministry of Health. The latter supervises its activities but does not intervene in its decisions. In particular the government cannot review a decision by the HFEA, it can only give its opinion. The number of members has not been set and currently stands at 19. Members are appointed by the Minister for Health.

In 2000, a report on the new developments in stem cell research was published.

Following this report and a very broad parliamentary debate, the Human Fertilisation and Embryology Act of 1990 was revised in 2001 in order to authorise nuclear transposition and to:

-Increase knowledge on the development of serious diseases;

- Strengthen knowledge on serious diseases;

- Allow this knowledge to be applied in the development of new treatments for serious diseases.

In 2001, the British government also voted an Act banning reproductive cloning.

The procedure before the HFEA is as follows regarding public and private research on embryonic stem cells:

- Researchers explain first of all the aim of their research and then make a written application after obtaining the agreement of the ethics committee of their establishment;

- This application must specify the: composition of the team which is going to perform the research, number of gametes employed, aim of the research and how this aim complies with legislation;

- Three international experts study the application which is then examined by the research board;

- Lastly, the HFEA regulation directorate gives its decision on the licensing of research.

I was told that if the application concerns a field where the possibilities of adult stem cells have not been explored, the HFEA recommends using them. In effect, research on the embryo must be necessary and essential to be authorised.

The research licence is granted for one year. An appraisal is then made.

To date, the HFEA has granted:

- Nine licences for embryonic stem cells,

- Two authorising nuclear transposition,

- Two on parthenogenesis.

The two nuclear transposition licences were granted to Mrs Alison Murdoch of the University of Newcastle upon Tyne and to Mr Ian Wilmut of the University of Edinburgh.

Only Mrs Alison Murdoch has performed a nuclear transposition without however managing to derive cell lines from it. Mr Ian Wilmut told me he does not have any ovocytes to begin his activity.

From this viewpoint, the HFEA launched in September 2006 a public consultation on ovocyte donation for research. I will refer to this consultation in the chapter on ethical issues.

The reactions I have gathered on the HFEA's activities are quite mixed.

In effect, researchers like Mrs Alison Murdoch and Mr Ian Wilmut feel that its licensing decisions are rather laborious and far too long in being taken. As already seen, the time taken is approximately six months. They also feel that this authority tends to outstep its powers and encroach on the responsibility of politicians.

This is also the point of view of Mr Ian Gibson who felt that while the HFEA has a positive role in the public debate, it tends to deal with too many things and especially ethics. In doing so it goes beyond the rights of Parliament to his mind. He felt that this role regarding ethics could be better played by the Nuffield Council on Bioethics, a private structure which had participated in the preparatory reports for the 2001 revision of the Human Fertilisation and Embryology Act.

b – Development of research

All fundings (public and private) taken together, the United Kingdom devoted[59] in 2003 – 2004 21.8 million £ (i.e. approximately 32.5 million euros) and in 2004 – 2005 31.2 million £ (i.e. approximately 46.5 million euros) to research on embryonic and adult stem cells.

Public funds are in particular allocated by the Ministry of Trade and Industry and that of Health. These funds also transit via Research Councils, independent bodies funded by the British government and responsible to Parliament. As regards stem cell research, the Medical Research Council mainly intrevenes. For the greatest part, funding is allocated to adult stem cell work.

It should also be mentioned that English regions are now also participating in this research and have created regional networks like the East of England Stem Cell Network or the Scottish Stem Cell Network. A certain number of my interlocutors were moreover alarmed by this development of local networks in that competition is tending to arise between them, especially to attract the most prestigious researchers.

In December 2005, the British government announced that 100 millions pounds (i.e. approximately 148 million euros) were to be devoted in the following two years to stem cell research, from the most fundamental work to medical applications.

Lastly, mention is to be made of the major activity in this field of the Wellcome Trust, a charity foundation created in 1936 to fund biomedial research. Its contributions are very high, approximately 5 to 6 million pounds for the years 2003 - 2005.

[59] Source: *UK Stem Cell Initiative* November 2005.

Research is mainly conducted in four structures centered around the Universities of Cambridge, Sheffield, Newcastle upon Tyne and Edinburgh.

British research can now make use of a stem cell bank, the UK Stem Cell Bank.

Its creation dates back to 2003 and will receive from the Medical Research Council 9 million pounds over five years. This bank has been operating since 18 September 2006.

The bank currently groups 24 'research quality' human embryonic cell lines, 12 of which have been imported from the United States. A policy on access to these lines is going to be defined, only private companies paying the real cost of the lines.

Lastly, it should be noted that the city of Edinburgh has just announced the creation of a Stem Cell Research Institute which should receive an investment of 3 milllion euros. This not-for-profit institute aims to series-produce, in a few years time, embryonic stem cells according to an approved and stabilised industrial process. These cells will then be proposed to research laboratories.

British research on stem cells is therefore well structured and receives very large amounts of funding. However this situation has not yet led to major results since, while a nuclear transposition has been successful, stem cell lines could not be derived from it. The priority affirmed by the December 2005 plan will strengthen and even increase the British advance.

Great Britain's pragmatic approach to all these issues should be emphasised. This country is likely to attract in the future an increasing number of researchers not only from European countries but also from the whole world bearing in the mind the facilities offered.

This European panorama shows the very strong contrast among European countries regarding the embryonic stem cell issue. Only two countries are making great efforts: Sweden and Great Britain, alongside which France pales in comparison. These countries lead the way in rising to the stem cell challenge.

They rival with the United States and Asia, both of which have made considerable efforts in this field.

E – Organisation of research in the United States and Asia

1 – The United States

The restrictive federal policy leaves free scope to private initiative and to the States, among which California is making a major effort.

a – Regulatory framework

The United States does not have any regulatory framework comparable to what exists in particular in Europe. At the federal level, no text bans nuclear transposition and reproductive cloning.

The only framing existing at that level is that provided by the possibilities of federal funding of research.

Contrary to what is sometimes believed, the financial framing of research on human embryonic stem cells was not established by the Bush administration. It indeed dates back to 1995, and to the vote by Congress of the Dickey amendment banning the use of federal funds to finance research involving the creation or destruction of human embryos.

Consequently, the work by James Thomson that led to the derivation of human stem cell lines at the University of Wisconsin, and which was published in November 1998, was funded by the company Geron.

From then on a degree of uncertainty reigned: in January 1999, the American administration felt that the Dickey amendment could not apply to research using stem cells as these are not an embryo.

But, on 25 August 2000, the NIH guidelines on research on embryonic stem cells excluded the funding of any research involving the derivation of stem cell lines from embryos.

On 9 August 2001, President Bush announced that federal funds should be allowed to be used to fund research on human embryonic stem cells but that this funding would be limited to “existing stem cell lines, where the life and death decision has already been made”.

The President justified this choice “which allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction [...] further destruction of human embryos that have at least the potential for life”.

The following eligibility criteria were therefore established:

. Stem cells must have been derived before 9 August 2001 from an embryo created for reproductive purposes;

. The embryo must not have been used for these purposes;

. Enlightened consent must have been obtained from the donors;

. No payment must have been made.

On the basis of these criteria, federal funds can be used to fund work on the:

. Derivation or use of stem cells derived from newly destroyed embryos;

. Creation of embryos for research,

. Cloning of human embryos for whatever use.

To facilitate the use of stem cells, the NIH has created a data base (Human Embryonic Stem Cell Registry), which lists the lines, at variable stages of development, meeting the eligibility criteria and that can therefore receive federal funding. There are, at present, 22 available lines either in the United States or abroad (India, Israel, Singapore, South Korea, Sweden). These are called 'presidential lines' in the United States.

Since then, there has been a recurrent debate in the United Stats on the possibility of using federal funds to finance embryonic stem cell research. This issue was very widely debated during the 2004 presidential election campaign. It could again be aired during the 2008 campaign.

This debate has been growing because the 'eligible' lines are affected, as seen, by a certain number of phenomena making them less and less fit for research and because they have been in contact with animal products.

Members of Congress have therefore expressed their desire on several occasions that the constraint should be slackened on research financed by public funds.

On 18 July 2006, the American Senate approved bipartisanly a bill already voted in June 2005 at the House of Representatives (Stem Cell Research Enhancement Act of 2005) with a view to extending federal funding to newly derived embryonic stem cell lines. As we know, President Bush vetoed this legislation on 19 June 2006.

It should be noted that the traditional cleavage in the United States between Democrats, rather in favour of an opening up to more public funding possibilities for this research, and Republicans, rather opposed to these extensions, has changed. A certain number of Republicans have indeed abandoned the traditional positions

of their party in this respect, as shown by the action taken by the Governor of California, Mr Arnold Schwarzenegger.

The result of the last elections could, according to some observers, relaunch this debate.

b – Organisation of research: activity of the National Institutes of Health and of universities

➥ The National Institutes of Health (NIH)

The NIH fund research on adult stem cells and on human embryonic stem cells solely derived form 'presidential' lines.

The NIH conduct a very active policy in implementing federal policy, insisting on the therapeutic potential of human embryonic stem cells.

In this respect an NIH Stem Cell Task Force, chaired by Mr James Battey, was created to:

. Facilitate and accelerate stem cell research by identifying factors limiting present research;

. Obtain advice from scientists, who are experts in the field, to overcome the present obstacles.

One of the goals is to establish a scientific network of competences so as to assess the long-term genetic stability of lines. The NIH Stem Cell Unit was created to precisely characterise existing human lines and, as seen, establish a register available to researchers.

The NIH fund programmes (research projects, pilot studies, feasibility studies), post-doctoral grants as well as training workshops.

Funding has been as follows (in millions of dollars) :

Year	Human embryonic stem cells	Adult stem cells	Total
2002	10	170	180
2003	20	191	211
2004	24	203	227
2005	39	199	238

Source: NIH

It can be seen that the total sums invested in this research field have been regularly increasing since 2002 as well as the sums allocated to human embryonic stem cells. It can also be noted that adult stem cells take the lion's share of funding.

➥ Universities

A very large number of universities perform research in this field, on adult and embryonic stem cells.

As regards research on human embryonic stem cells, universities cannot receive federal funding unless they work on 'presidential' lines.

They can work on 'non presidential' lines but only with private funding.

However, at laboratories pursuing work in receipt of federal funding and also engaging in ineligible work, it is mandatory to separate very carefully, and physically, the equipment assigned to each of the two categories. The NIH make regular visits to check this separation.

I therefore saw at these laboratories a grotesque separation between 'presidential' research equipment and the rest.

This constraint has a cost which can be high. For instance, the University of California (San Francisco) is in the process of spending more than 5 million dollars to build a laboratory duplicating a large number of already existing facilities to comply with this rule. Harvard University has had to employ jurists to draw up a document establishing the rules on the separation of researchers' activities and time depending on the funding.

As there is no ban on nuclear transposition, two universities have recently stated their intention to employ this technique, using private funds, to create

human embryonic stem cells from somatic cells from persons affected by various diseases.

The University of California (San Francisco) is therefore going to resume a programme it had abandoned in 2001.

Harvard University, for its part, is going to try to create embryonic stem cell lines affected by juvenile diabetes, blood diseases and lateral amyotrophic sclerosis.

c – Organisation of research: states

A certain number of states have engaged in this research. Owing to the federal structure of the United States, the situations can very in an extremely broad manner.

The spectrum of situations[60] ranges, with many intermediary degrees, from the states of California, Connecticut, Maryland, New-Jersey, Massachusetts, and Illinois, which encourage research on embryonic stem cells and generally authorise nuclear transposition, to that of South Dakota which strictly bans any research on embryos of whatever origin.

The sums allocated by the various states can vary greatly[61] :

. Connecticut: 10 million dollars per year for 10 years;

. Illinois: 10 million dollars for a single year (2005). In August 2006 it was decided that an additional 5 million dollars will be allocated in 2007 to the stem cells research programme;

. New-Jersey: the first State to have allocated, in 2004, funds for this research – 5 million dollars for the creation of a new research institute. 23 million dollars are planned for the years 2005 and 2006 for the New Jersey Stem Cell Institute;

. Maryland: 15 million dollars for a new stem cell research fund.

All these states authorising research on embryonic stem cells have established rules of good practice, the reference being the National Academy of Science national guidelines. These guidelines, which are widely accepted and respected by the scientific community, are recommendations and not obligations.

California is however the flagship State in this field.

---

[60] Complete list in National Conference of State Legislatures
'State embryonic and fetal Research Laws'
www.ncsl.org/programs/genetics/embfet.htm

[61] Source: The Century Foundation - 2006

d – The flagship case of California

On 2 November 2004, nearly 60% of the voters in California adopted Proposal 71 setting forth the creation of a public research institute on embryonic stem cells with an allocation of 300 million dollars per year for 10 years.

This proposal authorises the State of California to sell 3 billion dollars worth of bonds over ten years to fund research on stem cells in California.

It sets up the California Institute for Regenerative Medicine (CIRM), a body which will distribute grants and loans for stem cell research.

This institute is managed by an organisation called the Independant Citizen's Oversight Committee (ICOC) composed of 29 members representing: Californian universities, research insitutions, companies developing medical therapies and patients' organisations.

Immediately after its adoption, opponents to this project – anti-abortion associations also defending taxpayer financial interests – lodged appeals.

The complaints concerned the fact that the adoption of Proposal 71 goes against taxpayer interests and would infringe the constitution of the State of California. According to these associations, the funding is apparently distributed by a body barely overseen by the State of California and too close to the biotechnologies industry.

A certain number of Californian elected representatives, whom I met, informed me that, while in favour of this Proposal, they were concerned that the State of California should exercise closer monitoring over the financial arrangements to be set in place.

On 24 April 2006, the complainants having suffered a refusal of their application to have the Proposal declared inconstitutional, expressed their intention to bring the matter before the Supreme Court of California.

However, on 10 October 2006, the CIRM presented to the ICOC its strategic plan project.

This plan lays down the long-term goals for the decade ahead.

It proposes to fund 25 stem cell measures and to allocate the following funding to them: 823 million dollars to develop fundamental cell biology research, 899 million dollars for preclinical research and development, and 656 million dollars for clinical trials, 273 million dollars being allocated for the renovation and construction of research laboratories. This plan sets five and ten year goals so that the progress accomplished can be measured.

Despite the difficulties and delays caused by the court trials, many initiatives have been taken by Californian universities and institutes to create new research centres in order to receive the funds resulting from Proposal 71.

In the United States, California currently presents undeniable attractiveness for cell biology researchers. A number of other states have perceived this attractiveness, which has no doubt stimulated them to offer, in turn, attractive funding for stem cell research.

The action undertaken in California and in an increasing number of states will perhaps offset the negative impact of the measures adopted by President Bush on 9 August 2001.

In effect, many observers have felt that these decisions had rather negative consequences as shown by the decrease in the past two years of the number of American publications in this research field.

A brain drain phenomenon has also started with, in particular, the departure of Mr Roger Pedersen, a former researcher at the University of California (San Francisco) who isolated the first murine embryonic stem cells. Mr Roger Pedersen became, in 2001, the director of the MRC Centre for Stem Cell Biology and Medicine at the University of Cambridge (Great Britain).

2 – Asia

Many of my interlocutors told me that Asia is the continent where research on stem cell research, and especially on human embryonic stem cells, could experience major breakthroughs.

Biotechnologies and medical sciences are indeed central to the development strategy of many Asian countries. Stem cell research appears all the more interesting as no fundamental breakthrough has yet been made and many scientifically important countries, I am thinking in particular of Europe, are highly reluctant to engage in this field. Some specialists even think that the stem cells topic could form for Asia the first opportunity to dominate a biology research field.

I feel these countries have the potential to be highly competitive in the stem cells field, bearing in mind the excellent level of their scientists and the very broad support of their populations for scientific goals. These countries also appear highly attractive to a certain number of Western researchers as a certain number of ethical questions are not addressed in the same manner as in Western countries, Asian moral concepts being very different.

Research is supported in these countries by very high quality scientists who were trained above all in the United States.

From this viewpoint it should not however be believed that any ethical concern is banned. China, Singapore, Taiwan and South Korea have for instance banned reproductive cloning.

However this attraction is perhaps going to decrease, bearing in mind the rollout of the Californian stem cell research programme.

I will refer only to the situation in Singapore and Japan, South Korea being the subject of the next chapter.

a – The situation in Singapore

Since 2000, Singapore has made the field of biomedical sciences and biotechnologies central to its development strategy.

Stem cells have been acknowledged as being a field of high economic potential and Singapore is today positioning itself as a world-class research centre.

Regulations have been set in place and major funding allocated in support of research players.

➥ Regulations

A legal and ethical framework was defined in 2000 for stem cell research. Singapore intends to take advantage of the restrictive policy of the United States, and attract more researchers by offering them an attractive framework to develop research in this field.

The legislation is that of the Human Cloning and Other Prohibited Practices Act.

Human reproductive cloning is formally banned as well as the export and import of cloned embryos, and the marketing of human embryos, ovocytes and sperm. Nuclear transposition is authorised. The legislation allows research on human embryos so long as they are not over 14 days old.

A certain number of rules have also been laid down, among which mention can be made of:

. The information of embryo and gamete donors, as well as their consent are required;

. The use and derivation of embryonic stem cells must be justified by a scientific challenge and a potential benefit;

. A specific authority issues licences and ensures the follow-up and monitoring of human stem cell research.

The following investments have been made in this field[62] :

. Singapore's annual expenditure on stem cell research is estimated at 40 – 45 million Singapore dollars, i.e. approximately 20 – 22.5 million euros, of which approximately 7.5 million euros for the public sector, and 12.5 – 15 million euros for the private sector;

. 70 million Singapore dollars, i.e. approximately 35 million euros have been invested in the Singapore Stem Cell Consortium;

. The Economic Development Board, tasked with the strategy of making Singapore a mandatory business and investment hub, including for private research, has invested 37 million Singapore dollars, i.e. approximately 18.5 million euros in the company ES Cell International.

Quite a large number of players intervene in this field.

Among these bodies, in the public research field and apart from the University of Singapore and Singapore General Hospital, mention can be made of the creation in 2005 of the Singapore Stem Cell Consortium.

This was created to coordinate and develop stem cell research in Singapore. It is in particular tasked with setting in place common resources in the field, such as a stem cell study laboratory, a stem cell bank and a cell therapy processes complex. It helps to group the various fundamental and clinical research groups in common projects.

Private research is represented by four companies, the largest of which is ES Cell International, created in 2000 to sell stem cell research products and technologies. Like all comparable companies, it has nothing to sell for the moment. However it holds the intellectual property of several stem cell lines, including six listed by the NIH Stem Cell Registry, and of culture techniques.

Singapore therefore has a proactive policy in this field. An indisputable scientific level has been reached both in the public and private sector. Foreign setups have developed, like, since 1998, a biomedical research division and a clinical centre of the John Hopkins University, and mention can be made of the signature of a stem cell research agreement with the US Juvenile Diabetes Research Foundation International.

b – Japan

The regulatory framework was defined relatively early in Japan, which has allowed the development of dynamic public research.

---

[62] Source: According to the note of 3 July by the French Embassy in Singapore: 'Cellules souches : aperçu de la recherche à Singapour' ('Stem calls: an overview of research in Singapore').

➥ Regulatory framework

The regulatory framework of stem cell research has been elaborated since 2000.

In 2000, Japan's Council for Science and Technology published a report on human cell research which:

. Approved human stem cell research by the use of spare embryos from the *in vitro* fertilisation process;

. Banned human reproductive cloning;

. Made recommendations on the approval of research performed in the framework of projects supported by public funds.

In 2001, the Act on Human Cloning Techniques and Other Similar Techniques:

. Expressly banned human reproductive cloning;

. Made it necessary for the Ministry of Education, the research supervisory authority, to publish national guidelines on the creation of embryos for research purposes.

This Act did not ban nuclear transposition, but governmental instructions strongly advised against it at the time.

On the other hand, this Act authorised the creation of human embryonic stem cells for therapeutic purposes under governmental control. Research centres are approved by the Council for Science and Technology which must give its support at the beginning of research programmes and can decide to interrupt such support any time.

Lastly, in 2004, nuclear transposition was authorised after a favourable opinion from Japan's Council for Science and Technology. However rules of good practice still need to be established.

➥ Research

As part of the year 2000 Millennium Project, Japan has made regenerative medicine, especially that targeted at the effects of ageing, one of its life sciences priorities. It has been decided to focus all the country's efforts in this field on one pole located in the region of Kansaï around Osaka, Kyoto and Kobe.

Japanese research is placing the emphasis on the development of fundamental biological research and that of techniques using animal models. It is based on an excellent synergy between fundamental research establishments,

industrial technology development centres, applied research hospitals and an emerging industry.

Two centres dominate this research: the RIKEN Centre for Developmental Biology and the Kyoto University Frontier Institute of Biomedical Research.

The RIKEN Centre for Developmental Biology, created in 2002, is devoted to two main topics; developmental biology and regenerative medicine in the framework of support for Japan's ageing population.

It has a major programme in the stem cells field: molecular markers, differentiation factors, maintenance at the undifferentiated stage, nerve cell induction… Three project using human embryonic stem cells were approved in 2005.

This centre groups 30 research team bringing together 400 researchers and 160 technicians. Its annual budget is approximately 50 million euros.

Kyoto University, for its part, is working on the isolation and characterisation of human embryonic stem cell lines.

This work is taking place at the Regenerative Medicine Research Institute created in 1998 and where the Stem Cell Research Center was established in 2002.

Only Mr Norio Nakatsuji's laboratory at Kyoto University is presently authorised to create stem cell lines in Japan.

This research institute groups 13 laboratories in three divisions bringing together 300 persons including 40 professors. The research performed here lies between fundamental research and clinical applications.

Three stem cell lines were created here using frozen embryos. For 2006, Mr Norio Nakatsuji told me that it was envisaged to create ten of so new lines. It is planned that these will be transferred to all the Japanese laboratories to promote research in the pharmaceuticals industry.

A certain number of projects exist in this field and, in particular, the creation of an embryonic stem cells bank.

While the overall appraisal of Japanese research is therefore very positive, a certain number of difficulties exist.

According to Mr Norio Nakatsuji, there is firstly the problem of the delayed publication of rules of good practice which are necessary to implement nuclear transposition legislation. He also emphasised the length of the waiting period (one year) for governmental and scientific approvals to use human embryonic stem cells.

Lastly, in Japan the issues arise of the: definition of the embryo; use of stem cells from embryos created through *in* vitro fertilisations*;* use of stem cells from embryos collected following requested legal abortion; ovocyte donation; and possible marketing should these techniques prove successful…

I feel that what should be remembered about the Japanese situation, apart from the quality of the research performed, is the existence of a strong determination on the part of the public authorities to support this field and the choice of geographically concentrated means which proves to be entirely positive.

F – The Korean affair

South Korea and the developments of the 'Hwang affair' were on the front page of newspapers for a good part of 2005.

Everyone knows the outcome of this affair but it is useful to go back over the events. I'll outline the history of the affair centering around Mr Hwang Woo-suk, from his ascent to his fall, before addressing the consequences.

1 – Mr Hwang Woo-suk's ascent

The government's determination to make Korea the most developed country regarding stem cells certainly kicked off this affair. There was also probably the desire to take advantage of the situation created in the United States by the decision of 9 August 2001.

The Ministry for Science and Technology launched in 1999 the 21st Century Frontier R&D Programme to develop Korea's scientific and technological competitiveness in the emerging sciences sector.

An embryonic stem cells research centre was set up in July 2002 with Mr. Moon Shin-yong of the University of Seoul as chairman and Mr Hwang Woo-suk also participating in this work.

It is planned that approximately 150 million dollars will be allocated to it until 2012, 122 million being provided by the public sector and the rest by the private sector. The aim is to discover by 2012 more than 100 kinds of factors inducing cell differentiation and more than 10 kinds of cell differentiation pathways.

In February 2004, Mr Hwang Woo-suk and Mr Moon Shin-yong's team announced the creation of human embryos by nuclear transposition and the derivation of embryonic stem cells from them for the first time in history.

This 'first time event' was published in the 12 March 2004 issue of the journal *Science*.

Meanwhile, the legislative framework of this research was clarified by the Act of 29 January 2004 on safety and bioethics, but which entered into force on 1 January 2005.

This text strictly bans reproductive cloning. Research on nuclear transposition is authorised bearing in mind the rules of good practice decreed by the National Ethics Committee. It was laid down that ovocyte donation shall not be remunerated.

After the February 2004 paper, Mr Hwang Woo-suk became a media idol. Funding flooded in.

Apart from private donations which reached the sum of 1.2 million dollars, the Ministry of Health and the Ministry of Research and Technology funded, in 2005, the following projects:

- Frontier Program: Stem cell research centre:
  9.8 million dollars

- National University of Seoul (Mr Hwang Woo-suk's laboratory):
  2.95 million dollars

- Stem Cells and Gene Therapy Institute:
  1.4 million de dollars

Complementary funding was also allocated to Mr Hwang Woo-suk by the Ministry of Science and Technology: 2.95 million dollars per year for five years. Other sums were allocated to him by this ministry, in particular 2.45 million dollars to produce a cloned transgenic pig for xenotransplantation.

On 17 June 2005 the journal *Science* published a new article written in May 2005 and signed by Mr Hwang Woo-suk and twenty-four other persons, including Mr Gerald Schatten of the University of Pittsburgh, the last signatory, and therefore the scientific guarantor of the article. The authors related they had managed to produce 11 human embryonic stem cell lines immunologically compatible with the patients for whom they were intended.

World fame then came. The researchers I met all told me they were convinced this was a fundamental breakthrough. Nobody at the time had doubts over the effective achievement of the results documented in the successive articles of *Science*.

A large number of foreign researchers then went to Korea to meet Mr Hwang Woo-suk and visit his laboratory. Many were very impressed. For instance,

Mr Marc Peschanski told me that in his opinion the skilled personnel had obvious knowhow. Even if Mr Hwang Woo-suk has not elaborated an orignal concept, he was then credited with genuine technical knowledge.

In August 2005, Mr Hwang Woo-suk again attracted attention by announcing the birth of the first dog created by nuclear transposition from adult stem cells. This news appeared on the front page of the journal *Nature* of 4 August 2005.

In the wake of the results obtained in May and August 2005, a World Stem Cell Hub was inaugurated on 19 October 2005. Mr Hwang Woo-suk was appointed chairman. It was then planned that this centre was to have setups in Great Britain and the United States.

On this occasion, the President of Korea affirmed the government's support for research efforts on stem cells to increase the quality of medical services and make the Korean medical industry a strategic industry. The creation of an international stem cell bank was also envisaged.

Mr Hwang Woo-suk was then at the height of his success.

But the fall was to be swift.

2 – Mr. Hwang Woo-suk's fall

These events are still recent and quite broadly known owing to their wide press coverage, so I will summarise them quite briefly[63].

After 12 November 2005, events followed one another at a quick pace.

On 12 November 2005, Mr Gerald Schatten announced that he was stopping any cooperation with Mr Hwang Woo-suk after having learnt that the 2004 article was sullied by breaches of ethics.

On 21 November 2005, Mr Sun Il Roh, a co-signatory of the *Science* article of 2005, acknowledged that some of the donors of ovocytes necessary for the work had been paid. A Korean television channel confirmed that students from Mr Hwang Woo-suk's laboratory had given ovocytes.

On 24 November 2005, Mr Hwang Woo-suk acknowledged that the ovocytes used had been partly supplied by students from his laboratory but that

[63] According to: *USA ToDay* of 10 January 2006,
Hervé Chneiweiss: 'Cloningate? La publication scientifique et le clonage thérapeutique face à la mystification Hwang' in *Médecine Sciences* no. 2, vol.22, February 2006. ('Scientific publication and thereapeutic cloning now face Hwang mystification: more than a Cloningate?)
The Korea Times of 16 December 2005.

other women had been paid for their ovocytes. He resigned from his post as chairman of the World Stem Cell Hub.

At the beginning of December 2005, two commissions of inquiry at the University of Seoul and the Ministry of Health cleared Mr Hwang Woo-suk of the accusations of breaching ethics. However, rumours began to circulate on the nature of the photographs in the 2004 and 2005 articles which were examined. A committee of inquiry was set in place at the National University of Seoul.

On 13 December 2005, Mr Gerald Schatten asked *Science* to withdraw its signature from the 2005 article as he felt that the facts in the article had been entirely invented.

In the following days, Mr Hwang Woo-suk resigned from all his official functions and progressively acknowledged a certain number of 'mistakes' in the successive papers.

On 16 December 2005, Mr Hwang Woo-suk admitted that his laboratory had only eight stem cell lines when he submitted his 2005 article to *Science*. He declared that he had asked *Science* to withdraw the article. He claimed that some stem cells had been inverted.

On 20 December 2005, a first report by the committee of inquiry revealed that the results of the 2005 article had been deliberately falsified and that only two stem cell lines existed out of the 11 claimed.

On 23 December 2005, the National University of Seoul revealed that at least nine of the eleven claimed cell lines were faked. An investigation was launched on the other main articles by Mr Hwang Woo-suk who resigned from his professoral post.

On 29 December 2005, the university inquiry also declared that the two remaining lines were also faked. The claimed stem cells had been obtained from embryos produced by *in vitro* fertilisation.

On 10 January 2006, the National University of Seoul affirmed that Mr Hwang Woo-suk had falsified the data in the 2004 article by claiming to have obtained human embryonic stem cells by nuclear transposition. On the other hand it confirmed the cloned nature of the dog.

On the same day, the management at *Science* announced that it was officially removing the two studies signed by Mr Hwang Woo-suk.

Lastly, in June 2006, Mr. Hwang Woo-suk was accused by Korean justice of fraud, embezzlement and infringement of bioethics legislation.

3 – What lessons?

As I stated in a communiqué on 11 January 2006, the 'Hwang affair' is a question of scientific honesty which must be addressed as such, completely independently of the field considered. It must not therefore heap opprobrium on all the sector of fundamental research formed by human embryonic stem cells.

Present at the time in Korea, I can bear witness to the effervescence this affair caused in that country where many people wanted to believe that extraordinary progress was being accomplished in their country to cure today's incurable diseases. I could measure the extent to which this event deeply distressed Korean society which really 'believed' in Mr Hwang Woo-suk.

Mr Hwang Woo-suk was undeniably the subject of major pressure on the part of the Korean public authorities. These, apart from the international fame for their country, hoped to be able to set in place a very large biotechnology sector which would have been the source of considerable economic power.

The possibility of holding a very large number of patents on nuclear transposition techniques and on the derivation of human embryonic stem cell lines certainly played a major role.

At the time of Mr Hwang Woo-suk's 'splendour', the Koreans had claimed the patent of the techniques presented as perfected. It would moreover appear that the issue of patent appropriation for these techniques played a major role in the breakoff of relations between Mr Gerald Schatten and his Korean partners.

Considerable competition indeed reigns in the embryonic stem cells field. A similar situation existed at the time of the 'race' to decipher the human genome bearing in mind the stakes represented by patents.

On the other hand, the situations are not entirely comparable.

The biggest difference is the position of withdrawal of the federal State in the United States which has caused a kind of 'vacuum' allowing 'small countries' to step into this breach.

This type of research does not need the massive infrastructure required by the deciphering of the human genome, especially as regards data processing means. It above all requires intellectual means which can move to all points of the planet, provided the offer is attractive. That is the wager of the authorities in Singapore or California. This was also certainly the determination of the South Korean authorities.

The country managing to attract the best teams could become a major power in this field.

This affair also brought into plain daylight the excessive mediatisation of science, which Mr Jacques Testart has called 'science as a show[64] ', a situation already mentioned in this report

Another difference with genome deciphering, this Korean affair placed the accent on the ethical issue of ovocyte donation for research.

This is indeed one of the challenges stem cell research must face.

[64] Jacques Testart 'L'affaire Hwang Woo-suk ou les dérives de la science spectacle' ('The Hwang Woo-suk affaire or science as a show running amok') in *Le Monde* - 3 January 2006.

Fifth part:
The challenges to be faced

The pursuit of research on stem cells requires answering four major questions: an ethical challenge, a social issue, an economic challenge, and the issue of the patentability of stem cells and its possible consequences.

A – Need for strict respect of ethics

Two major issues arise here: the issue of scientific fraud and that of human ovocytes for research.

1 – Scientific publications

a – Scientific fraud

Scientific fraud is not a recent problem, existing long before the 'Hwang affair'.

The definition adopted by the Office of Research Integrity which is answerable to the US Ministry of Health (US Department of Health and Human Services) distinguishes three different cases of scientific fraud:

. Fabrication of data or results leading to the pure and simple invention of scientific results;

. Falsification of data and results involving the rectification or selection of experimental results so that the results and the prediction of a theory coincide better;

. Plagiarism

Historically, scientific frauds have always existed.

The most famous case is certainly that of Gregor Mendel who, according to the most currently accepted opinion, discovered the laws of heredity by 'arranging' the results of his experiments to match the theory of which he had had the intuition.

Mention is also to be made of the 'water memory' affair, an experiment published in the journal *Nature*, but never proved.

Another case, not of fraud, but of undue appropriation of someone else's merits, is the recent admission by Mr Ian Wilmut that the main work that led to the birth of Dolly the lamb was not performed by himself but another researcher.

Mention can also be made of the fraud elaborated by the Bell laboratories in the United States, by Jan Hendrick Schön who had published articles in *Nature* and *Science* by presenting forged results revolutionising superconductivity and electronics.

Such fraudulent behaviour is apparently quite widespread as shown by the results of an inquiry conducted anonymously by three American researchers among 3,247 of their colleagues from the NIH and published in *Nature*[65]. According to this inquiry, 0.3% of researchers admitted they had entirely invented data, 1.7% acknowledged they had plagiarised colleagues, and 6% admitted they had omitted to publish data contradicting their research. Another worrisome response is the fact that 15.5% declared they had modified their experimental protocol under pressure from their funding sources.

The scientific fraud problem is becoming worrisome.

Everyone knows what has caused it: researchers must 'publish or perish' as a now common expression puts it.

If they do not publish articles in specialised journals, researchers condemn themselves to obscurity with respect to the general public and also their peers who will not quote them in the ever more abundant bibliography accompanying each article.

As time has gone by, these bibliographies have become one of the main indications of the fame of researchers or research organisations and, therefore, one of the bases of international comparisons of the efficacy of research policies in different countries. This fame based on journal articles has become the prerequisite not only for recognition but also, and above all, for hierarchical advancements and the allocation of funds.

Apart from characterised fraud, the arrangement of results or their skewed announcement is also becoming worrisome. The latest affair in this respect concerns Mr Robert Lanza and has already been mentioned.

A development has very recently occurred in this affair.

---

[65] Brian C. Martinson, Melissa S. Anderson, Raymond de Vries 'Scientists behaving badly', *Nature* 9 June 2005.

The team at the company Advanced Cell Technology led by Mr Robert Lanza had announced it had managed to derive embryonic stem cell lines from a single cell taken from 16 embryos without destroying them. These results were published on 23 August 2006 in the journal *Nature*.

On the same day, a first rectification stated that several cells, and not one, had in fact been extracted from the embryos.

On 25 August, a second rectification stated that 'the embryos had not remained intact.' The 16 embryos were in fact destroyed to extract 91 cells from them.

On 23 November, *Nature* published a corrected version of this paper in which Mr Robert Lanza et al. acknowledged they had taken several cells from the embryos and had destroyed them. Two lines were created.

This affair is not a fraud in the sense of the Hwang Woo-suk affair but, at the least, it is a lie. It calls for a certain number of comments.

First, it is not a matter of a breakthrough, for sampling a single cell from a human embryo without destroying it is no longer an exploit. It is simply the technique used to perform a preimplantation diagnosis.

Second, it is an affair which must be placed in the context of the United States. In effect as federal funds cannot be used to fund research involving the destruction of embryos, a success such as that claimed could allow the creation of new embryonic stem cell lines with public funds.

It should however be observed that the same reasoning could apply at European level bearing in mind the hesitation in the European Union regarding the derivation of lines involving the destruction of embryos.

At end August, the enthusiasm of the generalist press on hearing the news of the success of this work could be noted. However, I feel it is necessary to remain confident in scientific journals and I approve the position of Mr Jean-Yves Nau who writes[66] : 'What credit should be granted to the seriousness of the work published in internationally renowned journals and to their expertise capacities? Total confidence in the majority of cases.' Yet these journals are faced with a difficult situation, as we will see in the following paragraph.

Last, this affair, occurring after others, reveals the extent to which embryonic stem cells are the subject of intense international competition as the economic stakes are considerable. France and Europe must therefore make a considerable effort in this field.

---

[66] In 'Une nouvelle affaire sur les cellules souches' ('A new cell stem affair'), *Le Monde* - 23 November 2006.

It also brings to light the great danger of leaving it to private companies to undertake most of this research. Indeed, as these companies have nothing to sell, they must be able to pool capital and support their stock prices: this encourages them all the more to announce results that do not exist, or skewed results.

b – Validation of scientific publications

The first step after a researcher obtains a result that appears interesting is for him to draft an article that is submitted firstly to his colleagues and his hierarchy. The article is then sent to a journal that, as a rule, has it reread and assessed by high-level specialists (the referees) who must be capable of detecting mistakes or absurdities.

There are a very high number of scientific and technical journals, approximately 200,000, publishing roughly 25 million articles. Naturally, they are more or less renowned, *Nature* and *Science* undeniably being the most renowned. These are the journals with what is called the biggest 'impact factor': their articles are the most generally quoted and they also act as major information channels for the generalist press, especially via their websites.

These journals are private companies engaged in very fierce competition. They are therefore sometimes tempted to 'accelerate' the rereading process and publish an article more rapidly at the risk of not detecting anomalies.

Rereaders may also be in good faith when they let some mistakes pass. In effect they must always content themselves with examining the coherence of the results with the data sent to them and the coherence of the conclusions. They cannot have access either to all the data and the primary results, or to the methods used to obtain them.

As stated by Mrs Debra JH Mathews, on 7 March 2006, during a hearing at the American Congress devoted to these ethical issues in research: *'peer review can detect bad science and poor fraud, but not 'clever' fraud. If someone wants to deceive intentionally and does so cleverly, it is very difficult to discover the fraud.'*

The 'Hwang affair' was a perfect illustration of this state of affairs, despite closer attention on the part of the journal *Science*.

For instance Mr Donald Kennedy, chief editor of this journal, admitted[67] that, in the *'Hwang affair',* the '[rereading] *process was intensified which is what we decide when the subject of publication is either controversial or can have major and unforeseen consequences.'*

[67] Interview with Mr Jean-Yves Nau in *Le Monde*, 11 January 2006.

c – How can frauds be combated?

In the interest of science and the public's confidence in it, measures must be introduced to dissuade such fraud. The difficulty consists in imposing constraints on journals which are private bodies that have freedom to publish.

It can be suggested that they make it mandatory for all the authors of a study (the 2005 *Science* article was co-signed by Mr Hwang Woo-suk and 24 persons!) to state the respective contribution of each of them. This is already the policy of the journal *The Lancet*.

As the absolute validation of a new experiment is its reproduction by an independent laboratory, it could be very useful to also mention, in these journals, the success or failure of the reproduction of the experiment.

A certain number of proposals could help combat scientific fraud.

For instance, Mr Marc Peschanski suggested the development of open access online publication forums on the Internet, an already old practice in physics and mathematics. In this respect, Mr Harold Varmus created, two years ago, the open access Public Library of Science (PLoS) site. Researchers publishing on this site expose themselves directly to the criticism of their peers.

I suggest that any author of a paper that proves to be deceitful or based on knowingly erroneous or rigged bases, or for any other reason demonstrating a determination to fraud, should be sanctioned by the suppression of national or European public subsidies which he might be in receipt of.

This will be a recommendation of this report.

I also feel it is essential to introduce, during the training of all students, for instance at the level of the master's degree, whatever their speciality, education in research ethics.

This will also be one of my recommendations.

2 – Human ovocytes for research

The possible success of nuclear transposition will require human ovocytes being available. All my interlocutors insisted on this issue and recognised it would be difficult to have a large quantity of them.

A certain number of attempts have been made to avoid the use of human ovocytes bearing in mind the risks related to their donation and to overcome the ethical problems. The rules to possibly authorise this type of donation must be carefully examined.

a – Avoiding the use of human ovocytes

A certain number of researchers have already tried to find substitutes for ovocytes.

These attempts have currently not been crowned with success.

A study that appeared in *Science*[68] related the success of the derivation of ovocytes from mice embryonic stem cells. Unfortunately this result could never be reproduced. This pathway should be the subject of intensive research. This will be a recommendation of this report.

The cryopreservation of ovocytes is also envisaged. But this technique is still in an experimental phase as it is difficult to freeze them.

Another possibility would reside in the use of cells generating ovocytes. These would be taken in the immature state from embryos, from foetuses from abortions, or from fragments of ovaries especially at the time of operations. They would then be brought to maturation *in vitro*. But this cannot be performed at present.

Another pathway which could be explored is that of the creation, for research purposes, of chimeras by fusing for instance human cells with animal ovocytes. This operation is already said to have been performed in China. A British journal[69] recently mentioned an authorisation application apparently made to the Human Fertilisation and Embryology Authority by three research teams to create this kind of chimera. But no confirmation of these applications has been given.

b – Risks of ovocyte donation

These risks have been studied in the framework of donation to perform *in vitro* fertilisation.

While ovaries are very rich in ovocytes, these are immature as well as the ovarian follicles in which they are found. If more than one a month is sought to be obtained, the growth of several follicles at a time must be induced. This is made possible by the use of a certain number of hormones to block the patient's hormonal secretions, trigger ovarian stimulation and, lastly, to induce ovulation during which ten or so ovocytes can be collected. Monitoring of the donor is necessary and a certain number of controls are essential. As a whole it is a rather serious process.

Apart from the risks of the process, mention is to be made of the possible effects on the donor's health.

---

[68] www.scienceexpress.org 1 May 2003.
[69] *The Guardian*, 5 October 2006.

Apparently the long term risks due to ovarian hyperstimulation products are still not very well known, despite the high development of this practice over the past 25 years in relation with medically assisted procreation.

In the short term, the most frequent consequence is what is called the 'ovarian hyperstimulation syndrome' which is not defined in a very precise manner since it can range from mere nausea to, very rarely, renal problems or even death.

The possible long term problems are barely documented. Studies performed in the 1990s suggested a possible link between drugs taken on this occasion and cancers of the ovary and breast, although it is still not very clearly known how these types of cancer could appear.

Obviously, if ovocyte donation for research were to be developed, these risks could also increase very considerably. An epidemiological study must therefore be performed on the short and long term consequences of ovarian hyperstimulation, which could moreover be undertaken in the European framework. This will be a recommendation of this report..

While ovocyte donation risks therefore exist at the physical level, a considerable ethical issue also arises.

c – Ethical issue of ovocyte donation

This situation came brutally to my attention during my trip to the United States. While leafing through the newspapers distributed at universities, I was shocked by the advertisements making financial offers to young women accepting to give, in exchange for remuneration, their ovocytes for *in vitro* fertilisations.

These practices are completely commonplace in the United States, especially in student circles. Many young women pay for their university studies this way. Internet search engines come up with tens of links to agencies organising these sales and purchases.

Remuneration is on average around 5,000 dollars, i.e. approximately 4,000 euros. Higher sums are proposed that can reach 15,000 or 20,000 dollars depending on the profile of the desired young woman. It is a real market where not only the physical characteristics of the donors are detailed, but also their special aptitudes, for example music or drawing.

There is no control or regulation over this 'market', which can encourage a certain number of young women to undergo ovarian stimulations several successive times.

The authorisation of nuclear transposition will lead to a high rise in demand for ovocytes, in the present state of research.

The marketing of ovoyctes should therefore be strictly banned. This is a major ethical debate which is becoming very important in the United States.

Mr David Magnus and Mrs Mildred K. Cho[70] for instance propose the creation of a new category of 'research donors' to describe these women running physical risks only for the benefit of someone else.

The issue of the possible remuneration of these donors is also giving rise to a debate.

In France, Mr René Frydman[71] has just proposed that ovocyte donation for the purposes of *in vitro* fertilisation, but which can tomorrow concern donation for research, should no longer be done free of charge. He therefore suggests that *'a joint indemnification of this act of generosity could be calculated in such a way that it does not become a subject of lucre'* and that this *'financial compensation'* should be managed by a public organisation such as the Biomedicine Agency.

In California, ovocyte donors who participate in the stem cells research programme will be indemnified only for their expenses so as not to encourage women in need from having recourse to this expedient. It should also be noted that a Californian Act proposed by the Californian Senator, Mrs Deborah Ortiz, has just been promulgated, and provides also for the reimbursement of possible medical costs in the event of complications arising from donation.

In Great Britain, the HFEA has just authorised women, who do not have the financial means to have *in vitro* fertilisation performed, to share ovocytes in exchange for lower cost IVF treatment. It is Mrs Alison Murdoch's team in Newcastle which received this authorisation. This decision has however been commented on unfavourably.

The HFEA has also just launched a public consultation on ovocyte donation for research. This institution has created a complete dossier on this issue on its website by asking the public for its opinion on the following matters:

. Relevance of ovocyte donation for research;

. Relevance of the egg sharing practice;

. Guarantees to be determined in the event of authorisation of this donation;

. Additional comments.

I feel that this issue will also finish by being posed in France. A debate should therefore be organised in France and could be taken care of by the Biomedicine Agency along the lines of the action undertaken in Great Britain. This will be a recommendation of this report.

---

[70] www.scienceexpress.org, 19 May 2005.
[71] *Le Monde,* 2 November 2006

In this matter, I am torn between two positions:

- A woman, like a man, must be free to donate human tissues for she (he) must have free disposal of her (his) body;

- On the other hand, there is so great a risk of exploitation that such donation must be strictly regulated.

It should however be borne in mind that, if a total ban is introduced, trafficking will inevitably arise, if it does not already exist, especially via the Internet. It would then not be possible to avoid the exploitation of the misery of a large number of women. It is therefore better to regulate strictly than to completely ban.

d – Regulating such donation strictly

I will give hereafter a few principles that appear essential to me. This will be a recommendation of this report which I would like to see submitted to a public debate to be organised:

. Ban on minors making such a donation;
. Prior and enlightened consent;
. Donation free of charge (ban on remuneration);
. Reimbursement of costs incurred to make the donation;
. Compensation for wages not received;
. Post donation medical follow-up reimbursed 100%;
. Collection of ovocytes only in public centres;
. Total separation between collection centres and research laboratories;
. Complete anonymity for donors to research laboratories.

Women should be considered as 'donors' and not as 'sellers' of ovocytes. The detestable American practices in this field should absolutely not become the rule worldwide.

A donation procedure respectful of women's rights should also be introduced internationally. I also propose that scientific publications on research requiring human ovocytes must compulsorily mention their origin in order to avoid the exploitation of women, especially those from developing countries. These will be recommendations of this report.

B – Social challenges and the economic issue

Stem cells pose a certain number of social challenges and an economic issue.

1 – Social challenges

While the ethical problems of stem cells are addressed in detail, the social problems likely to arise in the event of the development of cell therapies are almost never envisaged.

Some of my interlocutors felt it was premature to launch studies on the consequences of these therapies on social protection systems, bearing in mind the uncertainty as regards the outcome of the present experiments.

Entirely to the contrary, I feel it is time to begin to address these topics before being forced to do so by the advances of science, perhaps swifter than planned.

A certain number of subjects should therefore begin to be analysed:

- Who will be the possible beneficiaries of this type of medicine?

Normally, at least in France, everyone would be in a position to take advantage of it. The financial consequences for the collective social protection system should therefore be examined bearing in mind the fact that the costs will undoubtedly be very high.

- What will be the funding procedures for cell therapy treatment for an individual?

The possible future cell therapies will be strictly individualised treatments. Isn't this situation likely to lead to individual funding, bearing in mind the sums at stake and, therefore, to an individual insurance logic, which would be a source of health inequalities?

Lastly, it would also be necessary to take account of the fracture which will not fail to deepen worldwide between countries which could benefit from these techniques and developing countries which of course would not have access to them.

These are merely research avenues which require to be opened and studied. This will be a recommendation of this report..

2 – The economic issue

The stem cells market is still an immature market which has not attracted risk capital and large companies.

a – A still immature market

Medical discoveries generally give rise to great hopes for the curing of diseases and also regarding potential economic gains.

At present, there are very few forecasts concerning the future economic importance of stem cells. The unfortunate forecasts on gene therapy are certainly still present in many minds, which no doubt explains the prudence exercised in this new field.

Apart from some estimations that can appear completely unreal, for instance a 10 billion dollar market for stem cells in 2010, mention can be made of the study that appeared in *The Economist*[72]. According to this publication, this market would be around 100 million dollars in 2010, and may reach 2 billion dollars in 2015.

This study notes that there are approximately 140 cell products being developed for various disorders: cancer, diseases of the liver and other diseases. But more than four fifths of these products are still at the clinical trial stage which can still end up in failures.

A very big potential market obviously exists for cell therapy products. However, the scientific and regulatory uncertainties are presently so great that turnover projections are certainly very fragile.

This sector is therefore so uncertain that it is deserted by risk capital and large companies.

b – A sector deserted by risk capital and large companies

The comparison between the genome deciphering sector ten years ago and that of stem cells today is quite striking.

At the time, a very large number of start-ups built up their shareholding by highlighting their patents. They therefore garnered millions of dollars even if, and this was most often the case, they had absolutely no product to place on the market. And yet investors flocked to their pools. They were attracted by the hope that the patents would allow products to be sold in millions of copies, providing them with comfortable returns on investment. These imprudent investments have very often led to very great disappointment.

The lesson has obviously been learnt by the business world. Risk capital is indeed absent from the stem cell sector, whether in France, the United States or Great Britain.

[72] 22 September 2005.

As recalled by Mr Jean-Thomas Vilquin[73], the stem cell sector suffers from a lack of short term visibility, the yield of cell therapy products is not yet known.

Additional difficulties certainly exist. Gene therapy prospects were barely any clearer ten or fifteen years ago. The moral and ethical implications of cell therapy research are certainly a major obstacle. It should be remembered that gene therapy did not cause such controversies at the time.

Prospects of return on investment are obviously still very uncertain and Mr Philippe Pouletty considers cell therapy *'as one of the high risk and long term fields.'*

Presently, major pharmaceutical companies are not taking any interest in this sector except, as noted by Philippe Pouletty, for some such as Genzyme, Baxter and GlaxoSmithKlein somewhat.

He felt in fact that this field is not very attractive for a pharmaceutical group or a biotechnologies company. Tissue engineering indeed poses major problems of logistics, production costs, traceability, control and quality assurance.

A major disadvantage is that cell therapy is aimed at a single patient. He gave the example of a small Swiss company producing heart valves from umbilical cord blood cells: the valves are individualised for each patient, which leads to very high production costs.

For a pharmaceutical company producing a molecule in millions of copies with quite simple packaging and quality control, tissue engineering therefore appears extremely complicated. Mr Christian Pinset summarised the situation by noting that *'the pharmaceutical industry works to obtain a product that can treat millions of persons',* whereas for cell therapy *'entirely the opposite applies: a product treats a single person'.*

Mr Philippe Pouletty considers that large pharmaceutical companies are likely to experience difficulties if and when when cell therapies are perfected, insofar as they will then not have performed all the necessary upstream work. I feel this difficulty will be merely relative as it can be expected that small companies having performed research will then be simply bought up by big ones. The model that prevailed in the genomics field will apply. The disadvantage of the present situation is that research on stem cells does not receive financial and intellectual means from the major pharmaceutical groups. This situation therefore implies that the upstream fundamental research work will have to be performed by public research.

[73] On 22 November 2005.

C – Stem cell patentability and its consequence

Stem cell patentability is already a reality. For instance a search[74] on American patents identifies more than 1,400 patents in this field, whereas a British inquiry of 2005 listed almost 18,000 worldwide.

The field is dominated by the patents held by the University of Wisconsin, while European practice is still searching for an identity. The consequences of these appropriations lead to refusing stem cell patentability.

1 – University of Wisconsin patents

After referring to the genesis of these patents, we will see that their scope is giving rise to a protest movement against their validity.

a – Genesis of these patents

The University of Wisconsin has successively obtained from the American Patent Office (USPTO) three patents, no. 5843780 of 1 December 1998, no. 6200806 of 13 March 2001 and, very recently, no. 7029913 of 18 April 2006.

The first two concern the preparation, purification and production, respectively, of primate stem cells and of human embryonic stem cells. The third concerns:

- A purified preparation of primate stem cells characterised by specific surface makers, as well as an isolation method;

- A primate stem cells line isolation method.

The situation of these patents, and especially of the first two, is quite complicated.

In effect the work that led to patent no. 5843780 of 1 December 1998 was funded by the NIH, which makes the latter the holder of the rights over this first patent.

The work that led to patent no. 6200806 of 13 March 2001, on the other hand, was not funded by the NIH, bearing in mind the 'Dickey ' amendment. Funding was provided by the company Geron which obtained a certain number of advantages in exchange.

[74] *Intellectual Property & Technology Law Journal*: *'Stem cells:The Patent Landscape',* January 2006.

WARF (Wisconsin Alumni Research Foundation) is the owner of these patents. The University of Wisconsin has created a subsidiary, WiCell, to licence its stem cell lines.

A dispute broke out between WARF and Geron in 2000 over the scope of Geron's rights, which was settled in 2002 by an agreement giving, in particular, to Geron:

- Exclusive rights to develop diagnostic and therapeutic products from three types of human embryonic stem cells: neural and pancreatic cells, and cardiomyocytes. These moreover are probably the types of stem cells with the biggest future from a clinical viewpoint. Any researcher wishing to use these lines for research must obtain a licence from Geron;

- Non exclusive rights to develop the same types of products from hematopoietic cells, osteoblasts and chondrocytes.

Agreements have been concluded between WARF and the NIH. They grant the researchers of this institute, and those in receipt of one of its grants, the possibility of using cell lines for research, in exchange for the payment of a sum of 5,000 dollars. In 2005, more than 200 American research institutions benefited from this type of agreement.

On the other hand, if the lines are used for commercial purposes, a different agreement must be signed with WARF, as the exclusive commercial rights are as a rule covered by these patents. This is the case with the contracts that have been signed with a certain number of commercial private companies. According to an article in *Nature*[75], the tariffs would be around 100,000 dollars for access to lines, along with a royalty of 25,000 dollars per year.

These patents are valid, for the moment, only in the United States and Canada, the European Patent Office having reserved its decision over WARF applications.

The scope of these patents and, above all that of no. 6200806, commonly called 'patent 806', forms a worrisome problem.

b – Scope of these patents

As emphasised by Mr Hervé Chneiweiss[76], ***'The problem is the same as that we already encountered with genes. These patents, through the claims, cover the product, the patented matter***[77]*. In this instance it is a matter of human embryonic stem cells. In particular,* ***patent 806 claims as products mesodermal,***

[75] *Nature* 19 May 2005 '*Licensing fees slow advance of stem cells'.*
[76] On 22 November 2005.
[77] I put the sentence in bold.

endodermal and ectodermal human stem cells, in other words all the basic cells of the human body[78] *From the moment that it is a product patent, it entitles to all the products derived from the initial product and all the ways of obtaining these products derived from the initial product.'*

Another very worrisome difficulty arises from the fact that, while WARF patents are valid for the time being only in the United States or Canada, what would happen if an external company, in Europe for instance, wanted to market a human cell therapy product?

Mr Hervé Chneiweiss also answered: *'If, after having derived a line of European human embryonic stem cells, a European company tried to market a product in the United States, it would then come within the ambit of the two WARF patents and would have to find a licence agreement or a secondary patent agreement to market its product. In the American territory and [in] countries like Canada which recognise American patents,* ***the company would have to find an agreement with Geron and WARF to sell its products.*** *[...] As I stated, as patent 806 covers the three embryonic germ layers,* ***it presently appears difficult to imagine a product derived from a human embryonic stem cell not coming within the ambit of this patent in one way or another***[79]*.'*

As noted lastly by Mr Hervé Chneiweiss, 'by taking out this patent, WARF is granting itself a right over all embryonic stem cells, whatever they are, and of whatever origin, and for the next 15 years!'

It is therefore a very worrisome situation

This is also beginning to be the case in the United States where a protest movement against the triangular monopoly, WARF- Geron- NIH is beginning to develop.

c – Development of a protest movement against these patents

This movement arose from the protest by a certain number of researchers and small research companies.

The protest by researchers arose from the fact that WARF has absolutely banned them from sharing lines, bought at the price of 5,000 dollars, with other researchers, including in the same laboratory.

Small research companies that have managed to develop marketable products from stem cell lines must purchase an additional licence and are very often unable to muster the sum of 100,000 dollars.

---

[78] I put the sentence in bold.
[79] I put the sentence in bold.

This protest movement against the scope of these patents appears to be widening, as evidenced by the rise in the number of articles published on this topic in several Anglo-Saxon scientific journals.

A protest has also arisen in California following the vote of Proposal 71. The offensive is led by a not-for-profit organisation, the Foundation for Taxpayer and Consumer Rights.

This organisation feels that Californian taxpayers risk having to pay twice for the marketing of possible discoveries in this field: once by virtue of the expenditure by the State of California following the vote of Proposal 71, and once by virtue of the patents held by WARF.

Another not-for-profit organisation, the Public Patent Foundation, an association combating abusive patents, has also protested against the validity of these patents.

These two organisations have chosen to attack these patents regarding their novelty. They feel they have proof that the claims of these patents are based on previously published facts. According to them, these patents therefore do not fulfill one of the necessary conditions for patentability: novelty. Appeals were therefore lodged on 3 October 2006 before the USPTO which accepted to receive them.

We can therefore now expect a legal battle that will undoubtedly last quite a while.

In the meanwhile, Europe is waiting for a decision on these WARF patents.

2 – The European situation

In the European Union, Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions poses the principles applied by the European Patent Office (EPO).

a – Provisions of Directive 98/44/EC

A distinction is to be made between adult stem cells and embryonic stem cells

. Adult stem cells

The provisions of this Directive on adult stem cells do not appear to pose any special difficulties for jurists. In effect, subject to the limitations of the provisions of Article 5 - 1 (the human body as such cannot constitute a patentable invention) these cells, designed as products, can be patented if they meet the

classical conditions of patentability: novelty, inventive activity and industrial application.

. Embryonic stem cells

The question of embryonic stem cells is more difficult to assess.

First, according to Article 6 – 1, inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality.

The continuation of this article lays down the applications of this principle. The following shall be considered unpatentable: processes for cloning human beings (Article 6 – 2a) and uses of human embryos for industrial or commercial purposes (Article 6-2c).

In its report of 14 July 2005 to the Council and to the European Parliament on the development and implications of patent law in the field of biotechnology and genetic engineering, the Commission took stock of these questions.

It therefore acknowledged that 'the provisions are clear concerning totipotent stem cells'. In effect each of these cells can itself develop into a human being. Bearing in mind the provisions of Article 5 – 1, they cannot be patented.

On the other hand, concerning pluripotent embryonic stem cells, the Commission took up the analysis of a group of experts according to which 'the issue of patentability is closely linked [on the one hand] to the definition of what forms an embryo and [on the other hand] to the authorised research field which is determined by the national legislation.'

The Commission therefore felt that it was presently premature to pursue harmonisation in this field. It has however proposed to monitor the evolution of this issue by taking account of its ethical aspects and its potential impact on competitiveness.

b – Position of the European Patent Office (EPO)

The provisions of Directive 98/44/CE have been incorporated in the Implementing Regulations of the European Patent Convention by EPO's board of directors.

Adult stem cells and the methods or compositions using them are normally patentable, as confirmed by Mrs Siobhán Yeats[80].

The same does not apply to embryonic stem cells.

[80] On 22 November 2005.

Article 6-2c has been transposed into Rule 23d (c) of the European Patent Convention.

In two affairs, the University of Edinburgh's patent and WARF's application to obtain a European patent, EPO adopted a broad interpretation of Rule 23d (c).

It has therefore refused patent applications concerning stem cell extraction processes from a blastocyst, leading therefore to the destruction of a human embryo. It has also turned down applications concerning already established embryonic stem cell lines.

As Mrs Siobhán Yeats emphasised in substance, EPO, faced with these applications, has had to interpret the provisions of Directive 98/44/EC as, at the time of its adoption, human stem cells had not been isolated, unlike primate cells.

For the time being, EPO considers therefore that human embryonic stem cells cannot be patented for ethical reasons.

But WARF has appealed against this decision in a court of first instance. The chamber of appeal hearing the action decided to transmit the question to the EPO Enlarged Board of Appeal which takes fundamental interpretation decisions.

The decision by the Enlarged Board of Appeal should be given around the end of 2007, the chamber of appeal hearing the opposition against the Edinburgh patent probably awaiting this decision to give a ruling in turn.

Mrs Siobhán Yeats stated that all patent applications in this field are therefore blocked by EPO. As a result of these affairs pending before EPO, each European country is applying its own policy in this respect.

For instance, the UK Patent Office has adopted a rule according to which pluripotent human embryonic stem cells resulting from divisions of totipotent cells do not have the potential to develop into a complete human body. It therefore feels that patents can be granted for inventions comprising pluripotent stem cells provided they also meet the classical patentability criteria.

Mrs Siobhán Yeats emphasised that companies can therefore apply for a patent in Great Britain, obtain it and then apply to EPO for one.

3 – Refusing stem cell patentability

I feel that all these affairs must encourage more than ever the refusal of stem cell patentability as I had advocated in another report aimed at banning gene patentability.

Mr Hervé Chneiweiss's remarks on the scope of WARF patents clearly show, once again, where the real danger lies: the patenting of knowledge. As I had already emphasised in my previous reports, the patents system, introduced to promote progress and increase the collective wellbeing, can completely oppose the pursuit of these two goals.

This situation is perhaps due, at least partly, to the refusal to fund this research out of public funds. This has left an open playing field to private funding and its inevitable corollary, maximum extension of claims to benefit from the biggest possible return on investment. This is an additional argument to justify that this type of fundamental research should be funded by public funds.

We cannot of course anticipate the decision by EPO's Enlarged Board of Appeal. However, to encourage the development of stem cell research and the dissemination of knowledge, a provision must be introduced into the Convention on the Grant of European Patents (EPC) specifying that stem cells are not patentable and that patentability applies solely, in this field, to processes and applications.

So that this provision can really enter into force, I would like the French government to approach its counterparts on the EPO board of directors with a view to amending the EPC along these lines. The EPC Implementing Regulations would then be amended accordingly. This will be a recommendation of this report..

I reiterate my proposal, already made in my previous reports, to limit patentability to processes and application products. This will be a recommendation of this report.

Stem cell patentability is related to the goal of making them marketable like any other product.

Stem cell merchandising should be refused.

4 – Refusing stem cell merchandising

This recalls the debate on the merchandising of the genome which I have already addressed in my two previous reports.

Concerning stem cells, the National Consultative Ethics Comittee (CCNE) has just published an opinion (opinion no. 93), on 'La commercialisation des cellules souches humaines et autres lignées cellulaires' ('The marketing of human stem cells and other cell lines'). It addresses the 'ethical difficulties raised, or which would be raised, by a possible marketing of human stem cells, embryonic and non-embryonic, and of other cell lines.'

Potential investors in the stem cells field, it points out, want to have legal protection by holding a patent in order to profit from their marketing. Interestingly, it emphasises that biomedical research raises a conflict of interests between patients, investors, persons donating biological material, research and society.

The crucial question is therefore the following one: 'until what stage does the stem cell remain, strictly speaking, an element of the human body?' Do the transformations which it must undergo, to be stored and used, change its status to the point of transforming it into a therapeutic product?'

A fundamental principle is that elements or products of the human body, detached following a medical intervention, are the subject of free and voluntary donation, which does not prevent them from then having a transfer price or even the status of a drug, like products made from blood.

A link is therefore created between the scale of the transformations undergone by a product from the human body and the possibility of marketing it. This link is made by the supporters of patentability and gene marketing.

As stem cells must be collected, packaged, grown, multiplied and, where applicable, modified, they could therefore become marketable. A mere derived biological product would therefore be marketed, and not a product of the human body, which is banned by Article 16-1 of the Civil Code[81] which said opinion recalls. In recommendation no. 9 of this opinion, CCNE therefore feels that 'the possibility of patenting stem cells as products of the human body would infringe the non-marketing principle of products of the human body, **unless such products have become derived products, no longer having the characteristics of a biological product.'**

The difficulty of this issue is recognised. CCNE indeed notes that *'from what time can these cell elements be considered as sufficiently detached and different from the human body to be traded.?'* The answer is then as follows: ***'Any separation line, any criterion appears impossible to fix.'***

However, it advocated in its recommendation no. 3 that when *'an ingenious human activity has sufficiently modified the cell to make it a product that has lost the phenotypic and functional characteristics of the cell, the possible marketing of the product obtained should be submitted to an agency like the Biomedicine Agency, quoted by way of example.'*

I feel that this last suggestion is highly criticisable as I am not sure that an agency like the Biomedicine Agency is capable, in an undisputable manner, of

[81] 'Everyone has the right to respect for his body.
The human body is inviolable.
The human body, its elements and its products may not form the subject of a patrimonial right'.

stating this limit, notwithstanding the appeals which would not fail to be lodged against such decisions.

We are faced with the same problem that arises in the genes field and which I developed in my two previous reports. We are again faced with the likening of living organisms to a mere chemical product

We must continue to vigorously oppose these attempts to merchandise living organisms.

After having already proposed this in a previous report[82], I therefore reiterate that a debate should be organised on the status of living organisms in our society. This will be a recommendation of this report.

[82] 'La brevetabilité du vivant' ('The patentability of living organisms') , a report by the Parliamentary Office for Science and Technology Assessment, 20 December 2001.

Conclusion

Life sciences are undoubtedly today at a watershed. In effect, the success of the sequencing of an ever greater number of genomes, including that of man, has not led to deciphering the mystery of life as had sometimes been hoped.

This hope was inspired by the growing predominance of genetics which has focused on one of the components of the living cell, DNA. But the recurrent difficulty, despite very many efforts, to precisely define the functions of the gene is leading us to go beyond the approach banking entirely on genetics.

Of course that does not mean throwing overboard all the advances which genetics has allowed over the past fifty years. Genetics must simply be placed back in a more physiological setting, in the concrete living world.

This more concrete, more living perspective cannot be refound unless research is reinvigorated on DNA's environment in the cell, and on all the cell's components.

Very special attention must be paid to stem cells, whether adult or embryonic, of which I have tried to show all the possibilities in this report which sets out primarily to take stock of the situation.

Admittedly the report is not exhaustive but it has attempted to present all the important issues arising, with their most recent developments. It has also placed the accent on the ethical problems which genomics did not pose. I am thinking here mainly of the issue of ovocyte donation, which absolutely must be settled if we wish to pursue research on human embryonic stem cells.

I very sincerely hope that this report is considered as an introduction to the public debate, which I hope for with all of my heart, on stem cells with their impressive potential, and also all the difficult issue they pose for us. This would allow a collective discussion to be held on the possible authorisation of nuclear transposition, which I am in favour of, provided the very difficult issue of ovocyte donation and the real risk of the merchandising of the woman's body is settled in a strict manner. This debate on the possibility of ovocyte donation should be launched as soon as possible in France, by the Biomedicine Agency, in the wake of the debate just launched in Great Britain.

Over and beyond the situation in France, I feel that safeguards must be introduced as swiftly as possible worldwide. Such arrangements would be aimed at

avoiding organised exploitation of the distress of women from the poorest countries. It would be absolutely condemnable from an ethical viewpoint that the health of the populations of rich countries should depend on such a situation.

I feel that swift organisation of this debate is all the more opportune as it could fit into the preparation of the revision of the 2004 bioethics Act which should take place at the latest in 2009. I would like this revision to take place as of 2007, as this is necessary to give clear prospects back to French research in this field. It is indeed necessary to try and make up for the time lost on two occasions, by the late revision of the 1994 Act and the late publication of the implementing decree of Article 25 of the 2004 Act.

My overall impression of the state of research in this field is that uncertainties and gaps in knowledge dominate. There is therefore still a very great need for fundamental research in this field.

The two categories of stem cells appear entirely complementary and I hope that a kind of war of religion will not develop between the specialists of each. I am entirely convinced that any progress in either of the two field will necessarily have a positive impact on the other.

The situation in France will have to be improved by vigorous action by the public authorities through the National Research Agency (ANR) which will have to make this field a major priority and balance its invitations to tender between the two categories of stem cells.

This intensification in fundamental research will therefore require an increase in public funding in order to ward off the development of patents on knowledge.

This public funding will also have to be committed at European level in order to obtain a mass effect allowing Europe to support the competition of the United States, which is going to increase, and the growing competition from Asia.

The European situation is quite worrisome, bearing in mind the fundamental divergences between the Member States, which surfaced at the time of the preparation of the seventh FPRD.

Stem cell research will not replace the efforts made in the field of the genome, but will complete them so as to have an ever greater insight into the fundamental mechanisms of life, the human being's eternal aspiration.

Recommendations

The protection of mankind is central to bioethics legislation. The latter must be confronted with the realities of research and emerging knowledge. It must be placed at the service of a living society and living research.

In order to respect the dignity of human persons, bioethics legislation absolutely must reconcile three principles:

- Freedom of thought, in other words freedom of the researcher who must know what limits society intends to set for his activity;

- The rights of the sick and of the handicapped to have their sufferances lessened and their hopes for a cure raised, which requires research and experimentation;

- Respect for the human person and body.

I – The Act of 2004

The recommendations of this part concern the 2004 Act and will have to be examined when this Act is assessed by the Office and the Biomedicine Agency.

1 – Revising, as of 2007, Article 25 of the Act of 6 August 2004-800 on bioethics.

The revision of this Article 25 is a necessity as of 2007, without waiting for 2009, so that the ban regime, even combined with derogations, on research on the embryo, is suppressed for the benefit of a monitored authorisation regime.

2 – Authorising research on the embryo.

All of the provisions of Article 25 of this Act, that are taken up in the drafting of the first four paragraphs of Article L 2151-5 of the public health code, concerning research on the embryo, must be deleted. On the other hand, the provisions on the role of Biomedicine Agency should be kept.

The deleted provisions would be replaced by those of the first two paragraphs of Article L 2151-3 of the public health code, in the drafting given by Article 19 of the bioethics bill voted at first reading by the National Assembly on 22 January 2002.

3 – Authorising nuclear transposition.

Nuclear transposition should be authorised by the bioethics Act, which should provide for a strict control regime implemented by the Biomedicine Agency.

4 – Organising a Biomedicine Agency debate on ovocyte donation for research.

This debate should be organised as of 2007 on the model of that which has just been started by the British HFEA.

It could propose discussion of the following principles:

. Ban on minors making such a donation;
. Prior and enlightened consent;
. Donation free of charge (ban on remuneration);
. Reimbursement of costs incurred to make the donation;
. Compensation for wages not received;
. Post donation medical follow-up reimbursed 100%;
. Collection of ovocytes only in public centres;
. Total separation between collection centres and research laboratories;
. Complete anonymity for donors to research laboratories.

Referring to the conditions in which this type of donation will be authorised, the summary analysis of this debate will serve as the basis for the revision of the bioethics Act.

5 – Examining the issue raised by the possible ratification of the European Council Convention on Human Rights and Biomedicine ('Oviedo Convention').

The aim is to examine the compatibility of the second paragraph of Article 18 of this Convention with nuclear transposition which would be authorised by the revision of the 2004 Act on bioethics.

The provision of Article 1 of the Additional Protocol to this Convention banning human cloning should be clarified. France should reaffirm its opposition to human reproductive cloning.

II – Ethics

6 – Proposing international action in favour of regulations on ovocyte donation for research.

Such action is essential to prevent the exploitation of women's bodies, especially in developing countries. The aim is thus to combat the creation and

development of ovocyte trafficking which would not fail to become organised if the use of nuclear transposition were to grow.

7 – Proposing, internationally, that the authors of publications related to research involving the use of human ovocytes should be obliged to state their origin.

This proposal completes the previous one to combat the development of international ovocyte trafficking.

8 – Refusing the patentability of adult and embryonic stem cells by the introduction in Directive 98/44/EC of 6 July 1998 of provisions formally banning this patentability. Patentability can concern only processes and application products.

Through the intermediary of its Implementing Regulations, these provisions would be imposed on the European Patent Office. The aim is therefore to oppose the ever greater slippage towards patentability of living organisms. It is necessary to avert the threat of patents, such as those held by WARF, which can oppose scientific progress. Patents should be reserved for methods, processes and application products.

9 – Suppressing, for life, the possibility of obtaining national, European and international public funds for a researcher who is convicted of having infringed scientific deontology.

This recommendation is aimed at combating scientific fraud which jeopardises the repute of science.

10 – Introducing education in research ethics into the training courses of students of all disciplines.

This training could take place at the level of the master's degree.

III – Research policy

11 – Organising a debate on the status of living organisms in our society.

I reiterate a recommendation already expressed in my report on the 'Patentability of living organisms'. The pressure that has already been applied for the patentability and marketing of genes is certain to be repeated for stem cells. This debate is therefore all the more necessary before taking measures which could prove hasty.

12 – Developing public umbilical cord blood banks in the wake of the CCNE recommendation of 12 December 2002 and taking action at

international organisations for their development worldwide in preference to private banks.

Given the remarkable possibilities of these cells in treating many diseases, it is opportune to develop in France umbilical cord blood cell banks. The attention of international organisations must be drawn to the dangers presented by the development of private banks. These are indeed likely to oppose the principle of solidarity and pursue mercantile interests on the pretext of helping children.

13 – Listing as soon as possible all the research activities performed in France on adult and embryonic stem cells, whether human or animal.

This recommendation aims at taking stock precisely of the situation as this is a prerequisite to elaborate a research development policy in this field.

14 – Drawing up as soon as possible a precise list of all public (national, European) and private fundings, allocated to this research field.

The aim here is to complete the previous recommendation.

15 – Presenting each year to Parliament a public report assessing the results obtained, both in France and abroad, regarding research on adult and embryonic stem cells.

This report would help to take stock of the progress of knowledge in this field and could also possibly influence public action in this respect.

16 – Setting out public authority priorities as regards research on adult stem cells and embryonic stem cells through the National Research Agency's (ANR) specific invitations to tender.

By setting out the priorities, the efforts made by the public authorities in favour of this sector will become visible. ANR must display its invitations to tender in a specific manner. This visibility will be an aid for researchers insofar as it may mean the perenniality of public effort.

17 – Starting a debate on the creation in France of one or two poles of excellence on stem cells.

This (or these) creation(s) should take the form of a 'wall-less laboratory'. It (they) would allow the concentration of public means by avoiding their 'scattering'. The examples of RIKEN in Japan or of Cambridge in Great Britain could inspire this (these) creation(s).

IV – A few research fields to be explored

18 – Starting a research programme on the derivation of ovocytes from embryonic stem cells.

This would eventually help do without the use of human ovocytes.

19 – Developing a European epidemiological study on the short, medium and long term consequences of ovarian hyperstimulation.

This study is essential if the donation of ovocytes for research is authorised. It would have a large initial base made up of the women who have accepted this hyperstimulation for more than twenty years to perform *in vitro* fertilisations.

20 – Starting studies on the social consequences of the possible introduction of cell therapies.

These studies should, inter alia, examine the following issues:

- Who will be the possible beneficiaries of this type of medicine?

- What will be the funding procedures for cell therapy treatments?

- What measures would have to be taken to avoid the development of an individual insurance logic in this field?

Examination of the report by the Office on 5 December 2006

The Office examined the report by **Mr Alain Claeys**, deputy, on *'research on the operation of living cells'*.

Mr Alain Claeys, deputy, rapporteur, after having noted the complex nature of this issue, presented the methodology followed to prepare the report.

A day of public hearings was organised in November 2005 with French researchers working on human adult stem cells and human embryonic stem cells. In derogation from its common practice, the Office accepted that the report of this day be published even before its adoption, so as to reassure researchers who were disconcerted by the 'Hwang affair'.

The ministers for health and research and a large number of researchers were heard by the rapporteur, who also made trips to Japan and Korea, during the 'Hwang affair', to the United States, Great Britain, the European Patent Office (EPO) in Munich, and also to Brussels.

The recommendations of the report concerning possible amendments to the 2004 bioethics Act may be examined during the assessment of said Act by the Office and the Biomedicine Agency.

Mr Alain Claeys then emphasised the great topicality of his report, bearing in mind the very recent and very positive declarations by the President of the Republic in favour of the Telethon.

He stated that, in accordance with the referral letter, his report did not address the very serious ethical issue of the origin of life, which depends on what everyone feels in his heart and soul and not on the legislator.

Three principles, that are very broadly accepted, must be reconciled:

- Freedom of the researcher who must know what limits society intends to set for his activity;

- The rights of the sick and of the handicapped to have their sufferances lessened and their hopes for a cure raised;

- Respect for the human person and body.

The rapporteur felt that public opinion is permanently wavering between fascination, as health depends on scientific progress, and mistrust, due to the recent crises which have shaken research in this field. In the face of this situation, the development of scientific culture must be favoured. But science advances slowly, produces few media personalities, gives rise to doubts and criticisms and is subject to facts, whereas the press, for its part, tends to announce discoveries and remedies for straightaway. This contradiction is harshly felt by patients when the hopes raised prove to be unfounded. It is therefore irresponsible to say things that do not represent reality; the truth must be said.

Addressing the issue of gene and cell therapies, the rapporteur noted that the deciphering of the human genome between 1990 and 2003 has helped to obtain a better understanding of genes and their links with hereditary disorders. This has led to the concept of gene therapy, which corresponds to the introduction of a functional gene into the cells of an organism. The great enthusiasm of the beginning has not been followed by major benefits for patients as the function of genes has not been elucidated, and the importance of their environment, epigenetics, has been discovered.

A certain number of difficulties have appeared, related in particular to the targeting of diseased cells or the regulation of introduced genes. However, gene therapy is not a dead end, as shown by the success, despite three failures, of the treatment of the severe combined immunodeficiency syndrome ('bubble babies' syndrome) by Mr Alain Fischer and Mrs Marina Cavazzana-Calvo. Research efforts must therefore be pursued.

Cell therapy, for its part, aims at implanting, in a patient, cells that recreate, on diversifying, the damaged organs or functions.

Mr Alain Claeys insisted on the fact that the report addresses both adult and embryonic stem cells. Research on these two types of cells must be pursued parallelly, but adult stem cells do not pose the same ethical problems as embryonic stem cells. Much fundamental research still remains to be performed in this field, particularly on the isolation of stem cells, their purification, growth and differentiation.

The rapporteur then addressed the state of research in the world.

The situation in European countries is highly varied. Three countries (Great Britain, Sweden and Belgium) authorise nuclear transposition, whereas others either ban any research in the field (Austria, Poland, Ireland), or do not have any legislation on it (Malta, Cyprus, Estonia).

Great Britain is one of the most active countries in this field thanks to the flexibility of its legislation and the efficacy of its regulatory authority on ethics and

research protocols. This authority, sometimes criticised as overly finicky, has just launched a public consultation on ovocyte donation.

Sweden, for its part, is one of the first European countries to have authorised, as early as 1991, research on fertilised human ovocytes.

This disparity in Europe gave rise to difficulties during the elaboration of the 7th Framework Programme for Research and Development (FPRD), as some countries that have just entered the European Union are hostile to human embryonic stem cells. An agreement has nevertheless been reached.

In the United States, neither human reproductive cloning nor nuclear transposition are banned. On the other hand, federal funds cannot fund research involving the creation or destruction of human embryos. President Bush's decision of 9 August 2001 has limited the possibility of federal funding to embryonic stem cell lines existing on that date. But these cells pose problems, especially genomic degeneration.

A recent bipartisan attempt by the Senate to broaden the possibilities of federal funding met with President Bush's veto on 19 July 2006.

Private funds can fund all types of research which are also beginning to be supported by a certain number of States. This is the case of California, the flagship State in this respect which, following the vote on 2 November 2004 of Proposal 71, is going to devote to this research 3 billion dollars over ten years. This State will become very attractive for a large number of American researchers who might have been tempted by expatriation to Asia.

Asia is the continent where research on embryonic stem cells could enjoy major success in the future. Bioetchnologies and medical techniques are indeed central to the development strategy of many countries, and they could benefit from European and American hesitations. They also have a pool of excellent level scientists.

Singapore is applying a very proactive policy with very high investments in public and private research. The aim is to attract internationally renowned scientists, by excellent work conditions, and also foreign investments.

Japan has developed dynamic public research by concentrating its means in the region of Kyoto. Nuclear transposition is authorised but no team is working on it.

South Korea was, last year, at the heart of current events with the 'Hwang affair' which was a gigantic fraud.

Turning to the situation in France, **Mr Alain Claeys** recalled that the 2004 bioethics Act had been discussed under two legislatures with a different majority.

The recommendations concerning the proposed amendments to the 2004 bioethics Act will have to be examined by the Office and the Biomedicine Agency during the assessment of said Act.

After having emphasised that we should not wait till 2009 to revise the Act, he referred to various issues.

- The European Council Convention on Human Rights and Biomedicine, known as the Oviedo Convention.

Two provisions of this Convention, which was adopted on 19 November 1996, must be clarified before France can ratify this text. One, in the second paragraph of Article 18, setting forth that 'the creation of human embryos for research purposes is prohibited', could be considered as banning nuclear transposition. The other, in Article 1 of the Additional Protocol to this Convention, sets forth that the cloning of a human being is prohibited. The interpretation by the Netherlands, which considers that the term 'human being' refers exclusively to an unborn human individual, should, according to the rapporteur, be adopted.

- Article 25 of the bioethics Act

A positive contribution of the second reading of this Act has been the creation of the Biomedicine Agency which meets the ethical requirements of framing research on living organisms. This agency has demonstrated its efficacy under the leadership of Mrs Carine Camby.

On the other hand, the procedures for research on embryos adopted in first reading in January 2002 were more satisfactory than those provided for by the final text of the Act.

The 2002 text indeed authorised embryo research on spare embryos left over from IVF, subject to abandonment of fertility treatment and non-reimplantation. These embryos were previously destined for destruction.

The provisions of the Act are ambiguous for they ban research on the embryo, while providing for the possibility of derogations during a five year period. A derogation is possible only when research is likely to 'allow major therapeutic progress and provided it cannot be pursued by an alternative method of comparable efficacy.'

Clearer and less complex provisions are necessary as therapeutic applications cannot be foreseen at the fundamental research stage.

The rapporteur concluded this part of his overview by welcoming the evolution of attitudes regarding this point.

- Nuclear transposition and ovocyte donation

The expression 'therapeutic cloning' has been banned as it is misleading. Its opponents place the accent on 'cloning', this technique then being likened to reproductive cloning which nobody in his right mind defends. Its supporters insist on 'therapeutic', which could allow it to be believed that the technique is ready to cure diseases still incurable today. In fact it is not yet known if it will be possible to use it and if it will provide the expected results.

It is not a neutral technique as it raises the issue of ovocyte donation.

Mr Alain Claeys then emphasised how shocked he had been during his trip to the United States by the advertisements in university newspapers and by websites offering to buy ovocytes from students for in vitro fertilisations.

He expressed his fear that such merchandising might develop. A public debate must therefore be launched on this issue and the following principles should be discussed: ban on minors making such a donation; prior and enlightened consent; donation free of charge (ban on remuneration); reimbursement of costs incurred to make the donation; compensation for wages not received; post donation medical follow-up reimbursed 100%; collection of ovocytes only in public centres; total separation between collection centres and research laboratories; and complete anonymity for donors to research laboratories.

- Weakness of human and financial means in France

France is very much lagging behind in this field. The State must therefore set out its priorities regarding research on adult and embryonic stem cells through the invitations to tender by the National Research Agency (ANR).

The press addresses embryonic stem cells far more often than adult stem cells but, as in all countries, there are far more teams conducting research on the latter in France than on the former.

- Scientific publications

The 'Hwang' and 'Lanza' affairs attracted attention to scientific publications of which there is a very large number: approximately 200,000 publishing 25 millions articles. These private companies are engaged in very fierce competition which has worsened with the appearance of electronic publications on the Internet. They are sometimes tempted to 'accelerate' the rereading process so as to publish an article more rapidly, at the risk of not detecting anomalies.

These journals form the main source of information for the generalist press. Insufficiently controlled publications therefore lead to the spread of errors. This was the case in these two affairs.

The rapporteur made the suggestion that each author should state his real share in the published work in the event of co-publication.

As regards public policies, he recommended that any researcher convicted of scientific fraud should have the benefit of national or European public subsidies removed once and for all.

- Patentability and merchandising of living organisms

Patents facilitate innovation and the dissemination of knowledge. He recalled that he had already opposed the patenting of the gene and its application, which is tantamount to patenting knowledge, and that he supported the authorisation only of application patents.

The same difficulties are to be found with stem cells, a field where the University of Wisconsin's patents dominate. The European Patent Office (EPO) does not issue patents for embryonic stem cell lines, its Enlarged Board of Appeal currently having this matter before it.

After having mentioned the confused nature of the opinion of the National Consultative Ethics Committee (CCNE) on the 'Marketing of stem cells and other cell lines', he recommended that it should not be possible to patent stem cells, elements of the human body, but only application products.

- Social and economic challenges

Before being forced to do so by the advances of science, thought should be paid to the social challenges, especially:

- Who will be the possible beneficiaries of this type of medicine?

- What will be the funding procedures for cell therapy treatment?

- As strictly individualised treatments, aren't the possible future cell therapies likely to lead an individual insurance logic?

From an economic viewpoint, genomics had allowed start-ups to attract considerable sums. Stem cells are funded only by public funds and patients' associations. It is understandable that these associations seek immediate results but this should not lead to ambiguous relations with the public authorities.

Mr Pierre-Louis Fagniez, deputy, congratulated the rapporteur for the quality of his work. He felt that this work had arrived opportunely at the time when the Telethon has just been greatly supported by the President of the Republic.

After having recalled the first successful bone marrow graft by Mr Georges Mathé in 1959, he felt that Mr Alain Claeys' report, like that which he has himself recently handed to the government, showed that this issue should be reviewed

regularly every five years. He therefore said he supported compliance with the five year period laid down by the 2004 Act for its review.

On the other hand, he supported Mr Alain Claeys' proposal to review Article 25 of this Act, feeling that it was no doubt time to submit research on the embryo to an authorisation regime.

He welcomed the rapporteur's remarks emphasising the quality of the action by the Biomedicine Agency of which he a member of the steering board.

Referring to the Oviedo Convention, he approved the Rapporteur's proposal to follow the example of the Netherlands in their interpretation of Article 1 of the Additional Protocol.

In conclusion he felt that nuclear transposition should be envisaged by taking into account the central issue posed by ovocytes and that it should be possible to find a solution without exploiting women.

Mr Alain Claeys, deputy, rapporteur, mentioned in this respect recommendation 18 which sets forth the pursuit of a research programme on ovocyte derivation from embryonic stem cells.

In addition, he felt that the principle of free donations and anonymity is perhaps threatened as shown in some press declarations. He felt that the legislator should be very firm on this principle and that the remuneration of products of the human body should be avoided at all costs.

Mr Claude Birraux, deputy, first Vice-President, congratulated in turn the rapporteur for his work, while emphasising that the praises made by Mr Pierre-Louis Fagniez had all the more weight as they came from a hospital practitioner who was a university professor.

He felt that the topic addressed in the report was one of the subjects over which the Office has to exercise permanent assessment, and that it should regularly address these issues.

After having recalled that, during the examination of the 2004 bioethics Act, Mr Jean-François Mattei had stated that cloning had not been framed in the first bioethics Acts, as it was believed that this prospect was far too distant in the future, he felt that the rapidity with which evolution is occurring in this field justifies monitoring of the issue going beyond a mere technological watch.

He also noted that the recommendations by the rapporteur were giving rise to questions, insofar as, in addition to the general recommendations related to the topicality of the issue, proposals aimed at revising the Act of 7 February 2004 on bioethics were formulated.

He recalled in this respect that this Act entrusts to the OPECST a twin assessment task in accordance with a precise schedule. First, in 2008, it must make a global assessment of said Act, which assessment is laid down in its Article 40. Second, in accordance with its Article 26, four and a half years after the intervention of the Council of State decree of 6 February 2006, i.e. in 2010, an assessment is to be made of the application of the provisions on research on the embryo and embryonic stem cells. This assessment is to be made in conjunction with the Biomedicine Agency.

Concluding that the assessment work which the Office should perform pursuant to the Act should not be overly anticipated, and that the margin of appreciation of the appraisers appointed after 2007 should not be inordinately restricted, he expressed his preference for a different classification and presentation of the recommendations.

Regarding proposal 5 on the Oviedo Convention, he suggested, in agreement with the rapporteur on this point, correcting the drafting of the explanatory memorandum, considering it preferable to stick to a strict opposition to reproductive cloning, without launching into new controversies, in a context marked by strong pressure from the extremes: on the one hand those who wish to restrict the present legal framework or deny the ethical legitimacy of research performed in compliance with said framework and, on the other hand, those who call for an exaggerated relaxation of this framework.

Last, he wished to obtain clarifications on proposal 18 on the derivation of ovocytes from embryonic stem cells, which is deemed to help do without the use of human ovocytes.

Mr Alain Claeys clarified that nuclear transposition requires many human ovoyces as shown by the 'Hwang affair', and that research was ongoing to derive ovocytes from embryonic stem cells, which would avoid instrumentalising women.

Mr Daniel Raoul, senator, emphasised the highly educational nature of the Rapporteur's presentation and suggested that the title of the report should mention 'human' cells rather than 'living' cells, which have a broader acceptation.

He then insisted on the fact that the patentability of the gene and of its function should not be authorised.

Mr Alain Claeys approved Mr Daniel Raoul's suggestion concerning the report title.

Mr Henri Revol, senator, President, said he would like a glossary to be added to the report to make it easier to read. He then proposed to approve this report, which was adopted unanimously.

Composition of the steering committee

The steering committee for this report was composed of:

Mr Michel Caboche, research director at INRA, member of Académie des sciences,

Mr Hervé Chneiweiss, research director at CNRS, professor at Collège de France, member of the Office scientific board,

Mr Axel Kahn, research director at INSERM, correspondent member of Académie des sciences, member of the Office scientific board,

Mr Daniel Louvard, research director at CNRS, research section director at Institut Pasteur, member of Académie des sciences.

List of persons heard

France

Private hearings

- Mr Xavier Bertrand, minister for health and solidarities
- Mr François Goulard, minister delegate for higher education and research
- Mr Gilles Bloch, director of Agence Nationale de la Recherche
- Mr Gérard Bréart, technical adviser in the cabinet of Mr Xavier Bertrand, minister for health and solidarities
- Mrs Carine Camby, director general of Agence de la biomédecine
- Mr Cédric Grouchka, deputy director in the cabinet of Mr Xavier Bertrand, minister for health and solidarities
- Mr Gabriel Keller, ambassador tasked with bioethics
- Mrs Anne –Marie Masquelier, director general of Généthon
- Mr Marc Peschanski, research director at Inserm, coordinator of the I-Stem project
- Mr Anselme Perrier, research attaché at Inserm, research officer at I-Stem
- Mr David Sourdive, delegate director general of Cellectis
- Mrs Laurence Tiennot-Herment, chair of Association française contre les myopathies

Public hearings of 22 November 2005

- Mr Daniel Aberdam, research director at Inserm
- Mr Jean-Claude Ameisen, university professor, hospital practitioner, chair of the ethics committee at Inserm, member of Comité consultatif national d'éthique
- Mr Christian Bréchot, general director of Inserm
- Mrs Marina Cavazzana-Calvo, university professor, head of the biotherapy department service at Hôpital Necker-Enfants malades, coordinator of the biotherapy integrated clinicial investigation centre at CHU Necker-Enfants malades
- Mr Hervé Chneiweiss, research director at Inserm, professor at Collège de France, member of the steering committee
- Mrs Laure Coulombel, research director at Inserm

- Mrs Anne Fagot-Largeault, philosopher and doctor, professor at Collège de France, member of Académie des sciences
- Mr Alain Fischer, professor of medicine, director of Unité 429 at Inserm (Hôpital Necker-Enfants malades), member of Académie des sciences
- Mr René Frydman, university professor and gynaecologist
- Mr Jacques Hatzfeld, research director at CNRS
- Mr André Hovine, chair of France Parkinson
- Mr Bertrand Jordan, research director at CNRS, adviser at Marseille-Nice Génopole
- Mrs Evelyne Jouvin-Marche, deputy scientific director of the living organisms department at CNRS
- Mr Axel Kahn, research director at Inserm, member of the steering committee
- Mr Daniel Louvard, research section director at Institut Curie, member of Académie des sciences, member of the steering committee
- Mr Philippe Ménasché, thoracic and cardiovascular surgery professor at Université Paris V, heart surgeon at Hôpital Georges-Pompidou, unit director at Inserm
- Mrs Marianne Minkowski, deputy director of the cancer biology department at Institut national du cancer
- Mrs Marie-Odile Ott, manager of the 'research' sector and of international programmes at Agence de la biomédecine
- Mr Marc Peschanski, research director at Inserm
- Mr Roger Picard, spokesman of the Alliance maladies rares
- Mr Christian Pinset, founder and chief executive officer of Celogos
- Mr Philippe Pouletty, chair of France Biotech
- Mrs Ketty Schwartz, vice-president of the board of directors at Inserm, former research director at the ministry of research
- Mr Didier Sicard, chair of Comité national consultatif d'éthique
- Mr Claude Sureau, honorary chair of Académie nationale de médecine, member of Comité consultatif national d'éthique
- Mr David Sourdive, delegate general director of Cellectis
- Michel Van der Rest, director of the living organisms department at CNRS
- Jean-Thomas Vilquin, founder of the company Myoxis
- Mrs Siobhán Yeats, biotechnologies director at the European Patent Office
- Mr Bernard Zalc, research director at Inserm

Belgium

- Mr Jean-Michel Baer, director of the European Commission research directorate-general

- Mr Thomas Brégeon, adviser at the European Commission health and consumer protection directorate-general
- Mrs Bénédicte Caremier, adviser in the cabinet of the European Commission research commissioner
- Mrs Jacqueline Minor, director of the European Commission 'Internal Market' directorate-general
- Mr Jean-Philippe Müller, adviser (industrial property) at the European Commission 'Internal Market' directorate-general
- Mr Fabien Raynaud, legal adviser at the Conseil d'Etat, legal adviser at the permanent representation of France to the European Union
- Mr Nicolas Rossignol, scientific and technical projects officer at the European Commission Industry directorate-general
- Mrs Caroline Trouet, adviser at the European Commmision health and consumer protection directorate-general

Korea

- Mr Philippe L. Bernstein, scientific affairs and international relations officer at Institut Pasteur Korea
- Mr Régis Grailhe, research coordinator at Institut Pasteur Korea
- Mrs Kim Jung-hee, director-general of the tecnology assessment bureau at the ministry of science and technology
- Mrs Lee Soo-young, chair of an ovocyte donors association
- Mr Moon Shin-yong, director of the National Stem Cells Research Centre
- Mr Ulf Nehrbass, director of Institut Pasteur Korea
- Mrs Park Ki-young, former scientific adviser to President Roh Moo-hyun
- Mr Park Kook-in, director of the gene and cell therapy research laboratory at Yonsei University
- Mrs Park Young-wook, chief of staff to Mrs Kim Myung-ja, MP in the Korean National Assembly
- Mr Yang Sam-sung, former chair of the National Ethics Committee
- Mrs Suh Hae-suk, Korean National Assembly MP
- Mrs Yoon Jeung-huh, political director of the political committee of the Uri party

United States

- Mr Roscoe Bartlett, member of the US Chamber of Representatives
- Mr James F. Battey, director of National Institutes of Health
- Mr Louis Casteilla, professor (tissue and cell plasticity) at Toulouse University, seconded to Pittsburg University
- Mr Nicolas Charles, post-doctoral fellow at National Institutes of Health

- Mr Linzhao Cheng, associate professor of gynaecology/obstetrics and oncology at John Hopkins University
- Mr Tao Cheng, director of the stem cell biology department at Pittsburgh University Cancer Institute
- Mr Michaël Clarke, deputy director at Stanford University Stem Cell Research Institute
- Mr George Q. Daley, professor of paediatrics, biological chemistry and molecular pharmacology at the Children's General Hospital, Boston
- Mrs Laure Croisille-Péault, professor of pathology at Pittsburg University Cancer Institute
- Mr Djibril V. Diop, assistant to Mrs Carole Midgen, member of the Senate of California
- Mr Albert D. Donnenberg, professor of medicine, director of Pittsburgh University Cancer Institute
- Mrs Vera S. Donnenberg, professor of surgery and pharmacy at Pittsburgh University
- Mr Kevin C. Eggan, assistant professor of molecular biology at Harvard Medical School
- Mr Lino S. Ferreira, research attaché at Massachusetts Institute of Technology
- Mr Thomas F. Finneran, president of Massachusetts Biotechnology Council
- Mr Don Gibbons, vice-dean tasked with public relations at Harvard Medical School
- Mr Armand de Gramont, post doctoral fellow at National Institutes of Health
- Mr Henry T. Greely, professor of law at Stanford University
- Mr Louis Mr Guenin, professor of bioethics at Harvard Medical School
- Mr Peter Hansel, member of the research Office of the Senate of California
- Mr Robert G. Hawley, professor of anatomy and cell biology at George Washington University
- Mr Johnny Huard, associate professor of orthopedic surgery and molecular genetics at Pittsburgh University School of Medicine
- Mr Rudolf Jaenisch, professor of biology at Massachusetts Institute of Technology, founding member of Whitehead Institute
- Mr James C. Kennedy, research director at the Chamber of Representatives of Massachusetts
- Mr Douglas Kerr, associate professor of neurology at Johns Hopkins University
- Mr Robert Klein, chair of the Independant Citizens' Oversight Committee
- Mr Eric Lagasse, associate professor of the department of pathology at Pittsburgh University
- Mrs Jane S. Lebkowski, vice-president of Geron, tasked with regenerative medicine

- Mrs Annie LeGuern, licences officer at the intellectual property bureau of the Children's General Hospital, Boston
- Mr William Lensch, research attaché at the Children's General Hospital, Boston
- Mr Paul Lerou, research attaché at the Children's General Hospital, Boston
- Mr Arthur S. Levine, first vice chancellor of Pittsburgh University, dean of Pittsburgh University School of Medicine
- Mr Bernard Lo, professor of medicine, director of the medical ethics programme at the University of California (San Francisco)
- Mr David C. Magnus, professor of paediatics at Stanford University
- Mrs Debra JH Mathews, director of scientific programmes at Phoebe R. Berman Institute of Bioethics at John Hopkins University
- Mrs Margaret C. McDonald, vice chancellor of Pittsburgh University, tasked with research affairs
- Mr Alexandre Méjat, post doctoral fellow at National Institutes of Health, director of the Centre d'étude des cellules souches (CECS/I-Stem)
- Mr Eran Meshorer, researcher at the National Cancer Institute (National Institutes of Health)
- Mr Gene Mullin, member of the Chamber of Representatives of California
- Mrs Pearl O'Rourke, research director at Parners Healthcare system Inc.
- Mr Amit N. Patel, professor of heart surgery at Pittsburgh University Presbyterian Hospital
- Mr Bruno Péault, professor of cell biology and physiology at Pittsburgh University School of Medicine
- Mrs Lucilia Pereira-Mouries, post doctoral fellow at National Institutes of Health
- Mr Brock Reeve, executive director of Harvard Stem Cell Institute
- Mr Jeffray D. Rothstein, director of the Robert Packard research centre at John Hopkins University
- Mr George Runner, member of the Senate of California
- Mr Jeffray Sanchez, member of the Chamber of Representatives of Massachusetts
- Mr Andrew W. Siegel, professor of gynaecology/obstetrics, director of research programmes at Phoebe R. Berman Bioethics Institue at John Hopkins University
- Mrs Sonia S. Sutter, professor of law at George Washington University
- Mr Robert E. Travaglini, president of the Senate of Massachusetts
- Mr Rocky S. Tuan, director of the cartilage biology and orthopedics laboratory (National Institutes of Health)
- Mrs Nicole Vasquez, consultant on the health committee of the Senate of California
- Mrs Monique Yoakim-Turk, pediatric products officer at the intellectual property bureau at the Children's General Hospital, Boston

Great Britain

- Mr Geoffrey Boulton, professor at Edinburgh University
- Mrs Jane Bower, professor at Dundee University, chair of the Scottish Stem Cell Network
- Mr Ian Gibson, MP, former chair of the House of Commons Science and Technology Committee
- Mrs Petra Hajkova, post doctoral fellow at Wellcome Trust/Cancer Research UK Gurdon Institute
- Mrs Anne McLaren, research director at Wellcome Trust/Cancer Research UK Gurdon Institute
- Mrs Angela McNab, executive director of the Human Fertilisation and Embryology Authority
- Mrs Alison Murdoch, professor of reproductive medicine at Newcastle Fertility Center at Life
- Mrs Christine O'Toole, director of the regulations and research department at the Human Fertilisation and Embryology Authority
- Mr Mark Pitman, director of the scientific programme and of international affairs at the Medical Research Council
- Mr Harald Schmidt, deputy director of Nuffield Council of Bioethics
- Mrs Alison Stewart, research director at Cambridge Genetics Knowledge Park
- Mrs Sandy Thomas, director of Nuffield Council of Bioethics
- Mr Matthew Wakelin, director of the developmental biology programme at the Medical Research Council
- Mrs Susan Wallace, director of research at Cambridge Genetics Knowledge Park
- Mr Ian Wilmut, professor of reproductive science at Edinburgh University

Japon

- Mr Hideo Funabashi, deputy director of the RIKEN Centre for Developmental Biology
- Mr Ryuichi Ida, professor at Kyoto University Faculty of Law, former president of UNESCO Bioethics Committee
- Mr Hiroo Imura, chairman of the Foundation for Biomedical Research and Innovation
- Mrs Yoko Matsubara, professor of science history at Ritsummeikan University, Kyoto
- Mr Takahido Mori, chair of the bioethics committee of the Japanese Society for Fertilization and Insemination

- Mr Yoshiharu Morimoto, chair of the Japanese Society for Fertilization and Insemination
- Mr Kenzo Nakajima, president of Stem Cell Science KK
- Mr Norio Nakatsuji, director of Kyoto University Stem Cell Research Centre
- Mr Yoshiko Sasai, director of the organogenesis and neurogenesis group at RIKEN Centre for Developmental Biology
- Mr Masatoshi Takeichi, director of RIKEN Centre for Developmental Biology

UNESCO

- Mr Henk ten Have, director of the science and technologies ethics division (social and human sciences)

Germany

- Mr Manuel Desantes, vice-president of directorate-general 5 of the European Patent Office
- Mr Alain Pompidou, professor of medicine, honorary European deputy, president of the European Patent Office
- Mr Pierre Treichel, jurist at the patent law directorate at the Euorpean Patent Office
- Mrs Siobhán Yeats, 'bioetechnologies' director at the European Patent Office

Public hearing of 22 November 2005

Summary

Foreword

Ladies and Gentlemen

As part of the preparation of my report on 'Research on the operation of living cells' which the National Assembly Bureau commissioned from the Office, I wanted to organise a day of public hearings, open to the press, on the specific issue of adult and embryonic stem cells.

The hearing of specialists of the field proved to be absolutely necessary for at least two major reasons. First, the extreme rapidity of the work performed in this field makes precise follow-up difficult as well as critical hindsight allowing proven facts to be distinguished from unfounded announcements. Second, delay has been incurred in implementing the Act of August 2004 and there are dangers of embryonic stem cells being bunched together with nuclear transposition.

This need also came to my attention given the avalanche of media information that accompanied, throughout 2005, the news from Korea. In effect, a Korean team claimed to have produced several human embryonic stem cell lines using the nuclear transposition technique.

The transition was then made quite blithely: the possibility of curing still incurable disorders, such as Parkinson's and Alzheimer's diseases, was in sight, within reach, achieved! Moreover this was not just the attitude of some media but also of eminent professors of medicine who irresponsibly gave false hopes to patients and their relatives.

It was therefore necessary to take stock very precisely of the state of research in this field of stem cells.

I felt it was essential that this overview should be made publicly so that, in addition to the rapporteur, public opinion should be informed of the main and real challenges of this field.

I also wanted a public exchange of views to take place, in preference to the conventional private hearings, to give rise to a debate on this subject.

I hope this discussion will be taken up very broadly at the national level as has already been the case in a certain number of countries like the United States at the time of the 2004 presidential election, and in Switzerland at the time of the referendum of 28 November 2004.

I therefore brought together at the National Assembly the most competent French researchers of this field, on 22 November 2005.

I wish to thank them for having kindly accepted to give an account of their work and their analyses of the research performed in their field internationally. May they accept all my gratitude for their presence that day.

The debate was enthralling and very dense from end to end. It was sometimes highly animated but always remained extremely courteous.

What do researchers say?

Their main message is that France is presently falling behind with respect to its European and world competitors.

Researchers indeed pose very clearly the issue of the introduction of the authorisation of nuclear transposition in Act no. 2004-800 of 6 August 2004 on bioethics.

However, as they admit themselves, problems will have to be solved should this Act be amended.

The biggest difficulty resides in the need to have large quantities of ovocytes to perform a nuclear transposition, bearing in mind its low success rate.

This situation introduces a very real threat of the marketing of ovocytes and therefore of their merchandising, which must be resolutely opposed.

Researchers have also levelled other reproaches against the Act.

They therefore criticised it for having introduced overly complex and therefore penalising procedures for their work. I will examine this issue in my report, especially by assessing the practices of the Biomedicine Agency that is just being set in place.

In this respect, it should be emphasised that more than one and a half years after the entry into force of the Act, the implementing decree on the conditions for the authorisation and implementation of research on human embryos has just been published, in other words eighteen months after the publication of the Act. This delay has certainly disadvantaged French research.

This situation is all the more prejudicial as world competition is growing fiercer in this field, as I was able to see during a recent trip to Asia.

To draft my report, I indeed decided to travel to some of the most advanced countries in this field in order to very precisely assess their situation. I indeed feel that such a subject cannot be addressed and dealt with as a matter of urgency and in a hurried manner as that certainly detracts from in-depth, documented and balanced analysis.

The work on embryonic stem cells is still a matter for the field of fundamental research alone.

As it undoubtedly wanted to take short cuts, the Korean team that hit the headlines in 2005 went astray in a large-scale scientific fraud. Nevertheless this affair, which is to be assessed solely from the viewpoint of scientific honesty, must absolutely not cause the whole embryonic and adult stem cells research sector to be slandered.

Nor must research on nuclear transposition fall victim to its proximity to reproductive cloning which I very firmly condemn.

I fully appreciate Mr Alain Fischer's viewpoint in this respect.

In effect, during the public hearing, the latter stated that nuclear transposition is not to be condemned as 'per se, a scientific development is neutral: it is neither positive nor negative. It is to be regulated so that socially 'useful' development is promoted while avoiding a development which society, rightly, does not want.'

This subject must once more be approached serenely.

That certainly calls into question the precipitation which, in 2006, has too often obscured the debate on this highly complex subject.

Once again it has proven to be true that 'scientific time' must in no way be forced to comply with 'media time'. In this field, indeed, 'time should be given to time'.

I am convinced that stem cells, both adult and embryonic, certainly have an immense potential. They will first allow a better understanding of the tremendous secrets of life. In a future which still remains uncertain today, hopes will perhaps arise for a certain number of disorders today incurable.

I will be led to make very concrete recommendations on the use of stem cells in the report that I will be drafting in the months ahead.

Apart from scientific problems, this matter raises immense ethical issues which should be debated publicly. As emphasised by Mr Jacques Chirac, President of the Republic, in the letter he sent me on 15 December 2006, 'in this field, it is

necessary to act with discernment so that any utilitarian use of human beings is excluded'.

I too feel this is an essential matter of concern in this field. Yet, at the same time, our researchers must feel they are firmly encouraged to make progress so as to 'reduce sufferance, diseases, and handicaps' as also noted by the President of the Republic in the same letter.

Alain Claeys
Deputy, Vienne

The session was opened at 9 a.m. under the chairmanship of Mr Alain Claeys, deputy, Vienne, and rapporteur.

Opening by Mr Alain Claeys, Deputy, Vienne, and rapporteur

Ladies and Gentlemen, Thank you for having responded to my invitation. I am going to say a few words on this day and on the approach I have adopted.

As a deputy in La Vienne, I first wish to state that I am neither a doctor nor a researcher. I had the opportunity to take an interest in all these bioethics subjects as of 1997, when the Parliamentary Office for Science and Technology Assessment (POSTA) assessed the 1994 Bioethics Act. The legislator had decided that this Act had to be assessed after five years by the Parliamentary Office.

In the framework of said Office I made this assessment with Claude Huriet who was a senator at the time. It was from then on that I started to take an interest in bioethics. We wrote two reports, then I coordinated at the National Assembly the fact-finding mission with a view to the preparation of the bill revising the 1994 Bioethics Acts. At first reading I was the rapporteur of the bioethics bill.

After the change in majority, the bill was adopted at second reading in August 2004. At the same time, on request by the Office, I have written two reports on intellectual property and patents. The first dealt with an analysis of the European Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions which has been transposed into French law. The second concerned intellectual property in the living organisms field. We will have the opportunity to return to that this afternoon, more specifically in the fourth roundtable.

Today's hearing enters into the framework of a new study which the National Assembly Bureau commissioned from the Office, on cell research. Through this subject we will address the issue of stem cells and what is called therapeutic or scientific cloning, but other expressions must be used. If we could today clarify these notions, that would be a good thing.

I hope that during this day everything can be said, on your appreciation of the 2004 Act, its implementation, the challenges in research and health terms, and to take stock quite precisely of the subject of cloning, the situation abroad, today's results and ethical problems. All of this is necessary for a good

understanding of this subject and so as to go beyond journalistic announcements that are sometimes sensational and that hide reality to a certain extent.

I would like to excuse one of the planned contributors who cannot, to my regret, be present. In effect, Mrs Carine Camby, director-general of the Biomedicine Agency will be leaving her post in a few days time. She told me that unfortunately she could not therefore represent the Agency today. She was to participate in the second roundtable.

We are going to begin.

First, I would like to thank Mrs Ketty Schwartz for accepting my invitation and agreeing to open our debates. The task is by no means simple. The first question I want to ask her is for her to explain to us how what is happening today regarding stem cells constitutes a revolution in research and how we are addressing this challenge in France. Also what is her vision of what is happening abroad? We can then pose the debate, which will allow us to go deeper into the subjects in the successive roundtables.

Introduction:
Stem cells in the evolution of biology

Mrs Ketty Schwartz, vice-president of the board of directors at Inserm, former research director at the Ministry of Research.

Mr Deputy, Ladies and Gentlemen, It is a very great honour for me to try and answer the simple, obvious questions you have asked me, especially before such a prestigious audience of scientists, politicians and representatives of civil society of France. I also wish to tell you how grateful we are to you for having accepted the time-consuming task of preparing a new report on the operation of living cells. If we want to get legislation in France to make headway, this report could not have been committed to better hands than yours.

Today's topic, stem cells, is probably one of the fields of biology where evolution has been among the most spectacular in recent years. You spoke of a revolution, and the term is not too strong. This revolution is borne by the unprecedented expansion of our knowledge on the sequences of the genomes of living organisms in under a decade, on the structure and function of genes, on the way we have learnt to modify living organisms, especially small animal models, such as the mouse, by transferring or replacing genes, and by the development since ten years or so of large-scale biology and nanotechnologies.

The interest for stem cells today is considerable, on the cognitive, therapeutic and economic planes. In a field that is evolving as fast as this one and giving rise to so many ethical questions, it would be good if the time taken for ethical analysis and democratic debate would harmonise with that taken for research, so that control and decision mechanisms can be defined that are completely transparent and adapted to the evolution of scientific knowledge and so that they will allow French researchers to explore, entirely legally, new pathways and new avenues leading to knowledge.

To reframe the debate a bit, what is the meaning of 'stem cells' and what is meant by them?

Stem cells are characterised by three fundamental properties, whatever their origin or stage of development at which they are found.

On the one hand, they are undifferentiated cells, in other words they have no specific character of a tissue, and they are incapable of expressing a specific function. For instance, they cannot associate with their neighbour, pump blood, like the adult cells of heart tissue, and they cannot transport oxygen in the bloodstream.

They are cells that are capable, in specific conditions, both *in vivo*, and also *ex vivo*, in culture tubes, of dividing and proliferating in the undifferentiated state.

Lastly, they are cells that are capable of differentiating into specialised cells, which means that the some two hundred cell types forming our organism all originate from stem cells.

What are the steps of this differentiation, the differentiation of human tissues and of mammal tissues in general?

At the beginning, there is the egg, the zygote, the fertilised egg, which is called a totipotent cell because it can give rise to all cell types. As the divisions take place, the differentiation spectra of the daughter cells decrease, in other words in the blastocysts from which human embryonic stem cell lines derive, in this internal mass, cells are called pluripotent because they are going to be at the origin of three major lines (ectoderm, mesoderm and endoderm), which begin to lose a range of differentiation possibilities and become multipotent.

Precursor cells are then spoken of, like those of the skeletal muscle, which are cells that have only two differentiation choices: becoming fast or slow skeletal muscle cells. Precursor cells are found in adult tissues. These are what are called adult stem cells. In recent years, the existence of multipotent stem cells in adult tissues has been the subject of a certain number of studies. It clearly appears that they also exist in these tissues.

In the twentieth century, the study of these cells was included in the large field of developmental biology and France particularly illustrated itself here. Proof of this is given by the first slide that was presented to Mrs Judith Melki, Mr Guy Fuhrmann and myself during a trip to the United States, by Mr John Gearhart who was presenting the progress of his work at John Hopkins University in Baltimore. The slide in question showed Mrs Nicole Le Douarin, thereby paying homage to her work on chimera and the neural crest.

Therapies based on stem cells, or their therapeutic possibilities, date back to the second half of the twentieth century, through bone marrow grafts in leukemias and lymphomas where allogeneic hematopoietic stem cells have been widely used to replace patients' stem cells. The first embryonic stem cell lines considered to be such, came in fact from teratocarcinomas in the mouse and date back to 1960. The first real mouse embryonic stem cell dates back to 1981, in other words barely twenty-five years ago, when it was discovered by Evans, Kaufman and Martin,.

The first embryonic stem cell lines of non-human primates date back to the middle of the 1990s. But is was in 1998 that the first human embryonic stem cell

lines were obtained, either from the internal mass of blastocysts by Thomson et al., or from germ cells extracted from the five to nine week human foetus.

It was from then on, because there was the possibility of obtaining human embryonic stem cell lines, that the biology of cells in general, whatever their differentiation stage, attracted high media and scientific attention, and became a fully fledged field of biology. That's seven or eight years ago all told.

The reasons for this development are simple. They are extraordinary new subjects of study in understanding the mechanisms of development and evolution and also in undestanding human pathologies and treating and perhaps curing. Understanding the mechanisms of development and of evolution means understanding what molecular signatures and differentiation signals lead to maintaining a stem cell in an undifferentiated state, or, on the contrary, lead to its differentiation. It finally entails the exploration of all the way in which our organism is built from one cell and has built itself through evolution.

In this context, an extremely rapid research pathway was developed at the beginning of the 2000s, with the appearance of instruments that allowed global analysis of gene expression. In 2002, the first studies showing all gene products, transcriptomes, appeared using embryonic stem cells, neural stem cells or hematopoietic stem cells. These studies were hailed with great enthusiasm. Since then, despite a few leads, it must be admitted that the results are relatively disappointing. It appears that what was wanted to be proved, giving a molecular signature to a state (stemness), has not be achieved. It was expected to find a common genetic signature to all stem cells. In fact a few genes have been found (oct4, nanog), but that's about all and it appears more clearly now that there is no single genetic programme characterising stem cells.

Another research pathway followed at present, in particular for adult stem cells, is that of the interactions existing between stem cells and their immediate environment. This immediate environment has in a sense paid homage to France known as it is by the name of 'niches'.

This very recent research pathway demonstrates how, from a totipotent cell, the cell differentiates little by little to reach the adult state as a differentiated cell. The hypothesis is that, at the surface, at the interaction between the embryo and adult part, the cell is maintained in an undifferentiated state by its very high interaction with the niche around it. The signals emitted and the interaction between the cell and the niche condition the accessibility of genes to transcription. The common characteristic of stem cells would therefore be that they are stopped in their progression to a differentiated state by their immediate environment. We are perhaps reaching a hypothesis of a molecular logic for stem cells which would be quantitative, opening access to different genetic programmes, rather than qualitative, with a common transcriptional programme.

To study all that, this is merely an example. We should be able to have access to the lines of various species. A mouse is not a non-human primate, a non-human primate is not a man, and we already know that there are major differences of expression between a human embryonic stem cell and a mouse embryonic stem cell.

Understanding the mechanisms of human pathologies: the sequencing of the human genome has allowed the genes responsible for very many diseases to be found over the past decade.

If we interrogate the Human gene mutation database in Cardiff, one of the best documented at present, we find more than forty-seven thousand mutations that have been described and published and which correspond to nearly one thousand eight hundred genes causing human diseases The pathogenic mechanisms of all these mutations must therefore be understood. You all know that a plethora of murine models have been created. They are genetically modified models and have provided major information on these diseases. There is no doubt that a better experimental model than mice would help to study mechanisms with the same genetic makeup as the patient's. This can be done by deriving lines from embryos bearing the mutation and not reimplanted after preimplantation diagnosis.

The authorisation to import one of these lines bearing mucoviscidosis mutations was therefore given in France on 24 October 2006, and the authorisation for two other lines, bearing an extension in the huntingtin gene responsible for Huntington's disease, has been pending for over a month. Another way of proceeding in order to obtain the same genetic makeup as the patient's is to create lines by nuclear transfer (somatic cell nuclear transfer) or therapeutic cloning, which was the term used previously, which I did not like, or else scientific cloning, which is also used. International terminology is tending rather to adopt the term nuclear transfer or nucleus transfer.

Mr Alain Claeys, deputy, Vienne: I would like to say a word on this subject. Do all those present think that the term 'nuclear transfer' is the right definition? Even if it is not the definition felt to be the most explicit by the biggest audience... this term can therefore be adopted for the day.

Mr Claude Sureau, honorary chair of the Académie nationale de médecine, member of the National Consultative Ethics Committee: the term 'transposition' is often used by foreign researchers, for a simple practical reason. Transfer is a term which is also used for the transfer of an embryo into the maternal uterus. There are therefore two acceptations of the term transfer, which can be somewhat troublesome.

Mrs Ketty Schwartz: Indeed. The term cell transplantation was also given, but we have that of 'nuclear transposition'. I would agree on the face of it.

This nuclear transposition pathway appears very promising to me because it opens up a new era of animal models which could be obtained by the transplantation in immunodeficient mice of human cells bearing a mutation.

To treat and cure, bone marrow grafts have been performed for cancers as you know since the middle of the past century, with non-negligible secondary effects, especially the host's violent reaction against the graft. Many advances have been made since, and the field of hematopoietic system regeneration is today in the full swing of development.

Other fields are emerging, in terms of regenerative medicine. May I quote two examples. The first concerns heart insufficiency characterised by a destruction of heart muscle cells. This is a major public health problem. In the middle of the 1990s, with Philippe Ménasché, and others, we had explored the possibility of an autograft in the heart tissue of skeletal muscle precursor cells. This led, in 2000, to the first phase 1 trial, the world first trial in the heart insufficiency regenerative therapy field. For the past two years, a world double-blind phase 2 trial has been conducted. Philippe Ménasché will probably refer to it later on in one of the roundtables.

Transplanting skeletal precursor cells into a heat muscle is probably not the ideal pathway, but it has widely opened up heart tissue regenerative therapy worldwide. The other example I would like to quote is that of a rare neurodegenerative disease, the lysosomal disease called Batten's disease which is due to the mutation of enzyme-coding genes, thioestera or peptidases.

On 20 October 2005, in the United States, the company *StemCells* obtained the agreement of the FDA to commence a phase 1 trial on safety and primary efficacy using foetal neuronal human stem cells. The approach followed by this small company is quite exemplary. It has enjoyed know-how transfers from prestigious scientists in the differentiation and developmental biology field. Scientists will recognise here the names of Irving Weissman, Fred Gage or David Anderson. The first aim of this company has been to establish the feasibility of this regenerative therapy using foetal cells. They chose Batten's disease as the model disease, conducting tests in vivo on murine models of the pathology and they have developed a process to purify foetal neuronal cells to a very high degree. They showed that these repopulated the target tissue. This repopulation is low, lower than 10%, but sufficient to produce a functional improvement. Quite clearly the possibility of an immunological reaction against

allogeneic neuronal cells is relatively low, probably in the short term, no doubt because of the specific confinement of the nervous system. No teratoma was detected in more than three thousand animals which were treated for periods of up to more than sixty weeks.

Validation of this approach will then lead them to develop it in more frequent neurodegenerative diseases, like Parkinson's or Alzheimer's disease, medullar traumatisms, or multiple sclerosis. In terms of the development of a therapy and of knowledge on the possibility of using these stem cells, a very important step was taken by the regulatory authorities in the United States just under a month ago.

Treating and curing also involves the development of tests allowing high-speed screening of combinatorial libraries, whether private or public. It also entails developing tests allowing the assessment of the potential toxicity of the leads or drugs selected, without having, or complementary to, animal models.

Treating and curing also means finding new classes of drugs acting on new targets brought to light through fundamental research on stem cell differentiation pathways.

Treating and curing, in an ideal world, is also being able to regenerate destroyed tissues with cells whose nuclear genome would be identical to the patient's. For that purpose, the research possibilities opened by the use of cell lines obtained after nuclear transposition appear extremely promising.

To meet your request, Alain Claeys, I am going to finish this brief introduction by trying to situate in the European and international context our legislation today on human stem cells.

I am going to show you two very recent slides (November 2005) entrusted to me by the European Commission.

We can see the countries with the most restrictive legislation with respect to those with the most permissive. No research is authorised in Austria, Poland and Lithuania. In Germany and in Italy, new lines cannot be created, but lines prepared elsewhere can be imported. The twelfth import and research authorisation was granted in Germany barely a month ago to Institut Robert-Koch. These lines must correspond to the American lines, except for Germany, where they correspond to the implementation of the 2002 Act. In other countries (Finland, Denmark, France, Estonia, Hungary, Czechoslovakia, Slovenia,

Spain), the import and derivation of new lines from spare embryos are authorised.

I wish however to emphasise that in France, it is not a matter of an authorisation but of a ban, subject to derogation, and only for a length of five years. In a way, I therefore feel they are very 'kind' to have placed us among the leading countries. Also, as regards the authorisation to derive new lines from spare embryos, the implementing decrees have not appeared, and they are therefore still not authorised. We should be situated far more to the right on the graph.

May I mention the case of Switzerland, which is quite special and interesting, as it is the only country in the world today where citizens were asked by referendum if research on embryonic stem cells could be authorised, and 66% of the voters answered affirmatively a few months ago. In Australia, Brazil, Canada, Japan and Taiwan, it's the same situation as in the countries situated above. Lastly, in Belgium, Sweden, Great Britain, Israel, the United States out of non federal funds, China, India, Singapore, and South Korea, nuclear transposition is authorised.

A global analysis of all this data shows that the countries which have either a permissive policy, authorising nuclear transposition, or a more flexible policy, authorising the creation of new stem cell lines from spare embryos, today form more than half the world population. Given the present situation in France, in November 2005, we are today not quite in this half.

I very sincerely and deeply hope, and I am taking the liberty of addressing the decision-makers present, and especially Alain Claeys, that France's legislation is going to evolve very fast, and that not only the decrees authorising the creation of new lines from spare embryos are at last going to be promulgated, but that there will be a revision of the bioethics Act, even if the bill by Roger-Gérard Schwartzenberg, has not been adopted for the time being. I was one of the ten signatories of the petitition asking for the removal of the ban and the transformation of this removal of the ban into an authorisation, with of course strict framing, and with authorisation of nuclear transposition. This must be framed in a strict manner.

I wish to add that research today, in all countries, on human embryonic stem cell lines, is the most framed in legislative terms. Even in countries where transposal is authorised, nearly fifteen stamps are needed before such research is authorised and can be performed. To authorise and frame this research, the National American Academy promulgated in April 2005 very comprehensive cell guidelines.

Mr Alain Claeys: Thank you very much, Ketty Schwartz, for your speech, in which you have answered a certain number of questions.

I wish to make a clarification. The decrees of the August 2004 Act do not come within the jurisdiction of Parliament. It is the executive which must adopt this decree. At the time, I drew the attention of the Minister Philippe Douste-Blazy. I feel that a certain number of decrees, the main ones, are falling behind, and that we are presently operating only 'by derogation' in a way.

Mrs Ketty Schwartz: If I may say so, we are operating by derogation, since the law states a ban, save derogation, for a length of only five years concerning the import of lines. But the creation of new lines from spare embryos is for the time being dependent on the promulgation of the implementing decrees. We are therefore not even in this context. French scientists, doctors and researchers can work only with lines from abroad. They are therefore highly dependent on contributions from abroad. I think that's an extremely important point to be made.

Mr Alain Claeys: We will refer back to this, including the drafting of the Act as it came back to us from our senator colleagues. I will have quite precise questions during the day to see what the operational method is. It's an additional constraint for possible authorisations, isn't it?

This speech was useful for us parliamentarians in order to take stock in particular of the vocabulary, which is useful in our communication society, and to clearly distinguish today what is a matter of fundamental research and what are the first applications. As politicians, we must have the intellectual honesty and strictness to speak advisedly.

We are going to commence the first roundtable. I wish to present to you Mrs Anne Fagot-Largeault, philosopher and doctor, professor at Collège de France and member of the Académie des sciences. Next to you, Jean-Claude Ameisen, university professor, hospital practitioner, and president of Inserm ethics committee.

Roundtable no. 1:
Stem cell characteristics

Mrs Anne Fagot-Largeault, philosopher and doctor, professor at Collège de France, member of Académie des sciences. You asked me, Mr Deputy, to make a historic and philosophical overview of this matter.

Mr Alain Claeys: I think it is worthwhile, at the beginning of the day, to have this vision as well.

Mrs Anne Fagot-Largeault: To begin with I wanted to say that I fully share Mrs Schwarz's position on reform of the legislation. At the very least, depenalisation should be envisaged and, at best, authorisation and framing of cloning for therapeutic purposes, as it is currently called. I am not going to raise this question, but I'll refer to a certain number of historic considerations in order to situate the issue. I'll do so in five points

1) It was seen for the first time in the 17th century under a magnifying glass or a composed microscope that living matter had an alveolar or cell structure. From 1830 on, when the microscope made decisive progress, with achromatic microscopes, cell nuclei appeared before the eyes of observers. This allowed the first formulation (1838-1839) of what Schleiden and Schwann called cell theory. According to this first formulation: 'All living organisms are made of cells'. Twenty years later, Virchow completed the cell theory by posing that all cells only arise from pre-existing cells. It was therefore only in the 19th century that the awareness arose that living beings are all formed of cells.

In the second part of the 19th century, in 1868, Haeckel divided living beings into monocellular and pluricellular ones and conjectured that pluricellular beings derive from monocellular ones. A few years later, in 1875, for the first time, Hertwig observed under the microscope the fertilisation of a sea urchin egg, in other words the penetration of a spermatozoon into the ovum and combination of the nuclei. It is only since that period, the end of the 19th century, that it is known what fertilisation is and that its mystery has been elucidated.

2) It has therefore been known for slightly more than a century that all living organisms derive from a single cell. In the pluricellular organisms we are, it is the zygote, in other words the ovum fertilised by the spermatozoon. We have learnt, since slightly more than a century, the stages of the progressive division of this initial cell, which divides into two, four, eight, sixteen etc., which passes through successive differentiation states until, as mentioned by Mrs Schwarz, it

gives rise to approximately two hundred different types of cells forming our organism.

The differentiation stages have been given names. It is said that the first cell is totipotent, it can make all the cells. Then, we move through stages of pluripotency and multipotency, and the last cells that give rise to completely specialised cells are called progenitors.

The specific characteristic of stem cells is that they can divide to form other stem cells, in other words they can multiply identically, and at the same time they can divide to give rise to more specialised cells than themselves.

During the 20th century, the study of stem cells shattered a dogma that appears in almost all 20th century biology manuals, in other words that the differentiation of a normal cell is not reversible. Stem cells can apparently in fact present transdifferentiation phenomena. In the laboratory, it has been shown that mice hematopoietic cells, which normally give rise to blood cells, can under certain conditions lead to liver, muscle or lung cells. It has also been shown that neural stem cells cultivated with endothelial cells forming the wall of vessels can change their fate to become endothelial cells. The course of differentiation is therefore apparently not entirely determined. This is what is called the plasticity of stem cells, but this plasticity is today much debated and partly ill known.

3) It has therefore been known since the beginning of the 20th century that there are stem cells in our organism that are the precursors of differentiated cells. These stem cells are the source of the permanent regeneration of our organism. The example of blood cells can be taken. Every day, 1% of our red globules, 10% of our platelets and 100% of our white globules are eliminated from the blood stream, destroyed and replaced by cells formed in the bone marrow from precursors arising from the differentiation of hematopoietic stem cells. The same applies to muscle, intestinal and skin cells, and even most of the cells of the central nervous system. They are constantly destroyed and replaced by new cells derived from the stem cells we have in reserve. This cell turn-over is one of the aspects of a very long known phenomenon, called the 'vital circulus', 'vital vortex', or metabolism.

It can be said that our stem cells are the concretisation of the biological potential we have to constantly individuate ourselves while ensuring the continuity of our being. It is today known that, in adults, stem cells keep and transmit a potential that can be termed embryonic; the graft of a stem cell nucleus in an ovocyte can give rise to an embryo capable of developing as a clone of the organism donating the nucleus. While the existence of stem cells was known and while it was learnt to analyse their properties during the 20th century, it was only at the end of the 21st century that it was learnt to grow embryonic stem cell lines, firstly of mice, since the 1980s, and then of human stem cells, since the end of the 1990s. Attempts have also been made to control their differentiation, and it was

then that their therapeutic prospects were glimpsed leading to so-called regenerative medicine.

4) The regenerative properties of living beings have been known for long. In the 18th century, Réaumur studied the regeneration of crayfish legs, Spallanzani showed that the snail regenerates even its head and Tremblay discovered that freshwater polyps can be propagated by cuttings like plants, in other words a piece of polyp can lead to the formation of an entire polyp. In the 19th century, Claude Bernard, then Paul Bert, anticipated the possibility of placing tissues in culture; tissue culture techniques were developed around 1910.

Throughout the first part of the 20th century, researchers exercised their extraordinary ingenuity on plants, animals and man, to cultivate tissues and graft cultivated tissues. In the middle of the 20th century the vogue was for embryonic tissue grafts as it had been observed that embryo tissues are less often rejected than adult tissues. A certain number of cases can be quoted, for instance thyroid grafts in mice or thyroid tissue grafts in mice or rats. In humans, these grafts were performed with the collection of thyroid tissue from still-born infants and transplantation to infants suffering from congenital myxedema, in other words born without a thyroid.

Grafts of stem cells or of cells derived from embryonic stem cells present obvious advantages over the attempted grafts of tissues collected from live or dead persons. Cell cultures allow cells to be kept in banks, meaning it is no longer necessary to collect them from a dead person, or, when a graft is needed, to collect them from a live person. Furthermore, the properties of embryonic stem cells, the capacity of being derived, oriented and differentiated to all the cells of the organism, provide a ready stock of grafts of all possible tissues. The disadvantage has been mentioned by Mrs Schwarz: grafts of cells derived from embryonic stem cells are subject to graft rejections even if the rejections are less violent than in the case of adult tissue grafts.

5) The nucleus transfer technique then intervened. This would allow grafts which would not be rejected by the organism, using cells compatible with the organism. It should be noted that cloning was severely condemned before it was known if it was possible. Already in the 1980s, the Council of Europe expressed several warnings and at least verbal bans on human cloning. As said, the cloning technique consists in replacing the nucleus of an ovocyte with N chromosomes by that of a somatic cell with 2N chromosomes, which can be a common body cell. It is observed that the nucleus transferred this way is reprogrammed. It regains its embryonic potentialities. I previously mentioned that all our cells have embryonic potentiality in a sense as they all have the same genome.

The nucleus transfer or transposition technique is per se morally neutral. Everything depends on what is done with it. Reproductive cloning is aimed at using

this technique to make a child whose genome is identical with that of the donor of the transferred nucleus. A clone of its father, if you like. On the other hand, therapeutic cloning seeks to obtain by this technique a cell line that can supply a graft to treat the donor of the nucleus, for instance pancreatic cells producing insulin, aimed at treating a patient suffering from type 1 diabetes. If a nucleus from your own body is used, the graft will be immunocompatible with it. The advantage of this type of graft is therefore immunocompatibility.

The very recent character of the technique and of its successes mean that it is still poorly assessed, barely assessed or not assessed at all. It should be realised that the lamb Dolly was born less than ten years ago. The embryo had been obtained by transferring a lamb udder cell nucleus into a lamb ovocyte. It was the first reproductive cloning success, which then succeeded in other species. Malformations or developmental difficulties were believed to have been seen in cloned animals. I have recently spoken with Jean-Paul Renard who is highly experienced in cloning and knows all about these developmental difficulties. He told me that clones which survive the gestation difficulties have an entirely normal life, live very well and reproduce normally. A certain number of fears over the viability of clones have today apparently been overcome. But the important event, which partly explains today's meeting, is that at the beginning of 2004, then in 2005, a Korean team published quite convincing and dazzling results in the human cloning field.

Mr Alain Claeys: I wish to intervene on this specific point. Do all those present agree on the scientific relevance and undeniability of the results by this Korean team, or is there a debate in the scientific community?

Mrs Anne Fagot-Largeault: It's an incomplete result. Mr Hwang's team stated that it was not aiming at reproductive cloning and placed itself in conditions in which reproduction by this method was excluded.

Mr Alain Claeys: What are these conditions?

Mrs Anne Fagot-Largeault: This means that they did not reimplant in a uterus. What they aimed at and succeeded in doing was collecting skin cells from three types of patients suffering from an interruption of the spinal cord, type 1 diabetes, and a congenital immune disease. They transferred the nucleus of the skin cells of these patients into previously enucleated ovocytes. Using these ovocytes, where the patient's nucleus had been transferred, they succeeded in deriving cell lines in the three directions corresponding to the three layers of differentiation of the embryo at the beginning of development. The experiment stopped there. They showed the possibility of obtaining cells beginning to differentiate in the direction they wanted in order to eventually obtain cells that could be grafted therapeutically in a patient who was the donor of the nucleus.

This led to great enthusiasm and great hopes, especially at patients' associations. That's where we are. Proof that this can be a genuine therapeutical technique has not been given, but it is known that in Great Britain, for instance, at least one team is already working actively on the same line, to obtain pancreatic cells producing insulin to treat type 1 diabetes. We have reached the stage of hope which, according to the coherent results, appears serious.

Mr Alain Claeys: Thank you, Madam. I would like to ask a question. From an ethical viewpoint, does stem cell research require special precautions to your mind? Internationally, should legislation be adopted, and what analysis grid could guide the legislator so as to have all the guarantees?

Mrs Anne Fagot-Largeault: I have been disconcerted by the fact that French law authorises, even under certain conditions, with serious checking of the conditions in which it is done, the use of embryonic stem cells left over from fertility treatment, and which have been collected from embryos kept in a freezer initially to have a baby. French law authorises research to be performed in this pathway and yet heavily sanctions research on cells comparable to these but which were produced in a laboratory by nucleus transfer.

I feel that, on the face of it, we owe more consideration to cells left over from fertility treatment, which were therefore not initially created for research. The law provides for this, since the couple's consent is required. More respect is owed to these cells than to cells not created to make babies and produced artificially in a laboratory.

Mr Alain Claeys: You mean to say that, in the framework of French law, regarding what has been decided using spare embryos, the framing or precautions decided are not sufficient?

Mrs Anne Fagot-Largeault: I think that the framing is very strict and sufficient, but that we are right to impose consideration, especially the consent of the couple donating the embryo. However, I feel that it is entirely paradoxical that the law considers that it is acceptable to do this and that it is a crime to produce embryos artificially by nucleus transfer. We have no special respect for the ovocyte lost by each woman every month. The skin nucleus from which the nucleus is extracted is not respected either. We lose skin cells every day.

Mr Alain Claeys: In a nutshell, the paradox is saying that research is authorised on spare embryos, and concerning nuclear transposition, it is refused, whereas it poses fewer ethical problems. We will have the opportunity to return back to this issue of ovocyte donation, to which due thought must be paid.

Mrs Ketty Schwarz: I fully share this vision concerning the imbalance existing between authorisation and penalisation in France. I recall that we still do not have the authorisation to derive these lines.

Mrs Anne Fagot-Largeault: We can now derive ovocytes from embryonic stem cells.

Mr Alain Claeys: We will return back to this subject throughout the day. Thank you very much, Madam. I am now going to give the floor to Jean-Claude Ameisen.

Mr Jean-Claude Ameisen, university professor, hospital practitioner, president of Inserm ethics committee, and member of the National Consultative Ethics Committee: My research work does not directly concern stem cells. But it concerns cell renewal mechanisms, as they focus on the study of cell death and, more specifically, cell self-destruction phenomena, a form of terminal differentiation called programmed cell death, or apoptosis.

Since the past fifteen years or so, we have discovered that these cell self-destruction processes play an essential role, not only in the development of the embryo, but also after birth, in the child and adult, in the permanent deconstruction and reconstruction phenomena of our bodies, as well as in the development of many diseases.

The revolution experienced by research in the stem cell field has accompanied, like a mirror image, the revolution experienced by research in the cell self-destruction field. But it is not only a matter of concomitance. There is also a close link between these two processes, as a cell capable of self-renewing is, per se, a cell capable of suppressing the triggering of its self-destruction. The capacity of preventing or delaying self-destruction therefore undoubtedly plays an important role in a cell's capacity to become and remain a stem cell.

Ketty Schwarz emphasised that stem cell research helped to pose a certain number of fundamental questions on the mechanisms of embryonic development, and, more generally, on the evolution of living organisms. What is a stem cell? The cells forming unicellular organisms, whether the yeasts that appeared approximately a billion years ago, or the bacteria that appeared three to four billion years ago, are in fact all stem cells. They are capable of self-renewing and differentiating. These differentiation phenomena are often reversible, in other words the cell can switch back from a differentiated state to a stem cell state, save, of course, when this differentiation takes the irreversible form of self-destruction. The emergence of multicellular organisms, approximately one billion years ago, therefore appears to have been accompanied by a progressive restriction in the renewal and differentiation capacities of cells as they build the complexity of a body. But in our stem cells at the beginning of embryonic development we find some of the ancestral properties of the first cells which gave birth to us a long time ago.

A matter which appears important to me concerns the widespread notion of self-renewal and potential 'immortality' of stem cells. A long predominant idea in

biology has been that unicellular organisms, ancestral stem cells, divide identically, symmetrically, and self-renew without ageing, by having eternal youth therefore. Since the past few years, work performed on yeast and some bacterial species has shown that this was an illusion. The perenniality of a colony of yeasts is not due to eternal youth of the cells composing it, but to the successive genesis of ephemeral cells. Each mother cell divides asymmetrically, producing ten or so to twenty or so daughter cells, which are born with a fertility and youth potential identical to that which their mother cell originally had. But each mother cell ages, becomes sterile and disappears after making daughter cells.

What is the case with the stem cells in our body? Many studies suggest that they divide asymmetrically, producing a cell with the same potentialities as the mother cell, and another cell entering a differentiation pathway. At a time when we are attempting to understand and manipulate embryonic and adult stem cells, I feel it is important to ask ourselves if these notions of renewal, plasticity and youth should not be thought of and explored in terms of cell populations, and successive generations of ephemeral cells which are born, give birth, age, become sterile and die. It is possible that the illusion of an identical division, of a self-renewal, may be due most often to our incapacity to distinguish the discreet but crucial phenomena of breakage of symmetry which beget the phenomenon still mysterious from a molecular viewpoint which we call youth.

The second important issue alluded to by Ketty Schwarz and Anne Fagot-Largeault concerns the ever greater role granted to epigenetics in biology.

Mr Alain Claeys: Can you develop on this subject, with respect to this new concept entering the field of biology?

Mr Jean-Claude Ameisen: It is a matter of the relations between genes and their environment. An essential dimension of the complexity of living organisms is due to the fact that cells and bodies can use their genes in very different manners, and that, with an identical genome, various potentialities will open up in different environments. All the cells in our body, save a few rare exceptions, possess throughout our existence exactly the same genes. Their capacity to become and remain stem cells, or to transform into one of the two hundred families of differentiated cells in our body, is due to the fact that each cell does not use its genes in the same manner. The partly haphazard interactions which each cell establishes with its neighbours lead to more or less reversible modifications of the accessibility of some of their genes, and therefore to different use procedures of these genes. In other terms, the external environment of the cell influences the elaboration of its internal environment, which itself influences in turn the possibilities a cell has with its external environment. This clearly shows the broad ambiguity of the widespread notion of a 'genetic programme'. Genes do not determine the future: they give cells a certain number of constraints and potentialities - a field of possibilities – and the actual outcome will depend on the specific history of the interactions of the cell with its environment.

It has been known for long that two genetically identical bee egg cells can, depending on the external environment in which they live, give birth to a worker, which will be sterile and live for two months, or to a queen, which will be fertile and live ten years. This notion of epigenetics is old. But its importance and universal character started to be really envisaged only fifteen years ago or so.

To what point are the differentiation phenomena resulting from modifications of gene accessibility inside cells reversible? In plants, unlike in animals, somatic stem cells can spontaneously retransform, in certain environments, into embryonic stem cells, thereby giving birth to an embryo without passing via germ cells or fertilisation. Is the same transformation possible, spontaneously or artificially, for animal and human cells? This question is currently the subject of work and controversy.

You probably know that, a few months ago, work published in the prestigious journal *Cell*, but not yet confirmed by other teams, suggested that bone marrow stem cells could spontaneously transform into ovocytes when they migrate to the ovary, without it being known if they are real ovocytes or cells resembling ovocytes but incapable of being fertilised and of giving birth to an embryo.

What are the frontiers of cell plasticity? What determines the accessibility or inaccessibility of certain genes? The activity of some cell enzymes, for instance, modifies DNA by a mechanism called methylation, or it modifies the structure of the proteins surrounding DNA by a mechanism called acetylation. It is not currently known what modifications in the composition or molecular structure of the cell body - the cytoplasm – allow a fertilised ovocyte to give birth to embryonic stem cells, whereas a skin cell, possessing the same genes, is incapable of this. The most spectacular illustration of this effect of the environment on genes has been provided by nucleus transfer: a skin cell nucleus transplanted into the cytoplasm of an ovocyte allows a use of genes that may lead to the formation of an embryo.

The importance of the environment is illustrated, at another level, by the 'niche' notion referred to by Ketty Schwarz. A blastocyst pluripotent embryonic stem cell will, in the environment of the blastocyst, spontaneously and progressively lose its pluripotency potentialities. If this cell is isolated and cultivated *in vitro* in an appropriate manner, it will keep them. If this cell is injected into another blastocyst, it will participate in the development of the embryo. But if it is injected in another environment, in another 'niche', for example under the skin of an adult immunodeficient mouse, it can lead to a form of tumour.

The same embryonic stem cell will therefore use its genes in different manners depending on the environment, the ecological niche in which it is found. The niche notion is crucial. It poses, as in many other biology fields, the question of the links between the inside and the outside, between genes and cells, and between cells and other cells... The stem cell participates in the formation and maintenance of its niche, and the niche participates in the formation and

maintenance of the stem cell. These retroactive causality effects, this apparently very modern idea of spiral causality, correspond in fact to what Pascal was referring to when he spoke of 'both causing and caused things'.

The notion of the environment can take several forms. A first level of environment, for genes, is made up of the DNA surrounding them. 98% of our DNA which is not genes, in other words which does not allow the production of proteins, has been dubbed 'junk' DNA. In the past three or four years, it has been discovered that a large part of this 'junk' DNA allows the production of small RNAs regulating the expression of some genes and which appear to play an important role in maintaining and transforming the potentialities of stem cells. Another hitherto unknown level of regulation has therefore appeared.

As for the medical implications of research on stem cells, they probably concern most – if not all – the fields of health and diseases. Their potential therapeutic applications cannot be foreseen today, but could far exceed the approaches of regenerative medicine in the strict sense of the term, based on the idea of injecting stem cells into patients to replace cells that have disappeared. For instance, neurodegenerative diseases might not be solely diseases related to the excessive death of neurons, but also renewal diseases, related to the death of neuronal stem cells and degradation of the niches essential for their survival. Would it be possible, one day, to reconstitute these niches and thereby allow the emergence and renewal of stem cells? In an apparently paradoxical manner, stem cell research will perhaps lead one day to discoveries allowing regenerative medicine approaches which will not require the use of embryonic stem cells to replace cells that have disappeared.

Another point that appears essential to me concerns cancers. Cancers are increasingly appearing as stem cell diseases. First, cancers emerge from normal body stem cells: the greater the survival and renewal potential of a population of normal stem cells, the greater the probability that the occurrence of certain genetic abnormalities in these cells will lead to a cancer. Second, very recent work suggests that most cancerous cells, like most normal body cells, have only a very low renewal capacity: the capacities of renewal, propagation and resistance to cancer treatments would be due to the presence of cancerous stem cells. An understanding of the mechanisms regulating the survival and renewal of normal and abnormal stem cells therefore has important implications in understanding and treating cancers, independently of any use of embryonic stem cells for therapeutic purposes.

Another emerging notion which appears important to me concerns the relations between stem cells, our ageing, and our longevity. Recent work shows for instance that one of the signs of ageing, the fact that hair becomes grey and white, is due to the disappearance of stem cells giving rise to melanocytes, the cells producing hair pigments. Other recent work on muscle stem cells shows that when an old mouse receives young mouse serum, its muscle stem cells re-express the

same genes as the muscle cells of a young mouse, and acquire, *in vitro* at least, the same renewal capacities. Here again, the external environment of stem cells, and the body's environment, appear to exercise a major influence on the functional capacities of these cells.

In this context, it is important to note that the 2004 bioethics Act bans any research on embryonic stem cells, unless this research is likely to lead to 'major therapeutic progress'. This restriction is likely to slow down the advances of research insofar as it is highly probable that research on embryonic stem cells which would not have therapeutic applications foreseeable today, could disrupt knowledge acquisition and lead, in the future, to completely unforeseen therapeutic progress. The risk, as already mentioned a short while ago with reference to the inappropriate use of the term 'therapeutic cloning', is focussing research on the sole applications immediately foreseeable. Wanting to orient research to medically useful applications is a necessity when knowledge already lends itself to this end; wanting to systematically substitute, for exploration of the unknown, research that would be useful on the face of it because it would already be known what was sought, could prove catastrophic in the long run for research. By way of example, it is sufficient to try and imagine what could have happened in biology and medicine, if, 50 years ago, we had restricted for ethical or economic reasons, research on genes to the sole gene therapy forecastable applications: we would have probably lost most of the knowledge acquired in the genetic revolution.

Mr Alain Claeys: I would like to interrupt you on this subject which I feel is pivotal and which we will return to in another roundtable. The fact that the law states that there is a ban, with a five year moratorium, unless research projects filed at the Biomedicine Agency have therapeutic purposes, has always amazed me. What does that mean in practice and operationally for a researcher? How can he arrive with his research project while explaining the therapeutic purpose?

Mr Jean-Claude Ameisen: This could restrict all projects to the sole research aimed at therapeutic applications which has shown its efficacy in the mouse, such as embryonic stem cell transfer to repair a diseased tissue. There is a high risk in wishing to limit *a priori* the scope of research in a new field to the development of applications which appear the most forecastable and most useful at a given moment. More generally, there is a risk in promoting in society the idea that so-called applied research, aimed at short term therapeutic developments, is intrinsically to be given priority. All the genuine dimension of research – exploration of the unknown, calling into question of knowledge, and the discovery of genuinely new knowledge – is likely to be forgotten and abandoned.

Mr Alain Claeys: With this in mind, if we prolong a bit the study of the text, what does 'scientific relevance' mean?

Mr Jean-Claude Ameisen: To my mind, it should be a matter of research of great originality and raising important questions concerning health or diseases.

But I wish to address the issue of the reason for this specific restriction of research which appears to be connected to a problem of an ethical nature. I return to what Anne Fagot-Largeault said. I feel that research on cells isolated from spare embryos which have been destroyed after no longer being required for fertility treatment purposes, and subject to parental agreement, does not pose any specific ethical problem. I feel it raises the same issues as research on cells extracted from a dead foetus or from the body of a dead person at any stage of life.

Mr Alain Claeys: That was what was laid down in the 1994 Act which has never been applied. Any research was banned, but after five years embryos had to be destroyed.

Mr Jean-Claude Ameisen: From the moment there is destruction, it would appear strange to consider that, after destruction, a protective status be given to the embryo which, concerning the conditions of research on cells isolated after death, would differ from the protective status given to a dead foetus or to the body of a dead person.

I now wish to address the issue of nuclear transfer. I feel that there are least two questions in this respect.

First, what relates to fertilisation, in other words what concerns the conception of a child, and what could be considered merely as an *in vitro* cell manipulation? Everything that would have the effect of dissociating the two notions would appear to me to simplify the ethical issue. Work on the mouse suggests that ovocytes can be derived *in* vitro from embryonic cells. If, from a human embryonic stem cell isolated from a destroyed embryo, an ovocyte were obtained, a skin cell nucleus were transferred into this ovocyte and a new embryonic stem cell were obtained, I feel that we would be moving further and further away from the notion of fertilisation and would be drawing increasingly closer to the notion of *in vitro* cell manipulation. On the other hand, the creation for research purposes, of embryos by *in vitro* fertilisation appears to me to pose ethical issues of another nature.

The second question concerns ovocyte donation. As long as the source of receiving cells for the transfer of nuclei is an ovocyte, it would be necessary to establish a very clear difference, as regards information for and protection of donors, between ovocyte donation which is presently made for reproductive purposes, and ovocyte donation for research purposes. To my mind, these are the two questions which, in the context of a possible revision of the present ban on nuclear transfer for research purposes, should be debated serenely and openly in keeping with the ethical implications. Can fertilisation and fertility treatment matters be clearly distinguished from what is increasingly appearing as an *in* vitro cell manipulation. The day when it would be possible to transform *in vitro* a bone marrow cell into an ovocyte or an embryonic cell, we would be faced in a radically different manner with the question of knowing where the notion of cell

differentiation begins and where it ends. The more we enter the field of cell manipulations, outside any reproductive project, the more the ethical problem changes to my mind.

Mr Alain Claeys: Thank you very much. We will return to ovocyte donation during the day. It must be addressed as I need to hear you on this subject and see, if nuclear transposition were authorised tomorrow in France, what framing would be necessary for ovocyte donation.

Roundtable no. 2:
Research challenges. France's position

Mr Alain Claeys: We are now going to move on to an intrinsically French debate by examining the challenges of stem cells for research and the position and state of the situation in France. It is useful that Parliament and citizens should have the most exact knowledge possible of what is being done in France, of the problems arising here, of the funds mobilised, and of the coordination (I will question the director of Inserm in this respect) between research organisms like Inserm and the Agence Nationale de la Recherche (ANR) as regards projects. We must have a precise picture of these issues.

The following are going to participate in this roundtable and I wish to thank them: Christian Bréchot, director general of Inserm; I have excused for the already stated reasons Mrs Carine Camby, who will not be present today; René Frydman, university professor and gynaecologist; Mrs Evelyne Jouvin-Marche, deputy scientific director of the living organisms department at CNRS; Daniel Louvard, director of the research section at Institut Curie, member of Académie des sciences, and who did me the honour of participating in our steering committee to prepare the study we are making; and lastly, Michel Van der Rest, director of the living organisms department at CNRS.

Mr Christian Bréchot, director general of Inserm: I am going to give the viewpoint of a research organism whose mission is biomedical and health research. We have a major challenge before us, as widely recalled before, with a need for knowledge, fundamental research (this point has been raised but I wish to insist) and a need for the transfer of knowledge to clinical applications.

Before advancing, I would first like to state the ongoing research programmes and the challenges for us in the years ahead. I will then address the issue, referring back to the discussion that has already taken place, on the adapted or unadapted aspect of the ongoing legislation with respect to the ambitions we are speaking about.

For several years now, Inserm has committed major sums in this field. Without detailing the figures, Inserm spends approximately 15 M€ in aggregate cost for the units working in this sector. A very important point with respect to the question you asked about the Agence Nationale de la Recherche, since 2001, Inserm has, with several partners, especially AFM, the Juvenile Diabetes Research Foundation, the association *Vaincre la mucoviscidose*, the Ministry of Research, etc., supported project programmes to the tune of 8 to 10 M€ in all, leading to

nearly twenty-four research projects being submitted. I am quoting this figure to point out that there is a real need to clarify the situation and real demand on the part of a large number of teams. Inserm has committed itself regarding adult stem cells in the same way as for embryonic stem cells.

Mr Alain Claeys: You say that you devote 15 M€ to research on adult and embryonic stem cells and, at the same time, you have project programmes for 10 M€ with a certain number of organisms. How is this second item going to fit in with the Agence Nationale de la Recherche?

Mr Christian Bréchot: That's what I'd like to know. It's not for the director of Inserm to foresee the decisions that will be taken at ANR. In Inserm's demand and in that of many other partners that were proposed last week to ANR's board of directors, specific action by the latter was clearly discussed with regard to regenerative medicine, in liaison with what the organisms are doing. Our desire, and that's one of our demands, and it's a major point for 2006, is that there should be an ANR project activity that is complementary to the activities undertaken in the organisms.

Before advancing, I wish to underscore a point that appears essential to me. A certain number of these incentive schemes are leading to European projects. It is essential that France should take part concretely, and not only in words, in European projects. For instance the GENOSTEM project, on mesenchymal adult stem cells, resulted from one of these incentive schemes for an 8.6 M€ programme including twenty-five teams at the European level. There are currently at least six European projects based on the use of stem cells.

Lastly, in the framework of the legislative framework to which we will refer back, Inserm has participated in the import of twenty-three embryonic stem cell (ES) lines, thereby emphasising the real need, because since the setting in place of the *ad hoc* committee a large number of lines have been imported. We consider very important the fundamental research needs and the therapeutic consequences, especially for pathologies like cancer, neurodegenerative diseases and also many other pathologies. I have insisted on the European aspect. We call for France to be integrated in the action to set up international cell banks. This is a fundamental point, which cannot be obtained unless there is a clarification of our possibilities in terms of the type of research.

Mr Alain Claeys: What clarification are you referring to?

Mr Christian Bréchot: I'll come round to answering, but it's what has already been said concerning the implementing decrees really adopted, the use procedures really defined.

Mr Alain Claeys: Today, with the legislation in place and the possible derogations, can the teams easily participate in European invitations to tender?

Mr Christian Bréchot: The answer is clearly negative. We are perpetually negotiating. We also feel it is essential to have reference research centres on stem cells. These are activities being undertaken at several sites in France. Lastly, the clinical application of potential pathways requires the development of clinical investigation centres, especially in biotherapy, with all the partners. A set of activities can be performed. At the national level, there is real opportunity to develop ambitious activities with the major partners represented by the other organisms, in partnership with ANR. These activities can be based once again on participation in these international banks.

I would like to mention a very important activity which clearly poses the question of the present situation in France. I am referring to what is called the International Stem Cell Forum. This forum, set in place on the initiative of the United Kingdom, consists in evolving towards embryonic stem cell banks, and also, and it's at least as important, defining its quality and use procedures, and avoiding the circulation internationally of lines whose qualities and use possibilities are sometimes somewhat questionable.

Inserm has found itself, like its other French partners, in a rather delicate situation insofar as we have been present since the beginning of these activities. Quite clearly, if we want to continue participating in these forums, and this returns to your question on European programmes, we rapidly need to show that we can indeed work on this type of cells.

I would also like to say that we also consider as very important and a responsibility of Inserm's, the management of a certain number of forums, discussions, and Euro-conferences on this topic. The HERMES committee plays an important role.

To finish, and this is essential from the viewpoint of our organism, does the present framework allow us to really meet these ambitions? The answer is only partially positive. Inserm calls for the implementing texts to be set in place as quickly as possible. The *ad hoc* committee has allowed a transitional period to be managed and it should be thanked for that. I mentioned the fact that twenty-three lines had been imported. Without getting involved in controversy, but simply to analyse the situation, I wish to recall that Inserm greatly pushed for this *ad hoc* committee to be set in place. At the time, some people objected to us that it was not worthwhile because the implementing decrees were going to be adopted instantaneously. I feel it was better to set up this *ad hoc* committee. It will be necessary to closely follow the proposals made on the use of stem cells generated by nuclear transfer, by taking into account all the elements of the debate, but it is not my role to intervene in the subject.

To finish, whatever the provisions, I feel that what was said a while ago is essential: this research should not be linked solely to the notion of major therapeutic progress. For a research organism like Inserm, that appears entirely essential to us.

Mr Alain Claeys: Mr Director, I would like to ask you a question which we are often asked. Out of the funds devoted to stem cells by Inserm, what is the share of research programmes on adult and embryonic stem cells?

Mr Christian Bréchot: The immense majority of research programmes are on adult stem cells, for reasons to do with the law quite simply.

Mr Alain Claeys: I'll give the floor to René Frydman.

Mr René Frydman, university professor, gynaecologist-obstetrician: I'll give the viewpoint of a basic doctor, and not that of a director of an organism like my neighbour, and I'll refer to the symposia that are being held internationally, at which the French position is indeed very bad. I recently attended a symposium bringing together five thousand persons in the United States on the developments on the work performed using embryonic stem cells, fields in which we are merely spectators, and in difficulty. A global vision in this field is required today, as already emphasised by Ketty Schwarz.

Concerning *in vitro* fertilisation centres, a few figures can be recalled: in China there are two hundred of them, there are seventy in Pakistan and they are to be found nearly everywhere worldwide. I'm not saying they are all well managed from the viewpoint of bioethics legislation, since most countries do not have any. But they provide opportunities to make progress in knowledge, which, unfortunately, we are not entitled to do despite the knowledge we have acquired, given our regulations.

I wish to insist on a first point concerning spare embryos, to say again that the French situation is rather paradoxical.

When at last we obtained a precise picture concerning frozen embryos in France, everyone was frightened by their high number resulting from twenty years of storage. The freezing of embryos dates back in France to 1985-1986 and teams waited until the 1994 Act before knowing what had to be done. In 1994, we had the authorisation to destroy embryos conceived until that date, but nothing was said of the embryos that came under the following five-year legislature which in fact lasted ten years. As there was uncertainty regarding embryos before 1994 and after that date, most teams preferred to do nothing while waiting for the information that should have appeared in 1999, but which arrived in 2004, with decrees that have still not appeared.

Finally, most embryos have still been kept, explaining the large stock. Depending on the ideology you support, these figures can be put forward while underscoring a rather frightening aspect with respect to a situation that should be explained. Also, I believe, but other researchers are probably in a better position than me to speak of this, that finally, to establish lines, far fewer embryos are required than is believed, from the moment they are embryos capable of developing. There is therefore a balance between this very high number of embryos stored in freezers in French laboratories and the 20 to 25% share of them theoretically destined for research, according to the parents' will. These embryos are therefore not used, but their number is surely largely, if not over, suffcient to establish lines.

Mr Alain Claeys: What figure can be placed on their number?

Mr René Frydman: The last figure stood at approximately seventy thousand frozen embryos, half of which are destined for fertility treatment, the other half being divided between donation for someone else, pure and simple destruction, and destruction with research, since this difference was introduced very recently. Today, with the environment, mediatisation, the debates that are taking place, and even the Swiss referendum, to mention merely that one, many couples, more than previously, who no longer have fertility treatment plans or who do not accept donation to someone else, respond that destruction can be combined with the possibility of research during this destruction.

Mr Alain Claeys: You are the second person to mention the Swiss referendum. As a researcher and a scientist, but also as a citizen, do you feel that it is a decent procedure for such a subject?

Mr René Frydman: Today in France we are theoretically in a situation of authorisation according to the law, but of non-application in reality given the non-publication of the decrees. We already experienced this for preimplantation diagnosis. Rather than a referendum which will postpone matters even more, we want the decrees to be published so that they can be applied, at least partly: even if it means returning back to points raised, perhaps, on other amendments.

Among other teams, one of the specific characteristics we can have that are precisely related to preimplantation genetic diagnosis, concerns the cognitive plane. I agree in this respect with my colleagues on the need to employ broader words like scientific research, one of whose purposes will be to propose therapies.

A cognitive aim is extremely important, it is the first goal of the scientific approach. You must first understand to be able to use. In the field of reproduction, since the other researchers will be speaking of more general topics, there are three very interesting subjects, on the formation of placenta trophoblastic tissue, which is a major source of knowledge and which could be addressed by these techniques. There is also the creation of germ cells, which has been mentioned in animals, and

the creation of ovocytes or of spermatozoons, whose relevance and efficacy will have to be verified. Apart from the fact that germ cells could fit into a therapeutic programme, they could also be a source of ovocytes, as was mentioned, which would short-circuit the donation issue. These still remain unanswered questions but are worth reflection.

Mention can also be made of embryos with genetic, chromosomic or gene disorders. Owing to the existence of preimplantation genetic diagnosis, some laboratories have a major cognitive source. In effect there is no waiting to destroy embryos since they are destroyed every day. When embryos are affected, we destroy them, we don't keep them, since they are of no use. One of the issues would be to know if, already today, they cannot be considered as operative waste. As such, highly interesting research could be practiced on them at least. I pointed out that several statements had been read on this research at the October congress.

We feel things are evolving, and today's meeting is proof of that. Basically, hope exists for the implementation of these decrees and also for support from research organisms. Owing to the delay in the legislation, there is still a lack of clarity between all the participants who could support the creation of units. These must be world-class and not scattered units as the convergence of a certain number of talents is necessary to be able to advance and to be transparent. We would be tempted to say that with the impending decrees and the immense possibility that can be seen, efforts must be made to focus the means.

One of the essential points that must be examined concerns the creation of visiting posts and *postes fléchés*[83], whatever the organisms or the means. We are currently seeing, with a certain sadness, French researchers devoted to this research field emigrate, precisely because they do not have the possibility of working on stem cells, especially embryonic ones. Very recently, a lady French researcher was hired at Harvard, and we cannot hire her here.

A kind of emergency plan, like the many such plans in the health field, needs to be very rapidly and effectively introduced. This does not have the same importance here as the major plans of the cancer type. However, more than material means, and more than circulating ideas, we are going to lack, to begin with and in well defined centres, a handful of men and women who need to be attracted or re-attracted, because they have left. A training school must therefore be created for something that looks like being very promising.

Mr Alain Claeys: Thank you very much. Before continuing, I would like a clarification to be made. Mrs Camby is absent, but I want us to be clear about the legislation and the difficulties you are encountering today. Article 37 of the Act of 6 August 2004 laid down measures pending publication of the decrees. It is stated:

[83] Posts allowing the recruiter to define the profile and research topic of candidates or new recruits.

'Transitionally, and till the date when the decrees will be published at the *Conseil d'Etat*, the minister for health and the minister for research can, by an order, authorise jointly the import, for research purposes, of embryonic stem cells, and also study and research protocols on embryonic stem cells imported in compliance with the following conditions.' Regarding their import and the study protocol agreement, this is possible today. Is the Biomedicine Agency operational on this point today?

Mrs Evelyne Jouvin-Marche, deputy scientific director of the living organisms department at CNRS: A meeting of the board of directors is taking place tomorrow and this point will be raised.

Mr Alain Claeys: In practice, when a team wishes to import or submit a research protocol, what is the procedure?

Mrs Marie-Odile Ott, manager of the 'research' sector and of international programmes at the Biomedicine Agency: The Biomedicine Agency is still not in a position to issue these authorisations. It too is waiting for the publication of the decree on embryo research. For the time being the transitional *ad hoc* committee is still run by the ministry of research and is sitting this very morning.

Mr Alain Claeys: Since the Act was promulgated how many research projects or import authorisation applications have been submitted?

Mrs Marie-Odile Ott: Approximately thirteen teams have submitted import authorisation, storage and research project application files. There must be seventeen projects, some researchers having submitted four projects, others two and still others one.

Mr Alain Claeys: Have these projects been validated?

Mrs Marie-Odile Ott: Some are still being examined.

Mr Alain Claeys: For what reasons, if this *ad hoc* committee exists, cannot teams participate in European invitations to tender?

Mr René Frydman: We encountered a difficulty, which we have partly solved, from the European legislation viewpoint, at the time when the invitations to tender for the Sixth FPRD were being set in place. The difficulty was related to the transitional nature of the *ad hoc* committee. We had to work in an in-depth manner with the Commission for the participation of French teams to be accepted. It was simply a request for clarification on the part of the Commission.

Mr Philippe Ménasché: Mrs Ott has answered. We must first pay homage to the *ad hoc* committee which has worked a great deal. It is also necessary to underscore the gap which Ketty Schwarz alluded to, between scientific and administrative time. A precise example for instance is that it took ten months to

obtain the import authorisation. This length of time, in a field that is evolving as quickly, inevitably represents a loss of time and opportunity. This clearly shows the French inclination for administrative and regulatory complexification, whereas we are in a field where action should be taken quickly, which is not the case.

Mr Alain Claeys: I admit we are a country where administrative complexity is high, but you'll have to explain to me why it took more than four years between the 1994 Act and the implementing decree for preimplantation diagnosis to become reality in France. When we were asked, with Claude Huriet, to assess the 1994 Act, at end 1997, the implementing decrees, inter alia that one, had not been published. This poses the problem of the legislator's role.

Mrs Evlyne Jouvin-Marche: I am also research director at Inserm where I direct a team in an Inserm/CEA unit at the Grenoble scientific pole. I will speak more at the level of biology and I may well repeat the remarks made by Christian Bréchot.

At this level, support for fundamental research is essential. We need to increase knowledge and better understand the biological processes referred to by Jean-Claude Ameisen. Progress and the hope of using stem cells for therapies will result from the efforts made in fundamental research. More concretely, the department's efforts represent support for teams. There are thirty of so teams working on stem cells and cell differentiation supported per living organism department. They are mainly mixed teams made up of CNRS, Inserm and even university professor researchers.

This year we opened up a 'stem cells' post in section 30 for the recruitment of a 'CRA' researcher so that good researchers, who are often trained abroad, can return to France and develop the topics that we want. At European level, we also have support for our teams. To answer all the questions on the use of adult or embryonic stem cells, a person in the department can be consulted for all requests. That person responds effectively to all research projects on embryonic and adult cells whenever a CNRS researcher wants to be part of the project.

As regards fundamental research, I will limit myself to summarising the brilliant speed by Jean-Claude Ameisen, by stating the points that absolutely must be crossed and those where French teams have a very good level to do so.

The goal is to identify new stem cells in other tissues than those presently known. This will require having markers to be able to differentiate them, as this is a stumbling block of research. In effect we do not always have the means to identify stem cells. Another point which has been broadly discussed concerns knowledge of the molecular aspects of the maintenance of stem cells, in other words study of tissue plasticities, how stem cells proliferate, how they are maintained in the organism and how their self-renewal can be ensured.

I will not refer back to a largely addressed point concerning the study of their differentiation potential, but I will insist on their migration potential.

While it is now known that there are stem cells in tissues, these stem cells must be able to migrate to the places where they can be functional. That is a goal which has not yet been reached. These questions are raised not only by French teams but also internationally. The most important point, as already emphasised, is that it is necessary to examine their evolution to be sure that stem cells can be functional, in other words ensure the functions for which they are going to be reeducated. The karyotypes must also be checked, the fact that they will not have an abnormal division of chromosomes, that they are not going to develop tumorigenic characters and enter a malignant pathway. Above all they must be accepted by the organism so as not to develop immune reactions. These are broad programmes in which all the teams currently supported by CNRS are engaged. If such progress is achieved, we will then be able to meet the hopes currently nurtured by patients' associations and use stem cells in treatment. I think other persons will make remarks in this respect.

Mr Alain Claeys: Concerning the CNRS, we will return to this point later, but what sums are committed?

Mrs Evelyne Jouvin-Marche: The estimation is difficult, as the amounts are not enormous and the majority of our teams generally operate thanks to national or European invitations to tender. We will obviously support the ANR in the development of stem cell projects, as we ourselves are having difficulties in maintaining the research effort of our teams. However, the latter are indeed publishing. If you read the international press, you will observe that many French teams, Inserm, CNRS, Institut Pasteur, often have work quoted in the best journals. We are not showing ourselves unworthy, but we need more money.

Mr Alain Claeys: We are going to continue with Mr Michel Van der Rest.

Mr Michel Van der Rest: I would simply like to make a remark regarding the number of teams mentioned by Evelyne Jouvin-Marche. Approximately 10% of the research potential of the living organisms department is involved in this subject. Everything depends where the limit is placed and if in this calculation we go back to the cell differentiation notion. Obviously today nearly all those working on cell differentiation in the animal reign and in man, are concerned by this issue.

The CNRS fully concurs with the remarks made previously, which I will not repeat, especially as regards the importance of the studies on stem cells and all the upstream research, which is CNRS' basic task. In the present arrangements, there are obstacles to remain competitive worldwide. In particular, one of the elements which is very important in research is the notion of time, which has two aspects. First, as stated a while ago, it is difficult to remain competitive when you

are delayed nearly a year to obtain the essential material. Second, projects take place over relatively long periods. It is difficult, if you have time limits (I am thinking of the five year derogation of 2004) to make scientific projects in accordance with such a timeframe, especially with regard to our partners. It is therefore difficult to position yourself for projects that often last five or ten years, when it is not known if in three years you can continue. There's a real problem here.

Mr Alain Claeys: Can you put a figure to the amount spent by your management on this specific programme?

Mr Michel Van der Rest: It must be around 7 M€ for all the laboratories working on the topic as I have defined it.

Mr Alain Claeys: I suppose you have the same approach as the director of Inserm concerning the ANR/CNRS relation.

Mr Michel Van der Rest: Exactly.

I would like to add that CNRS must envisage everything concerning not only the ethical aspect, but, upstream, the notion of representation of living organisms. For today's meeting, I tried to obtain figures from my colleague in charge of the 'men and societies' department, but I couldn't get them in time to give you an idea of this type of debate. However, I have myself been involved in debate groups which were coordinated with teams, especially on the representation of sciences, and in particular living organisms.

In legislative work, it is lastly very important to know what is meant by the words used. When the word embryo is used, what exactly is meant? In this sense a great deal of work still remains to be taken further. I have brought the matter before the 'men and societies' department, and I know that work is taking place. I have been involved myself in work performed in Lyon on some aspects. A working group has been created on stem cells, coordinated by Professor Jacques Samarut. But it's still very imperfect and embryonic, and an effort still remains to be accomplished in this respect. This could contribute to the debate in an important manner by shedding light on our perceptions as a society in the face of this type of issue.

Those are the few elements I wanted to add. I wish to emphasise that I fully agree with what has been said, especially by Mr Bréchot.

Mr Alain Claeys: I'll return to the remarks made because I would like to obtain clarifications. First, regarding the difficulties we would have in participating in the creation of a stem cell bank internationally. What are the obstacles today for France to participate with a team of researchers? Supposing that the implementing

decrees are published, in what respects does our legislation prohibit you from participating in the creation of this bank?

Mr Christian Bréchot: There are two elements to the answer.

A rational and objective element, and another regarding the perception of the country's effort and its commitment. What I wanted to say concerns above all the second point. Presently, in a forum like the one I alluded to, we can barely claim to play a leading role, or in any case that of a high-level participant, in a situation where the legislation has not been clarified. But nothing is impossible, and we have proved that since we have managed to continue participating in this effort. For instance, Inserm is going to organise the next session of this forum at the beginning of January. I wanted to say that it is difficult to play a role commensurate with the competence of our teams, as emphasised for CNRS, in a situation that is still today transitional.

The second point is that it is now more difficult, for more rational reasons, to participate effectively, in a situation in which we are not capable of creating new lines on our own. And it is difficult to arrive in a forum, where the aim is to characterise new lines and demonstrate their utility, whereas we don't have the right to generate them. We therefore have difficulties of perception and rational difficulties.

Mr Jacques Hatzfeld, director of research at CNRS: René Frydman said earlier that we are ready to use operative wastes (I think that's the term he used), from PGDs. Lines could be made immediately, but the law bans that. We could gain a lot of time. With the Biomedicine Agency, it will still take months to have authorisations. It took me nine months, with eight return trips and a dialogue of the deaf, yet with a committee that was trying to do its best. I think we are still going to lose a lot of time, and I'd like the legislator to give a response. What prevents us from using these cells, which no longer have the state of an embryo and with which lines can be made immediately?

We can even do better than foreign countries. Usually these lines are made on cocultures with animal cells. We can make them not only without a coculture, but with only human molecules. It would be a world first. If we wait another few months, it is certain that this will not be done in France. It's really a question of months. We must have the authorisation on 1 January.

Mr Hervé Chneiweiss: Perhaps our competent guests could inform us why it is absolutely essential to create new lines. We could raise the question of using other materials. Jacques Hatzfeld has just alluded to this, but a clarification would be useful. It is also necessary to specify that time, which Mr Van der Rest spoke to us about, also represents know-how and competence which are not acquired or which others acquire instead of us.

Mr Alain Claeys: All the issues related to Article 25 of the 2004 Act must be addressed. There are three constraints. The first relates to authorisation limited to five years. The second constraint is that research programmes with a therapeutic purpose must be presented. Even myself, a non-scientist, I don't understand very well what that means. The third is that the research programme will be accepted, as everything can be blocked if there are no other possible techniques to reach the same research. The text states the following: 'Research can be authorised on the embryo and embryonic cells when it is likely to allow major therapeutic progress and provided it cannot be pursued by an alternative method of comparable efficacy.' As a parliamentarian, and that explained my vote at a given moment, I have still not understood what that meant. Or perhaps I have understood too well, because with this type of wording, everything can be blocked.

Mr Daniel Louvard, research director at CNRS, research section director at Institut Curie, member of Académie des sciences, member of the steering committee: I don't think I can enlighten you on this point. Many things have been said that are very interesting, and I'm not going to repeat them, but I will refer back to some of them regarding a few affirmations or comments. I am going to try and give a complementary, and even contradictory, viewpoint, to say first of all that, of course, as a researcher, I concur with what has been said. The therapeutic aspects are put forward that generate the ethical debate we know about, but there is above all a need to support fundamental research on a better understanding of stem cells. In a sense, the ethical debate is legitimate but it has made the debate slide terribly in favour of the issue posed by embryonic stem cells.

I was pleased to hear Christian Bréchot mention that Inserm devotes the majority of its means to the adult stem cells programme. I feel it is very important today to try and answer scientifically the questions posed by embryonic and adult stem cells. I sometime hear some circles of experts oppose the two types. That debate does not interest me but poses fundamental scientific questions.

When the two are opposed, adult stem cells are not very numerous. What do we really known about that? For some tissues, that's incorrect. Adult stem cells have a limited number divisions. That's incorrect. We know nothing at all about that. Adult stem cells have a limited potentiality. Admittedly, per se, embryonic stem cells are totipotent, whereas adult somatic cells are probably pluripotent. But what is their plutipotentiality, how are they to be compared with the embryonic cells from which they derive and which allowed these adult tissues to be formed? Nothing is known of that at all. It is said that embryonic cells can lead to tumours. That's highly likely and has been proved experimentally. It's also possible with adult stem cells, but nothing is known of that. Two hundred and thirty-five families of cells have been identified today in metazoa, mammals like us. The number of adult stem cells characterised today can be counted with the fingers of one hand, perhaps two. True, two hundred and thirty-five families derive from sub-families and common stem cells, but all these questions concern basic biology and need to

be posed. When we saw 'known', that means that these adult stem cells have been characterised, and that markers have been identified allowing them to be sorted and identified in terms of their origin and properties.

Major work therefore remains to be done and I hope that the scientific community will not remain divided in the framework of this ethical debate. Comparative work should be undertaken between an embryonic stem cell and an adult stem cell, to arrive at questions concerning the level of plasticity of an adult stem cell. The major questions have been referred to, and I hail Jean-Claude Ameisen's remarks on the major issues of biology. The mitosis of a stem cell is not the same as that of a germ cell entering a differentiation pathway. It is an asymmetrical mitosis. This is a fundamental question in biology, but unfortunately too few teams are working on these molecular mechanisms of asymmetrical division. There is admittedly the work on drosophila and simple organisms, but we would like to know how this division and this asymmetrical mitosis take place in other tissues, especially the stem cells of our tissues. Epigenetics is a vast issue that has become fashionable again, and it is known today that not everything can be explained by the genome sequence and that other solutions will have to be found.

The small RNAs referred to by Jean-Claude Ameisen show the vanity of a certain generation of having believed that everything had been explained, whereas everything undoubtedly remained to be explained. Stem cells, by the organisation of the specific chromatin that they have adopted given the inaccessibility of their genes that is essential to protect their genome, remain a vast field to be explored.

As I manage a cancer research centre, and as the capacities and possibilities of the use of stem cells, whether embryonic or adult, have been referred to for repair purposes, I believe that a major question is also posed with respect to therapeutic approach issues in various tissues.

A few words on cancer. The concept of cancerous stem cells is reappearing today. At the end of the 19th century, this hypothesis already existed. During the 1930s, it was also spoken of. Another period followed, during which Darwinist concepts, which I do not challenge, will have largely promoted the principle of selection and selection pressure in tumours, forgetting that tumours are not only heterogeneous from the genomic viewpoint, in the face of the genetic alterations during the tumoral progression, but also heterogeneous from the cellular viewpoint. Some matters have been known since the 1950s or 1960s: for example, why is the injection of a million tumoral cells into an immunodeficient mouse necessary to lead to a tumour? The issue was sidestepped by answering that, to clone cells, a certain number are needed for it to work. Nevertheless, with one cell, if it has the possibility of developing in an appropriate environment, we are capable of producing clones and therefore large cell populations. Today the concept is reemerging that it is probable that what ensures the perenniality and growth of a tumour is a minority subpopulation of cells which have something in common

without it being very well known what. They are called tumoral stem cells, but are they really stem cells or are they derived from progenitor cells, themselves derived from stem cells? The answer is not completely clear.

Nevertheless, today we have some certainties. That's the case for example with brain or breast tumours as they are groups where it has been managed to better characterise, better isolate, and purify almost to homogeneity subpopulations of cells populating these tumours. It has indeed been observed that it is not then a million cells bearing tumoral stem cell markers that are needed to created a tumour in a mouse, but the injection of several tens of cells, or less than ten, having this property.

This has fundamental consequences. As for therapy, and I am turning here to Marianne Minkowski representing here the chair of INCA, I sincerely hope that INCA will make up for this shortcoming in the cancer plan with respect to the research priority on stem cells for cancer therapeutic purposes. This is something I stated when I was vice-chair of the committee that established the cancer plan and this was not heard until now, either in the texts or in action taken.

Why, in effect, do we not manage today to eradicate tumours? Why do tumours grow after apparently effective treatment? Perhaps quite simply because we got the wrong target, because cells that proliferate and differentiate are killed, and because the 1 to 2% of tumoral stem cells populating a tumour are not killed effectively. This appears fundamental to me because it is possible, as with normal stem cells, and as with embryonic stem cells, that the pharmacology to which these cells are sensitive may be different. Because of the molecular mechanisms during division, because of the cell signalling, a major subject of biology, it is possible that, because these stem cells are different, they may have different properties that we do not know. I'd like to say once more: let's make way for science and let's make way for research.

Mr Alain Claeys: Thank you, Mr Louvard. We are not going to open the debate on adult stem cells and embryonic stem cells but I really do think your remarks were useful.

Mrs Marina Cavazzana-Calvo, university professor, head of the biotherapy department service at Hôpital Necker-Enfants malades, coordinator of the biotherapy integrated clinicial investigation centre at CHU Necker-Enfants malades: I wish to thank Mr Louvard for his remarks on the scientific bases, which we need to know, but I cannot let you support certain affirmations which are not quite correct...

Mr Alain Claeys: He can say all he wants to and so can you...

Mrs Marina Cavazzana-Calvo: Yes, but colleagues working slightly less on stem cells should have clear ideas. There is no plasticity of stem cells today. You cannot be left to say that.

Mr Daniel Louvard: What do you know about that? We cannot answer this question because we haven't been able to study it. Quote me the number of stem cells that have been isolated.

Mrs Marina Cavazzana-Calvo: The debate has been conducted by the main journals we use, *Nature, Science*, with persons who have worked worldwide on adult stem cells and on embryonic cells. It can be said today, without too much fear of being wrong, that there is no plasticity. By plasticity is meant the possibility for an adult stem cell to transform into another embryonic source. For hematopoietic stem cells and bone marrow, this has been proved.

Mr Daniel Louvard: I think we are calling two different things plasticity.

Mrs Marina Cavazzana-Calvo: That's possible, but we must work within the constraints of legislation according to which you must ask for authorisation to work on cells with well defined characteristics. These cells must be spoken of, they are to be defined, and it is necessary to work parallelly, without purposeless conflicts, both on adult stem cells and on embryonic stem cells. There are no conflicts on this point at present in the scientific community. I also wish to hail the work performed at Inserm on this question, even in a period of legal vacuum, as it has managed to bring together researchers so that we can avail of the knowledge both in the field of adult stem cells and also in that of embryonic stem cells.

Mr Jacques Hatzfeld: All the work that has been performed on MAPCs – these so-called adult stem cells that have the properties of embryonic stem cells –, are presently totally irreproducible. This work was performed with inbred mice lines and does not work at all with others, and even less with the wild mouse. There is a lot to be said on all the work on mice. In man, it is out of the question. People like Ron McKay, internationally renowned scientists, have told Catherine Verfaillie that when they would be given these cells, they could work on this question. For the moment, they can't do anything. Catherine has returned to Belgium and she no longer manages the Minnesota Institute where work was performed on MAPCs. It is necessary to stop saying things that are incorrect, saying that with cord blood a beating heart can be made, etc.

I wish to add that I am participating in the European GENOSTEM project on adult stem cells. Thanks to embryonic stem cells I am enabling this project to find the markers of adult stem cells, not by starting from downstream, as we did previously, but by starting from upstream, by deriving from embryonic stem cells, mesenchymal stem cells, which allows me to have a quantity of them, and study all the most primitive markers. If work is not performed on embryonic stem cells,

adult stem cells will never be understood. I will speak later of functional genomics which I feel is something very important.

Mr Daniel Louvard: I am surprised because while there is no controversy, the remarks you have just made prove there is one. Embryonic stem cells are totipotent, as I recalled, and adult stem cells are pluripotent

Mr Jacques Hatzfeld: We don't have the same definitions.

Mrs Laure Coulombel, research director at Inserm: There is an international consensus that the totipotent stem cell is the zygote with the first cell divisions, and that the pluripotent stem cells are the ES cell lines derived from the internal mass of the blastocyst. The consensus at present, but it can be challenged, is that, in adults, multipotent stem cells are spoken of. This is an international consensus.

Mr Daniel Louvard: We agree. What I wanted to say is that in an adult tissue, we indeed know there are stem cells that derive from the various embryonic germ layers, and that it has not been possible to explore exactly, outside the tissue in which they exist, or the organ in which they exist, if they recapitulate or not all of the properties of the cells of the germ layer from which they derive. Excuse me for the slip of the tongue, it's not pluripotent but multipotent that I should have said.

Mr Alain Claeys: Including at the Assembly, we can talk to one another. I'll give the floor to René Frydman, then we will suspend the debate for five minutes before commencing the third roundtable.

Mr René Frydman: I have the feeling that people working or who would like to work on embryonic cells in France are not at all opposed, on the contrary, to the fact that work is taking place on adult cells. There is the feeling that there is a certain group of persons who wish to work only on adult cells, without seeing the benefit that could be found. The scientific position has always been 'let the best win', let the studies be performed. If elements can be drawn from either of the groups we will see than, but we cannot view matters in an *a priori* manner The *a priori* position is very negative for scientific research.

Mr Alain Claeys: The parliamentarian I am still has present in mind the report commissioned by the ministry of the time, the Gros report, which pointed out that the two types of research had to be performed concomitantly.

Mrs Laure Coulombel: The term of alternative has been raised, and it is something that must be explained, if only for Hervé Chneiweiss's question. It is a matter of the alternative between the lines presently available and new ones, and of the adult stem cells *versus* embryonic stem cells complementarity. I think the term alternative is very important.

It is a matter of the problem posed by old embryonic cell lines. The problem of imported lines is that they were derived long ago, have undergone many passages, have not been the subject of any culture standardisation, and are grown in independent laboratories, and therefore in a wide variety of conditions. The second thing is that these lines were derived initially in conditions with animal type molecules and that it is excluded making use of them in a therapy. For all these reasons, it is essential to have access to new lines derived in standardised conditions and above all in conditions that will be applicable 'clinically', or in animal preclinical models. That was to answer the question raised.

Another question concerns the complementarity between embryonic stem cells and adult stem cells. I will rapidly address later on the issue of adult stem cells as there are enormous limitations on their therapeutic use. We are presently reconsidering previously artifactual and poorly interpreted matters. It is essential not to oppose them, for two reasons. The molecular mechanisms governing the fact that these embryonic cells can be amplified in an unlimited manner are probably quite close in molecular terms to the mechanisms used by adult stem cells, including by the mechanisms which mean that a stem cell is going to decide at a given moment to enter a differentiation pathway *versus* another. Also, embryonic stem cells give us accessibility in terms of their number which is absolutely impossible to obtain with adult stem cells. Any study, whether biochemical or molecular, needs accessibility in number, which is currently impossible with adult stem cells, as they self-renew very little, and above all, must be removed from a tissue and purified – that's very difficult at present, except for hematopoietic stem cells.

Roundtable no. 3:
What uses for stem cells: the health challenge

Mr Alains Claeys: The debate with which our second roundtable finished is perhaps going to be prolonged in this third roundtable. We are going to address more specifically the therapeutic aspect, but will also return back to questions referred to since the beginning of the morning.

I wish to present the speakers: Mrs Marina Cavazzana-Calvo, university professor, head of the biotherapy department service at Hôpital Necker-Enfants malades, coordinator of the biotherapy integrated clinicial investigation centre at CHU Necker-Enfants malades; Mrs Laure Coulombel, research director at Inserm; Mr Jacques Hatzfeld, research director at CNRS; Mr André Hovine, chair of France Parkinson; Mr Philippe Ménasché, thoracic and cardiovascular surgery professor at Université Paris V, heart surgeon at Hôpital Georges-Pompidou, unit director at Inserm ; Mrs Marianne Minkowski, deputy director of the cancer biology department at Institut national du cancer; Mr Roger Picard, spokesman of the Alliance maladies rares; and Mr Bernard Zalc, research director at Inserm.

Mrs Marina Cavazzana-Calvo: I wish to thank you in two respects. First, because you have given us the possibility of discussing matters between health authorities, research institutes, Inserm's director, directors of scientific institutes and representatives of biotechnology companies. Second, I have the impression that, because of the socially very awkward current events, the public authorities have forgotten to continue this debate, that is important for us and first-ranking, on stem cells and their implementing decrees.

For therapeutic use, we can move forward very fast or very slow. If attention could be focussed on the use of therapies and embryonic stem cells, very fast progress could be made but there are no on-going trials today using these cells. The debate can be broadened and the parallelism existing with adult stem cells can be introduced.

Mr Alain Claeys: Regarding therapeutic applications, can you specify what the exact situation is today in France and worldwide?

Mrs Marina Cavazzana-Calvo: The trials are focussing on the therapeutic use of adult type stem cells. I would like to give a definition so that we know what we are talking about. They are cells derived from differentiated tissues. There is no notion of an adult individual, but of differentiated tissue. If cells derived from amniotic liquid are used, and if the placenta 'annexes' are considered as

differentiated tissues, they can be defined as adult type stem cells derived from a completely differentiated tissue.

Mrs Ketty Schwarz: If I may interrupt, this morning I mentioned the authorisation given barely three weeks ago for a phase 1 trial using foetal neuronal stem cells.

Mrs Marina Cavazzana-Calvo: They are foetal and not embryonic cells.

Mrs Ketty Schwarz: Exactly, but that has a slightly moderating effect.

Mrs Marina Cavazzana-Calvo: It's for that reason that I wanted to divide this category of stem cells into three main chapters, even if from the development viewpoint, the division could be made otherwise.

There are stem cells derived from differentiated tissues, in which can be integrated amniotic cells, foetal type cells, and embryonic stem cells. To my knowledge there are no ongoing therapeutic trials today using embryonic stem cells. On the other hand, there are many trials using adult type stem cells, yet as I stated mainly concerning stem cells of the hematopoietic type. It is therefore a matter of multipotent stem cells located in the bone marrow, capable today of giving rise to mature cells of the peripheral centre and used therapeutically for that purpose. It is known today how to vaguely and roughly isolate them, as the phenotypic criteria are not sufficient to define them, and they are used routinely to make bone marrow grafts for instance.

I wish to recall that, worldwide, forty-five thousand people are benefiting from this type of treatment. It is known how to isolate these cells to the best of our capabilities, even if the criteria available to us are uncertain and do not necessarily define a homogeneous but heterogeneous cell in terms of cell division capacity, differentiation and self-renewal. It is known how to manipulate them and how to multiply them, but it is not known how to get them to return to the stem state (hematopoietic stem cells). It is known how to manipulate them from an *ex vivo* genetic viewpoint, in other words, introduce in an integrative or non integrative manner drug genes to diminish, attenuate or, in the best of cases, cure the symptoms of a disease. These are the most widely conducted therapeutic trials worldwide.

Pioneering work must be hailed which has been carried out in France on the use of stem cells other than hematopoietic adult stem cells, by Philippe Ménasché's team, with the use of adult muscle cells to treat heart insufficiency. Marc Peschanski's team is also a pioneering team by its use of foetal neuronal cells aimed at attenuating the syndromes of the central nervous system disease, Huntington's disease.

We remain pioneers in France for the clinical use of genetically manipulated stem cells. Even if a few toxic effects have been encountered, promising trials have been performed in severe combined immunodeficiencies, with the help of Inserm. The latter plays a fundamental role in therapeutic innovation and in the support it gives to the sole institution that has continued to support stem cells, despite the vacuum in which we found ourselves. Thanks to the massive intervention of this institution, two other therapeutic trials on genetically modified cells and on hematopoietic stem cells are going to take place in 2006. One will concern X-linked leukodystrophy, the first degenerative disease in children, and the other will be a far more restricted trial in the field of hemoglobinopathy (major thalassemia and drepanocytosis). That's the context in which we are today, as regards stem cell therapeutic use trials.

As for embryonic stem cells, I am not going to repeat all that has already been very clearly said this morning. We would like a few points to be solved, and we would appreciate if the authorities would give definitions especially on the status of the embryo, protection of ovocyte donations, and the methods that can be used for derivations of embryonic stem cells. For it is known today that they could be derived at an earlier stage, without affecting the embryo's integrity, as our geneticist and gynaecologist colleagues do with PGDs, preimplantation genetic diagnoses.

I would like to stress the constraints we must face today in France, even if there are star teams that are very well situated in international competition. These constraints are legislative. It's up to you, National Assembly ladies and gentlemen, to manage to remove them. They are constraints in the creation and characterisation of ES cells. Hervé Chneiweiss allowed us to point out, with his very precise question, that we are forced to create new human embryonic stem cell lines and characterise them if we want to continue competing internationally. In the opposite case, we will not have our place alongside the other international partners in forums devoted to stem cells.

There are also constraints related to researchers. We must give ourselves the means, as mentioned by Mr Frydman, to call back researchers who have left for abroad and ensure them good work conditions in France where they could create teams and train new researchers. I wish to recall that we also have material constraints. In a developed country, like France, I am surprised that we have not managed to create in the past decade a research institute worthy of this name on stem cells. With the existing means, we could very quickly get researchers to work together on adult and embryonic stem cells. They could progress much faster with other work conditions than the present ones.

Mr Alain Claeys: Does this cooperation exist?

Mrs Marina Cavazzana-Calvo: Fortunately, yes. Once again, Inserm's intervention has been unique in the national territory as it has grouped researchers working on embryonic and adult stem cells, muscle cells, intestinal cells, pancreatic cells and hematopoietic cells. We have meetings together, but that's not sufficient. Inserm has committed the means it could, but we need much more. An institute worthy of this name is needed, like the ones in Belgium, the United Kingdom, Sweden and the United States. I do not understand that, in a country like France, the material means cannot be found for this research in a slightly faster way than at present.

Mr Alain Claeys: Can you review for us Robert Lanza's work on the possibility, using an eight cell embryo, of taking a cell without that jeopardising the integrity of the embryo? Where does his research stand?

Mrs Marina Cavazzana-Calvo: I don't have an exact idea of where the research by this group stands. Others here perhaps know about it better than me. This work opens up a possibility of producing embryonic stem cells from a precocious stage, without affecting the integrity of the embryo, which could bring down certain ethical obstacles on this question.

Mr Daniel Aberdam: Experiments have indeed been attempted, some of which succeeded, but few have been published. Cells of the internal mass can be isolated even before the formation of the blastocyst, without really destroying the embryo. This is still at a very experimental stage. Other experiments are also very interesting regarding the fusion of ES cells with nuclei to increase the cytoplasm. Stem cells indeed have a nucleus/cytoplasm ratio that is in favour of the nucleus. To try and replace ovocytes, which poses a problem because in particular of the need for donations, serious ongoing work shows that embryonic stem cells can be used as an alternative to ovocytes, like other alternatives.

Mr Jacques Hatzfeld: In the case of PGDs, it is even more simple, because it is a matter of operative waste and lines can be made with it.

Mr Daniel Aberdam: I would like to react against the term tumour with respect to embryonic stem cells. This term has been used regularly for six or seven years and is scaring the public and the media with a notion that is incorrect. To demonstrate that an embryonic stem cell is pluripotent, one of the experiments that is performed is to inject these cells subcutaneously into the immunodeficient mouse. Teratocarcinomas are then obtained, which are benign tumours, but which can be obtained only with immunodeficient mice, in other words when the immune system cannot rid itself of them. It is clearly established that when embryonic stem cells are differentiated, these tumours are no longer obtained. The term tumour should therefore cease to be put forward when speaking of embryonic stem cells. If it is managed to purify differentiated cells from embryonic stem cells, all the published, non published or commented experiments show that there are no

tumours. I do not know if Philippe Ménasché has any hindsight with respect to the cells he injected, but I don't think he obtained any tumours.

Mr Philippe Ménasché: I entirely agree with the remarks by Daniel Aberdam. Embryonic stem cells preoriented to become heart cells have been injected both in small animals like rats, and in sheep or monkeys. The slightest tumour has never been seen from the moment that cells are correctly predifferentiated. I think that the scaremongering should cease.

Mr Daniel Aberdam: I would like the journalists present to take note so that, once and forever, we don't have to regularly return to this point.

Mr Hervé Chneiweiss: Before giving the floor to Laure Coulombel, as she will no doubt return to this point, I would like Marina Cavazzana-Calvo's extreme prudence to be underscored with respect to the clinical trials being performed and the link between fundamental research and clinical trials should also be pointed out for everything related to stem cells, whether embryonic or adult.

A parallelism should be drawn between this and another paradox which is presently emerging in international medical literature. In effect, under the pretext that they have a CD 34 antigen, that they are characterised like progenitors, or even hematopoietic stem cells that have long been used for bone marrow grafts, some hematopoietic cells are used in man in all kinds of clinical trials (acute cerebral vascular accidents, acute heart infarct) which makes us shudder in view of our ethical rules. I would like a parallelism to be drawn with this paradox.

René Frydman referred to globalisation. Today there is an increasing number of certain human clinical trials with certain adult stem cells. At the same time, there is an extreme prudence and trials that are being extremely well performed on stem cells are being slowed down, under the pretext that are they are embryonic.

Mrs Laure Coulombel: I would like to return to the precise definitions of what are called adult stem cells, which are what I know best.

In the first place, to date we have not been able to purify these stem cells to homogeneity. To my knowledge, there is no possibility in man to have a tube with 100% stem cells, which is totally different with embryonic stem cells. Complementarity begins there. Also, it is necessary to agree on a definition, and to date everyone almost agrees. For a stem cell, a function is necessary and therefore an experimental system to demonstrate its existence. That's the crux of the problem. I insist on the fact that it is very important in research to develop models, especially *in vivo*, allowing the existence of this function to be demonstrated, whether for embryonic stem cells or for adult stem cells.

The definition of a stem cell is as follows: it is a cell which is going to rebuild *in vivo* and in the long term the diversity of a tissue. I think everyone roughly agrees on this definition, with diversity by the production of differentiated cells. It is important to have an experimental system to highlight this. There are no other means at present. In itself it is a research pathway which must not be forgotten.

Returning to the therapeutic aspect, I would also like to insist, as far as adult stem cells are concerned, on the fact that there is a very great diversity between these stem cells. Distinctions must be made within specialised tissue stem cells insofar as, inside this very group, there is a diversity, with tissues that renew permanently, because cells die (the skin, intestines hematopoietic system). These tissues are therefore already used therapeutically, since it is known that these stem cells are functional *in vivo*. Also, there is another category of tissues which spontaneously do not renew, but a subdivision can still be made between those that are capable of responding to a lesion and repairing it by the activation of stem cells, and other tissues in which, even if stem cells are present, they are not capable of repairing, for the moment. This is an important distinction, because therapeutic applications and research in this respect are then not the same.

The question in therapy is therefore how a tissue can try to be repaired which does not do so effectively in a spontaneous manner.

From this viewpoint, three strategies can be formulated. Molecules can be found which will stimulate the stem cells present in the tissue. This is a research pathway which does not concern the cell but the molecule that will stimulate, which is very important. Here again, embryonic stem cells can perhaps serve for us as a screen for this type of molecules. There is a permanent to and fro motion between these two types of tissues. We can also work on salamanders, with molecules which may also be present in man. There is therefore work on the definition of cells and on the definition of molecules that can stimulate them. Perhaps cells can be stimulated that are in the tissue but which are not doing their work, or else we can try and purify these cells, amplify them in the laboratory and reinject them in the tissue. The cells in a tissue can also be taken, and we can do what is done in a marrow graft, in other words an immediate transplantation.

I am now going to refer to what has been described over the past two years, in other words the fact that in the bone marrow there could be many stem cells capable of repairing all tissues. We must be very clear at present. Medullar stem cells is meaningless. In the bone marrow, there are hematopoietic stem cells which Marina Cavazzana-Calvo spoke about, there are stem cells of which the term stem is perhaps totally inappropriate and which are cells which adhere when they are placed in culture, and which I would willingly call multipotent stromal cells, which are going to make bone, fat, and cartilage. There is another category of cells, which are progenitors, which will possibly make vessels, endothelium, and which are not

perhaps strictly speaking stem cells. Last, there is an enormous question mark concerning multi-tissue stem cells, isolated by two or three teams but whose work is not reproducible for the moment, which are cells which would be capable, *in vitro*, in experimental conditions (I insist, because we do not at all know their significance *in vivo*, if they exist), of rebuilding several tissues.

The first question is to know, first of all, what the facts are concerning these *in vivo* cells: do they exist and what do they do? There is no answer. Second, this is not reproducible and we are perhaps therefore faced with an event that occurred in a cell that proliferated during multiple divisions, or even sometimes for several months and which is a culture artefact, even if the experimental observation is correct. We must therefore be very clear. At present, the source of therapeutic cells from bone marrow concerns hematological diseases and the use of hematopoietic stem cells, possibly to help in the reconstruction of bone damage in the case of bone cells. For the moment there are no other applications for endothelial progenitors, except possibly in the case of a vascular repair.

This notion I am now reaching of transdifferentiation has absolutely not been proven at present. It tended to show that a hematopoietic stem cell was capable of making something else than hematopoietic cells. There is no experimental demonstration valid at present. With a single cell in the mouse, nothing else is produced but hematopoietic stem cells.

On the other hand, some derivatives of hematopoietic stem cells can fuse in the diseased tissue with a diseased cell, then granting it the capacity of becoming 'normal' again. In this case, we are faced with a case of somatic nuclear reprogramming. These two things must be well differentiated. From a therapeutic viewpoint, to my knowledge at present there is no application whatever of this fusion, but this can possibly be envisaged in the future, and we can think about it. At present there is no use of bone marrow from an effective therapeutic viewpoint for muscular, nervous or other pathologies. In our laboratories, we can get certain markers of other tissues to be expressed by hematopoietic stem cells but we are perhaps then faced again by a culture artefact. From a therapeutic viewpoint, bone marrow is fairly well known today but progress can still be made.

I wish to insist on the notion of accessibility which I have mentioned.

For adult stem cells, there is a major problem of accessibility. The tissue must first be obtained and they must be sought there and it must be possible to purify them, which is often very difficult because they often die very fast when removed from their context. In any case we will have worthless things. From this viewpoint, human embryonic stem cells are an absolutely considerable contribution in deciphering the mechanisms.

As this is true for embryonic stem cells, it can be envisaged that adult stem cells that are grown in laboratories may do things in culture boxes that they don't do in our organism. What can the therapeutic application of this be? It is necessary to be prudent to re-use these cells as a substitutive replacement for a tissue, but they can be used, when amplified in the laboratory, in a molecular screening application. I am returning to research on molecules capable of modifying or modulating the behaviour of stem cells. This certainly must not be forgotten.

Mr Alain Claeys: Thank you very much, Mr Louvard, on the last remark regarding stem cells...

Mr Daniel Louvard: I entirely agree.

Mr Alain Claeys: Jacques Hatzfeld, you were the first team to obtain authorisation, on derogation by a previous minister, to import stem cells. On what date was that?

Mr Jacques Hatzfeld: That was in 2002. We are therefore entering the fourth year of work on embryonic stem cells.

Mr Alain Claeys: Administratively, how did it take place?

Mr Jacques Hatzfeld: It was at the time when Mrs Ketty Schwartz was research director and Mr Schwarzenberg, minister. I was asked to drawn up a quite complete dossier, which I was asked to improve three times. It was totally wrong to claim that this dossier had been drawn up hastily, just before the 2002 presidential elections. Extremely comprehensive work was undertaken by the ministerial directorate. A committee of wise men reviewed all the dossier, and was not at all pleased when, on the following day, a senator said that they were being made fun of, that an authorisation had been given 'any old way'. It was unacceptable.

I regret I was the only one to have been able to work on stem cells.

Mr Alain Claeys: If I may, regarding this period, I affirmed my position to the minister. Hervé Chneiweiss should remember this. I was not against these derogations, but I wanted Parliament to previously, at least at first reading, authorise research on spare embryos. I indeed find it paradoxical (this is the situation in Germany) that research is not authorised in a country where the import of stem cells is accepted. That raised an ethical problem for me and still poses a problem to my mind.

Mr Jacques Hatzfeld: Later on, there was the *ad* hoc committee. We asked for new lines, and worked for three years with two lines from Australia. Recently, we were authorised to import three other lines. I would like great caution to be exercised so that the Biomedicine Agency does not get entangled in a system that is admittedly correct administratively but unmanageable. A tremendous amount of time is going to be lost to obtain authorisations which could be obtained very

rapidly in cases where the laboratory or the institute where that takes place is known. We must stop spending months in going back and forth with experts whom we do not know. We have the impression of being considered as people likely to be dishonest. We are really considered as researchers who have the intention to cheat the law. This attitude is unacceptable.

Mr Alain Claeys: The director of the Biomedicine Agency is not present, but if Mrs Ott wishes to intervene, then she must not hesitate. What are the present waiting times?

Mr Jacques Hatzfeld: I have spoken to several persons from the Biomedicine Agency, including Mrs Ott. I was told that to make new lines, it is first necessary for that to pass in the French Official Gazette, that at least four months will be necessary, after we have received information on the way we must make our presentation, as we still do not know the form in which we must present our dossier. Then it is a minimum four months. If there is the slightest problem, an additional four months is to be waited. Also, we will not be informed if there is an obstacle until after the four months, whereas the expert could ask us directly for the necessary clarifications before then in the event of difficulties.

I wish to recall the issue of PGDs, where lines could be made straightaway. We urgently need a rapid answer in this field as we could make up for the time we are losing now.

Mrs Marie-Odile Ott: I will leave the floor afterwards to Mr Picard for his experience of the *ad hoc* committee; he has put up with all the initial problems of these procedures.

Concerning the Biomedicine Agency, we have provided for authorisation periods which would take a maximum of four months. These are periods during which a dossier can be transmitted. From time 0 to the end of the period, there is a maximum of four months. The process can be faster if dossiers do not raise any problem. The dossiers must be submitted to scientific experts who submit their report to an orientation council, then the director general takes the decision. Between the moment dossiers are examined, the sending and the obtaining of a suitable expert's report, when people must be brought together at the same time, there are nevertheless constraints that are difficult to reduce. There will be an admissibility list, but should items be lacking or should complementary information be required, time will be suspended. Measures are also planned in the decree for which we are all awaiting.

Mr René Frydman: I would like to say a few words on the time period.

We indeed know that it can be shortened, or even extended, or become a period of indeterminate length. I would like to insist on the experience gained in preimplantation diagnosis. I must say very solemnly that I have just learnt that the

barely appointed person in charge of the Biomedicine Agency has just apparently been replaced. If she has been replaced by the person whose name is quoted, we are really in the most difficult situation. In effect, she is known for her reactionary positions concerning scientific progress, since we have already had experience with her on the same topics. Everything can be imagined, while remaining within the framework of the law. All procedures can be extended to the extreme and not lead to anything. With a certain number of researchers we have expressed our concern. At a time when an agency is being set in place, we wish to have information on the reasons for this replacement and on confirmation of the proposed line, which is manifestly ideological and regarding which we cannot but be highly concerned. This will no doubt lead in scientific circles to a very clear statement, as far as I am concerned in any case and for some of us, as this is counter-productive.

Mr Alain Claeys: Thank you. Daniel Aberdam

Mr Daniel Aberdam: I would like to add to Jacques Hatzfeld's remarks a personal testimony, since I am employed by one of the laboratories that have obtained the *ad hoc* committee's authorisation to import and work on human embryonic stem cells. We had to wait for months, but I would like to mention two things. Three authorisations were necessary: an import authorisation, another to work on human embryonic cells, and another for storage. I don't need to make any comments but I think there is an exaggeration.

Mr Alain Claeys: This concerns the regulatory level. It's not the law which dictates this.

Mr Daniel Aberdam: I don't believe so. For years, we have been storing lines from everywhere. But the storage conditions for these lines mean they are suspected of being very dangerous. They could very well come out of the laboratory to become 'monsters', or the opposite... Once again, perhaps we are not trusted and it is believed that lines can be given and that it is necessary for them to be locked away with padlocks, that's the truth of the matter. In Nice, we don't yet have a gene cell therapy centre, which is at the end of the building stage, and I therefore obtained the authorisation to import lines, and the authorisation to work on them but not that to store them in Nice. I therefore store them in Montpellier, so you can imagine how that facilitates work.

Mr Alain Claeys: On this specific case, can you tell me in a note about all these huge difficulties for your research. It will be useful for me.

Mr Daniel Aberdam: To finish, I have the feeling there is a permanent suspicion of scientists. We are assessed, as Inserm laboratories, by Inserm. Why is there a need to re-assess these research projects, which are accepted by Inserm's assessment bodies? Why add procedures to procedures, making a pile of them? It's a question of confidence: I consider the legislator must begin by trusting researchers. Let's stop adding agencies to agencies. This is my personal testimony.

Mr Alain Claeys: Mr Picard, you wanted to speak on this subject.

Mr Roger Picard, spokesman of the Alliance maladies rares: I was also a member of the *ad hoc* Committee that met this morning to deal with the latest applications to import stem cells.

I understand these criticisms. I am an association representative, I am therefore not a scientist. I have participated in many studies related to the thirty-five or thirty-six dossiers which we received and I was co-rapporteur with a scientist for twenty or so dossiers. Basically, it is not a problem of suspicion but of constraints, of the shackles imposed on us by the legislator, or of the interpretation of the law by the implementing decrees. We were asked to decide on import, storage and research applications. We were not asked for our opinion as to whether it was legitimate or not. This was the framework imposed on us in this committee, and we have tried to fulfill our mission as best as possible.

Mr Alain Claeys: You consider it is a cumbersome procedure.

Mr Roger Picard: To answer Mr Hatzfeld, as soon as there was a request for complementary information, it was transmitted immediately.

Mr Daniel Aberdam: That was never the case.

Mr Roger Picard: Then there is the committee meeting, and an administrative involvement which was no longer a responsibility of the Committee members, as all the administration is involved in the work. I have protested against the fact that the length of time extends to four months, which appears completely abnormal to me.

Mr Alain Claeys: Thank you for your testimony, Mr Picard. I'll give the floor again to Jacques Hatzfeld, but it was useful to take stock of the subject.

Mr Jacques Hatzfeld: The subject of our roundtable concerns the use of stem cells and health challenges. Cell therapy is spoken of a great deal, but very little is said of functional genomics. I would like to explain what this is, for journalists who do not know.

When adult stem cells are worked with, and when the stemness genes are sought, in other words the genes controlling stem cells, no consensus is reached between the various laboratories, even if, sometimes, the consensus concerns one gene. When embryonic stem cells are taken, and when several lines are compared (a recent study has been made on seven lines), four thousand two hundred genes were found for the self-renewal of these cells. These genes were ESTs, in other words genes whose function is still not known. There was a consensus between laboratories, between lines.

For self-renewal, it is known that there are four thousand two hundred genes, and I think there are as many for differentiation. For nearly a third of the human genome the function is therefore not known, yet it is understood that it controls development, and that these genes are expressed on embryonic stem cells. If we have embryonic stem cell lines, we are going to be able to know the function of these genes. Anglosaxon biotechnology companies understood straight away. Before having exact knowledge of the function of these genes, they understood that it was necessary to make the proteins and antibodies corresponding to these proteins. Corresponding to all these genes, we can now find all these proteins which will be tomorrow's drugs. In effect, we know the sequence of these genes, and it is known that they correspond to receptors, to growth factors, to hormones, and to transcription factors, which can interreact in human development. It is absolutely essential to stop opposing human ES cells and adult stem cells. I am continuing to work a lot and far much faster on adult stem cells since I have been working on ES cells.

I have given you the example where we are seeking to characterise mesenchymal stem cells through the European GENOSTEM project, but we don't start from adult stem cells, which are very rare, one for 10^7 cells, and which have already lost their stem cells property when placed in culture. We cannot therefore work with them. Mesenchymal cell lines obtained from embryonic stem cell lines allow us to have many stem cells and they can be characterised. We are in the process of finding mesenchymal stem cell markers, which we didn't find before, and we are in a position to find a lot more.

Functional genomics, for its part, is the study of the function of all these genes of which nothing was known to date and which represent a third of the human genome. When we have all these genes controlling cell development and cell therapy, adult stem cells will be thought of in a totally different manner. We will have factors and hormones allowing us to make much faster progress. In some cases we can undertake cell therapy studies straightaway, which was mentioned earlier. It is indeed very important, but I think we will progress much faster when we have done all this functional genomics work.

I would like to mention an example of absurd situations. At the CNRS, at the Institute of Natural Substances Chemistry, substances would enable us for example to work on mucoviscidosis, but at present we can work only on patients. This considerably complicates the study of these new molecules whereas we could presently perform these studies using cells from PGDs. We would prefer to immediately have very many lines corresponding to various diseases. That would allow us to have embryonic stem cell lines that could be developed to all tissues and we could see what happens for a given mucoviscidosis gene at each level of differentiation and how molecules are likely to intervene on these cells.

We must change our outlook, especially at the CNRS. I am pleased at the arrival of a new director of the living organisms department, previously called the life sciences department. I hope that Mr Van der Rest will help us along these lines. In effect, at the moment, and I am repeating what has been said, many researchers are retiring (in my team, it's the case of two research directors) and we have nobody to replace them. These are teams that are going to collapse. We need embryologists and we close Nogent, the Embryology Institute. Are all these persons retiring going to be replaced? The present age pyramid means that in the next six to eight years, half of CNRS researchers are going to retire. I think that the minimum would be to immediately replace those working on stem cells by a *poste fléché* in this field.

Mr Michel Van der Rest: I take note of the message but the aim is certainly not to see the number of researchers decline in the years ahead, quite the contrary. The stem cells field is obviously a field where we must pursue research very much upstream, as said several times this morning.

Mr Jacques Hatzfeld: I would like a rapid answer on the possibility of using PGDs. They are no longer embryos, but operative waste, and we could work straightaway. Or else it is desired to block the situation and prevent us from working but that's a political or partisan political act.

Mr Alain Claeys: Within the framework of the law today, authorisation is not possible. This supposes a legislative amendment. I don't think this can be decided by a regulatory measure.

Mr René Frydman: Within the framework of the law, we will see what concerns embryo research in the decree. Jacques Hatzfeld mentions, quite rightly, that they are not spare embryos waiting for a solution in accordance with the will of the parents, but embryos which are destroyed instantly. This destruction is imposed owing to disease, and even represents the validity of preimplantation diagnosis. The texts must follow and people must take the necessary decisions.

Mr Alain Claeys: Concretely, for the proposal that is made, it is not a decree that is needed.

Mr René Frydman: Despite what has been learnt concerning the appointment this morning, the proposal that is made consists in knowing, if we are led to make headway, what the orientation will be and whether we will be supported or not. We have already experienced this for a certain number of societal phenomena.

Mrs Ketty Schwarz: Insofar as we don't have the authorisation to derive new lines today without the decrees, what Jacques Hatzfeld proposes cannot be implemented. Yet couldn't this be implemented all the same?

Mr René Frydman: Depending on the interpretations, we can remain ten years on this or move forward very fast.

Mr Roger Picard: I would like to mention that among the stem cell research authorisartions given by the *ad hoc* Committee, two imported lines are to be found, derived from PGDs revealing a genetic disease. From the moment that research on imported lines is authorised, I cannot see why this could not be done? It would be totally illogical.

Mr Alain Claeys: At the same time as the work I am doing, I am going to bring this matter before the ministers, especially with regard to the decrees.

Mr Hervé Chneiweiss: It is necessary to be very clear, like René Frydman has just been. Tangible facts are at hand and the social and legislative interpretation made of it is different. The cell lines we are speaking of are cells which can lead only to other cells. There happens to be a reference to their origin. But in the interpretation made in 2002, and which led to Jacques Hatzfeld being authorised to import, it was considered that it was a matter of human cell lines, and that the legislation and regulations applying to these cells were the regulations and legislation of human cell lines, subject to different import rules.

Similarly, in the case of embryos for which a particularly serious genetic disease has been diagnosed, we are faced with cells which cannot in any case give rise to an implantation or future life. As stated by several speakers, in the medical sense, we are faced (cruel words must be used) with an operative waste. We are therefore in the same situation as when faced with a tumour to be removed, or a gall bladder with stones to be removed. Admittedly, we are faced with a human tissue but which no longer has a vital function or the possibility of vital development. As facts are facts, the law or the regulation will have to give an interpretation of them, which in any case will be an interpretation of facts which remain facts.

Mr Alain Claeys: I have thoroughly understood what you've said.

I think we will reach a balance, which may be deemed bad or good, it's not for me to say here. I have taken my responsibilities in Parliament, other colleagues have made another choice. But we must all comply with the law. There are two problems with respect to this legislation. First, the implementing decrees which are lagging behind. In this case, the legislator has a supervisory right as decrees must follow and it unacceptable that this should take so much time. The other subject dealt with by this report is how to get this legislation to evolve. The day today is providing us with a whole series of elements that will be useful for the legislator. The latter has desired that the updating of the law should not be rigid, every five years, but that there should be swifter updatings. I believe in the facts and in education to get matters to advance.

Monsieur Hovine, you are chair of the Association France Parkinson. Perhaps you can explain to us how your patients' association takes part in this debate, in these arrangements, how you are consulted, and see what topics interest you more specifically today and what you think of this legislation.

Mr André Hovine, chair of France Parkinson: The Association France Parkinson is a patients' association in the field of neurodegenerative diseases. While speaking about the specific case of Parkinson's disease, the problems of Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease, other neurodegenerative diseases, loom in the background. This represents a crucial challenge in public health terms and in terms of public funds, bearing in mind the number of persons concerned by these diseases. In effect, more than a million persons today are directly affected by these disorders, without mentioning their family circle for whom it is also a daily tragedy to experience these incurable and evolutive diseases.

If I take the case of Parkinson's disease, there is no cure for the disease and today, save a few short-term hopes, there aren't even any neuronal protection means, which would allow the evolution of the disease to be stopped. There are drug therapies, in the case of Parkinson's deep brain surgery, with stimulation of the black body. Progress has been made but there's no definitive cure or suspension of evolution. Everything related to new approaches to a therapy for the disease gives rise to immense expectations on the part of sufferers. Immense expectations, which must not be let down regarding several aspects. First, premature and inconsiderate hopes must not be given. This is very important, and I am turning more specifically to the press and journalists because scoops which interest journalists can lead to errors of interpretation, false hopes, and the backlash is generally harsh. We say they're still talking of that but finally nothing has happened and nothing has been found. From the sufferers' viewpoint, it is important to have information that is objective and moderate, so as not to give undue hope.

It was with great interest that I heard Mrs Schwarz speak of a trial which is to begin in the United States on Batten's disease. Regarding news like that, I believe that sufficiently prospective and objective, but also moderate, information should be tried to be developed, which can then be relayed by the various information organs constituted primarily by the internal information reviews of the various patients' associations.

Beyond the strict viewpoint of sufferers, I would also like to speak as an association and not of my experience as chair of an association in the cell therapy field, since we have not been associated in the commissions or ongoing work. I was however associated in another field, in close cooperation with Hervé Chneiweiss, regarding another important subject a few years ago, and which is still important, concerning the creation of tissue banks. The association is involved in the creation

of brain tissue banks or banks of tissues related to the evolution of neurodegenerative diseases and we have often run into problems of comprehension and interpretation of legislative and regulatory texts. On the basis of this experience, I believe transposal is easy into the field of interest to us today. I wish to attract the attention of the legislator and of those responsible for the appearance of regulatory texts to the need to have clear texts with as little ambiguity as possible and developing a maximum of coherence, which unfortunately is not always the case.

Mr Alain Claeys: I entirely agree with you, but we can do better.

Mr André Hovine: That pleases me a great deal because, for want of implementing decrees, we are seeking to interpret the legislator's thoughts and we do not have direct access to what would allow us to fully understand them. When we try to lobby an eminent body like the Conseil d'État, the latter prudently takes refuge in the fact that a referral, to interpret the legislator, requires very complex procedures. I wish to take advantage of the opportunity given to me here. I'll start once more from another field which does not directly concern today's discussion, but which, on account of the various speeches, I clearly feel underlies many problems encountered by scientists. It is very important for the implementing decrees to be coherent, devoid of ambiguity and clear, so that operational concerns can be integrated at the time of debate. Not only ethical concerns, which are essential, but also operational ones, in other words how it can work in the field. We have a perfect illustration with the 2004 text of the bioethics Act, in which the collection of a tissue is subject to the existence of a research project. Being a financier originally, I have always learnt that, in banks, you begin by collecting money before making loans. Unfortunately, in the scientific field, if the Act is to be believed, you must begin by having a house to build before starting to collect funds. It's rather paradoxical.

Mr Alain Claeys: You are asked to cure before being authorised to have a research project...

Mr Jacques Hatzfeld: We absolutely need these tissues. You don't need projects. It's precisely when we will have functional genomics, which will give us all these proteins, that we will be able to see what genes are involved thanks to the cuts we can make with your tissues. Automatically, your banks are important

Mr André Hovine: That's indeed why we did not step back because of the difficulty and we created them, but as persons in charge in this tissue bank in one respect or another, we sometimes feel in an unsound position with respect to the law. This is not a comfortable position, especially if you read the last chapters on penal provisions...

By the way, I would like to inform you that the concerns you have today as regards the public feeling on the issue will be taken up at European level in

Brussels in a month's time at a conference supported in particular by the European Federation of Neurological Societies. This two day conference will deal precisely with the public's position regarding cell therapy and all the scientific work we have heard about this morning.

Mr Alain Claeys: Thank you, Mr Hovine.

I'll now give the floor to Mr Philippe Ménasché so that he can give a practical explanation of what is being done today.

Mr Philippe Ménasché: I am going to make three practical remarks, since we are in the therapeutic field.

The first thing that must be said is that, in the cell therapy clinical trials field, leaving aside marrow grafts, which have long existed, experience to date is very limited. I am repeating what Mr Hovine has just said. Whether in the brain, pancreas, or heart field, few patients have today benefited from cell therapy and, to be honest, we are incapable today of saying whether the efficacy of cell therapy is going to be limited, very great or nil. Nobody can know, even if a certain number of signs are encouraging. If this were not the case, we would not continue. That's completely normal moreover, since the first trials performed are phase 1 trials testing feasibility and tolerance, and not really efficacy. We are now going to enter the phase of clinical trials designed to demonstrate efficacy, which remains to be proved. We must therefore remain prudent, especially with regard to patients, and not give rise to unfounded hopes.

The second point is that in the state of ignorance in which we find ourselves (I am repeating what has already been said), there is no sense in opposing adult cells and embryonic cells. The two pathways must be explored parallelly and we'll then see. I am not going to enter into medical details, but it is not impossible that the two types of cells may finally find their place in different pathologies. To give an example, it is known today that if we want to replace a heart cell, it is unlikely, in the present state of knowledge, that this can be achieved with adult cells. Embryonic cells are apparently capable of this. In contrast, if the aim is simply to get cells that can secrete insulin, i.e. Langerhans islets, adult cells taken from subjects in an irreversible coma can do the job fine.

To prolong what has been said on the absence of *a priori* positions, the opposition that sometimes exists between adult cells and embryonic cells is meaningless clinically. Both must be explored, which means that the embryonic cells pathway must not be cut off. We therefore return to all what has been said till now.

Lastly, I would like to say a few words on a last point. We always tend to moan about everything that happens to us, but France has real assets in this field, which are completely underexploited. It has assets owing to the scientific quality of

its teams and because, more than is believed, we have the capacity in this country to tear down silos and bring together around the same table hospital practitioners cum university professors, researchers, and biotech specialists, getting them to work together. There are many examples. We realise that this is not always the case in foreign countries, including the United States where structures are often more rigid, perhaps because of the size of the country. We also have 'financial' assets. Admittedly, there is never enough money, but major efforts have nevertheless been made by CNRS. The Assistance Publique has created a seed fund for biotherapies. Experience proves that even if it this takes time, when the project is good, it is funded. I don't think this is the 'blocking' element.

In addition, France has a quite specific asset, which is no doubt insufficiently recognised: the experience of a certain number of teams, like those of Marina Cavazzana-Calvo or Marc Peschanski, in particular. This is what is called translational research. It is very important to conduct fundamental research but our work is to treat patients and not rats. At a given moment, you have to pass from procedures developed in the laboratory to procedures applicable to man. It's a real job. We are very much helped by AFSSAPS (French Health Products Safety Agency), which is doing a remarkable job. Jean-Thomas Vilquin, who has participated with us in the cell therapy adventure knows that this translational work is something important and a certain number of French teams have acquired real expertise in this field. Interestingly, we are often questioned abroad about these translational aspects.

In view of these assets, frustration is all the greater in seeing this capital little valorised and underexploited owing to the legislative difficulties mentioned. Authorising imports while banning the creation of lines is extraordinarily hypocritical to say the least, without mentioning the difficulties of a purely regulatory type. I know that the *ad hoc* Committee has worked very well, but I want to repeat what has been said. In a field where matters are moving fast, the waiting periods imposed are perfectly unacceptable. It is not a responsibility of those on the *ad hoc* Committee. If there were just one practical thing we ask and even beg of you, it's to ensure that procedures can be lightened and that administrative time becomes more in line with scientific time.

I will finish by stating that we have reasons today to be very worried from this viewpoint and more today than in the recent past, because we are firstly waiting for the application decrees to appear. Once these decrees appear at last, they will have to be 'set to music', which is the work of the Biomedicine Agency. From this viewpoint, the shameful decapitation of this agency, owing to Carine Camby's departure, is catastrophic. Indeed everyone has recognised her merits and involvement, but it's more than just a relational problem. It's not merely an official being moved elsewhere. This means a six month, or probably a year long, hiatus, regardless of political lines for I do not know the person succeeding her. An agency and a performing team with good achievements are set in place and then everyone

is changed. At the time when the decrees are going to appear, the shameful departure of Carine Camby is a 'bad blow' to stem cell research. You'll excuse me for my surgical brutality but, as you know, surgeons are outspoken and I feel I am also giving the opinion of Marc Peschanski, René Frydman and others. Beyond a relational problem, it really means stem cell research being brought to a standstill, and we didn't need that.

Mr Alain Claeys: Thank you for the clarity of your remarks.

Mr Philippe Ménasché: I would like to add to what René Frydman said, that we hope to have a few explanations and a few clarifications on what the policy will be in the months ahead.

Mr Alain Claeys: You'll be able to speak again during the two other roundtables this afternoon. Mrs Marianne Minkowski, I think it's important to listen to your remarks. You are deputy director of the biology department at Institut national du cancer.

Mrs Marianne Minkowski, deputy director of the biology department at Institut national du cancer (INC): That's why I am going to speak of biology rather than therapy, even if the subject addressed is mainly linked to therapy. For the INC, it is also a matter of biology tweaked towards therapies. A great majority of the remarks I wanted to make have already been mentioned by several speakers before me on research on the biology of stem cells that are normal, to make the distinction with tumoral stem cells, which helps to obtain essential knowledge, and especially knowledge necessary to understand the cancerogenesis process. The second aspect is the identification and characterisation of tumoral stem cells whose existence is now apparently recognised and which should allow new approaches in treating cancer. But it's not for straightaway, for before that they must be really characterised.

It is currently accepted and demonstrated that, in some cases, tumours feature various cell populations that have different self-renewal and proliferation powers or capacities. Among these tumoral cells, there is a sub-population that has self-renewal properties and the capacity to initiate and sustain tumoral growth. These are what are known today as tumoral stem cells or tumour stem cells, and major work is getting under way on them. I have just returned from a congress on translational research in cancer, where it is clear that the 'stem cell' aspect of tumours now appears as something which can explain a certain number of difficulties, especially in standard therapies.

It is essential that the study of these stem cells be supported, in other words their molecular and functional phenotypic characterisation, in comparison with so-called normal stem cells. There's no use doing only half the work. These studies must be performed by comparing the differences and similarities of these two types of stem cells. This will lead to a better understanding of the tumoral initiation

process and, above all, it will help identify new markers and new targets for improved therapeutic efficacy. In effect, standard chemotherapies deal with cells that are dividing and stem cells are, per se, quiescent. Standard chemotherapies are ineffective on tumoral stem cells. Understanding the latter and their operation and reason for existence will no doubt help improve therapies for the various types of cancer.

I had thought about speaking to you about gene and cell therapy, but I don't think we will see this in the cancer field with stem cells at present. Daniel Louvard will correct me if I am wrong. There are a certain number of gene and cell therapy trials on cancer. A phase 3 trial is going to begin in the United States on a p53-expressing adenovirus developed in China, which should soon be licensed. There are also a certain number of phase 2 trials, and what is called immunotherapy, which consists in using the immune system to rid the body of cancerous cells. The memory I have of it is very distant, dating from the time I was a member of an association which greatly recommended gene therapy. So cancer trials exist, consisting in taking tumoral cells, manipulating them to introduce a killer gene into them, thymidine kinase, and then reinjecting these cells into patients and giving them Ganciclovir, which triggers cancer cells mortality.

To answer Daniel Louvard's injunction, INC is highly determined in its next invitations to tender that will be launched before the end of the year, to launch one on stem cells.

Mr Alain Claeys: How in fact does INC, a new organisation, fit into thse research programmes? How do you coordinate your own research programmes with other research organisations?

Mrs Marianne Minkowski: INC's role and the mission it has been given is to coordinate everything related to cancer, not only at the level of research, but also as regards clinical research, treatment, epidemiology, etc. In INC's biology department, invitations to tender are launched for the scientists of various organisations.

Mr Alain Claeys: How is this coordinated with research programmes at other organisations? There is the Biomedicine Agency, organisations, INC... Concerning these stem cell programmes, how is this coordinated, who is the pilot?

Mrs Marianne Minkowski: As regards the stem cells programme we would like to launch, we will quite clearly not launch it without knowing what ANR is going to do for its part, and also what the organisations are doing. We must be complementary, inciting, and not repeat twice the same types of invitations to tender.

Mr Alain Claeys: I have the feeling that research teams are going to face considerable administrative tasks to anwer all these invitations to tender.

Mrs Marianne Minkowski: This should be avoided, which has not necessarily been the case till now, but INC has existed only since May 2005.

Mr Alain Claeys: I am not blaming you at all.

Mrs Marianne Minkowski: We have tried to start a kind of coordination, in particular at the level of canceropoles (cancer networks) which have existed slightly longer.

Mr Alain Claeys: What do cancerpoles represent in terms of the actual research by Inserm and CNRS teams?

Mrs Marianne Minkowski: They represent research programmes and also hospital teams.

Mr Alain Claeys: Is INC ready to participate in these research programmes, and not recreate new invitations to tender?

Mrs Marianne Minkowski: Research projects at canceropoles have been started and selected following an invitation to tender by the ministry. We are merely continuing, taking over from what has already been done, to try and continue this structuring, both by the creation of canceropoles and so-called structuring research projects that are undertaken there.

Mr Alain Claeys: I think that a clarification must be made with respect to all these organisations and arrangements. Mr Picard, you are the spokesman of the Alliance maladies rares, but you were also a player on the *ad hoc* Committee which has helped to appraise dossiers. On this last point, do you have anything to add with respect to what you have said?

Mr Roger Picard: We were assured at the last meeting of the Committee, this morning, that the Biomedicine Agency implementing decrees are on the minister's desk and should be signed by the end of this month.

Mr Alain Claeys: I have another piece of information which I did not tell you about. I had proposed to Mr Xavier Bertrand, minister for health, to conclude this work. He told me he couldn't be present today as he is coming back from China tomorrow. If I understand well, the Biomedicine Agency is now seeking a research director?

Mr Roger Picard: We haven't been told about that. All I know is that two dossiers arrived this morning for study at the *ad hoc* Committee, and they will be dealt with by the Biomedicine Agency. Normally we have therefore set off, on the face of it, in the Biomedicine Agency circuit.

Mr Alain Claeys: You today announce that the *ad hoc* Committee will no longer be sitting and that the Biomedicine Agency will be appraising dossiers.

Mr Roger Picard: Provided all the conditions are met at the Biomedicine Agency. I don't know if that's the case.

Mr Philippe Ménasché: I don't know who the two unfortunate applicants are but it should be realised, from a practical viewpoint, that it probably means that their research work is postponed for at least one year.

Mr Alain Claeys: With respect to this information, and as rapporteur, I will deal with this. The ministries concerned, health and research, will be approached.

Mr Roger Picard: I cannot answer you on the identity of these two applicants as these dossiers have not been transmitted to us. I simply know that in the two applications there was one, the first one, from a private laboratory.

Mr Alain Claeys: We are going to ask for clarifications for the future. In effect, if as much time is needed for the rest, we risk losing a year.

Mr Roger Picard: Indeed. I answered your invitation as spokesman of the Alliance Maladies Rares, and I am also chair of the Fédération Huntington Espoir, representing sufferers of Huntington's disease. I was approached by the ministry of research, when the *ad hoc* Committee was being set up, as the representative of associations and not as a stem cells specialist, although in the case of Huntington's disease we are quite informed of these procedures. I accepted not by conviction with respect to the legislation, as it is a secret for nobody to say that it does not necessarily suit me, but through a democratic spirit. From the moment you are approached to participate in something, I feel that it's best to be involved to understand what is happening, rather than be outside and criticise. I have been globally quite satisfied with participating in this Committee, with all its unwieldiness and the constraints that has imposed. I think things are not necessarily going to be better in the future.

Concerning the legislation, we will no doubt have two requests from the associations. First, that the amendment of the 2004 Act, which should normally take place after five years, should not take the same route as that of the 1994 Act, for which it took ten years and whose decrees are still not published, which will mean twelve years. That raises problems for us. With respect to the evolution of research and science, it's dramatic. Amendments should 'stick' far closer to scientific reality and evolution.

Mr Alain Claeys: A reminder of the role of the Biomedicine Agency: according to the legislator it should transmit each year a report to adapt and make proposals. This should be much faster, without waiting for a new scanning of issues every five years. That's my idea, on the basis of the report conclusions, to get matters to advance.

Mr Roger Picard: Things will take place like that provided the management of the Biomedicine Agency plays a propulsive role and does not act as an obstacle. I don't have the impression that things are taking the right route in this field. A remark was made, when we had to deal with all the dossiers, that we will perhaps not be able to do without setting up one or several stem cell banks in France. Requests are arriving from a wide array of sources. Quite clearly traditional medicine has reached its limits, despite the research on so-called orphan drugs, which are highly supported at European level, but which remain the exception. Stem cells bear immense hopes for patients and their families, both concerning treatments and knowledge of diseases. Work on stem cells is therefore very important for us to treat diseases. But it is also important to understand how a disease functions by making use of the results of PGDs and by studying diseased stem cell lines.

I entirely agree with the fact that care should be taken not to give false hopes in the short term or make promises that are neither realistic nor ethically admissible. Patients have very great expectations. Worldwide, rare diseases represent seven thousand pathologies, and in France three million persons suffer from them, in other words one in twenty. That's an enormous figure. Patients do not necessarily expect to be treated or cured but at least relieved and taken charge of so that they can lead an almost 'normal' life integrating their disease, and what is very often related, a handicap that cannot be dissociated from the disease.

As for Huntington's disease, which concerns me more personally, it is a neurodegenerative disease affecting six thousand patients and twenty thousand persons at risk. Since 1993, a predictive genetic test has existed which allows you to know from the age of majority (it's forbidden before, which is a good thing) if you carry the disease, and if you'll suffer from it one day, in other words around age forty on average. Interestingly, 90% of persons at risk do not have this test performed. In effect, there is no prospect of cure, or of hope in the short term, or of any treatment. All persons at risk therefore live in a state of permanent anguish, and develop pathologies that could be characterised as collateral, to use a trendy term. It is hoped that, at a future date, stem cells will give reasonable hopes of treatment, which will mean that not only declared sufferers will be screened, but also all those who are in the chain, brothers and sisters, children and grandchildren, are going to be able to be screened since there will be a hope of cure. The isssue will then be reversed. Solutions will perhaps be advanced to treat patients, to prevent disease, make greater use of NTDs and PGDs, which is not done today. Disease is being perpetuated unceasingly. That's what I wanted to say as regards patients' expectations.

Mr Alain Claeys: Thank you. Please remember you can also intervene in the roundtables this afternoon. Mr Bernard Zalc, you have the floor.

Mr Bernard Zalc, Research director at Inserm: I will be brief. I think I am here because I am the coordinator, with Laure Coulombel, of the network using neural stem cells for therapeutic purposes. It is a network we created some time ago and which is very greatly supported by Inserm, the ministry of research and a few charitable associations.

I would like to make a few reminders about the nervous system, mainly made up of two main groups of cells, neurons and glial cells. Among the latter, I set slightly aside oligodendrocytes, the myelin-producing cells of the central nervous system. In neurodegnerative diseases a cell population is decimated, whether dopaminergic neurons in Parkinson's disease, cholinergic neurons in Alzheimer's disease, motoneurons in amyotrophic lateral sclerosis, or oligodendrocytes in multiple sclerosis. Until ten or so years ago, we lived with the idea that our brain cells were formed at birth and that beyond age twenty we progressively lost them. Approximately ten years ago, neural stem cells were discovered which has created an undoubtedly inordinate hope of a therapy with the idea that we could perhaps regenerate some of our brain cells.

The first movement, towards simplicity, has been to replace these cells by surgical approaches. Not only is it a simple strategy, stem cells are taken to introduce them into the brain and they replace the decimated population, but in addition, and there is undoubtedly here a researcher's ethical problem, with the fantasy of brain grafts. While these approaches have been highly mediatised, it is also because researchers have participated in them, with in particular the notion that we are going to change our brain and are going to take someone else's brain. It is easy to imagine all the fantasies this can cause in a population, whether of fit persons or of patients.

Other alternatives exist. In some pathologies, this surgical approach cannot apply. If we look at this cross-section of the brain of a patient with multiple sclerosis, each white area is a lesion. In the example shown, the patient has twenty-eight lesions. It can be estimated that in all his brain there are approximately fifty, and that's forgetting the spinal cord which has twenty or so lesions. The patient therefore has approximately seventy lesions. A surgeon who is ready to place seventy needles in a patient's brain is no longer a surgeon but an acupuncturist. There is another element which must not be forgotten in a disorder like multiple sclerosis: lesions move. In this patient, the surgeon would have to spend his time placing needles and injecting cells. It's not possible. Other approaches are therefore envisaged.

This is where fundamental research is crucial. It is known that around the ventricles there are stem cells, that we should be able to mobilise them and understand how not only they are to be mobilised and induced to multiply, but also how they can be induced to differentiate along a given pathway. If we want to obtain dopaminergic neurons as in Parkinson's disease, there's no use in generating

oligodendrocytes. On the other hand, if dopaminergic neurons are generated, that will in no way help a patient with multiple sclerosis. This type of approach is to be supported, and has already been supported, within the neural stem cells network with a therapeutic purpose. This approach must be pursued.

Mr Alain Claeys: Thank you very much. You can also speak again this afternoon. Thank you for having stayed all morning. We will resume at 3 p.m.

Roundtable no. 4:
Economic challenges

Mr Alain Claeys: We will now address a subject which is sometimes somewhat neglected, but which nevertheless appears essential and poses a certain number of ethical problems: I want to speak of the economic challenges. Mrs Siobhán Yeats, of the European Patent Office, is present this afternoon and I would like her to give my best regards to Alain Pompidou. We are very pleased to welcome you today and I think your participation is important. I plan to visit you at the European Patent Office in Munich in the weeks ahead. I wish to greet Mr Hervé Chneiweiss, research director at Inserm, professor at Collège de France and member of the steering committee. I also wish to greet Messrs. Christian Pinset, founder and chief executive officer of the company Celogos; Philippe Pouletty, chair of France Biotech; David Sourdive, delegate general director of Cellectis; and Jean-Thomas Vilquin, founder of the company Myoxis, who are also participating in this roundtable.

I will first give the floor to Mr Pouletty, followed by Mr Chneiweiss and Mrs Yeats.

Bearing in mind what has been said this morning, is there an economic interest? If so, is it compatible with the scientific and therapeutic interest? Can you tell us what is happening today in France, and compare the situation in France with the international situation?

I give the floor to Mr Philippe Pouletty.

Mr Philippe Pouletty, chair of France Biotech: Thank you Mr Chairman.

If I may, I will speak more globally of tissue engineering, and not only of stem cells. The economic interest will be considerable in the thirty years ahead. We must be patient: if the history of biotechnologies and tissue engineering is examined, this type of development does not take place in either three or five years. Why will the interest be considerable? If we examine the number of pathologies to be treated – very roughly – by a molecule, the genomics dream consisting in saying that we will have more and more targets and that we will develop more and more molecules which will solve all our pathologies, is a mirage. If man is made of cells and tissues, and not simply of a collection of small molecules or proteins, it's because normal physiology is very complex. Many diseases go beyond the simple administration of a single molecule. Another reason is that the barrier against the development of more effective therapies increases with technological progress: some people are therefore disappointed that there aren't more drugs approved by

the FDA. In effect, it does not suffice to have new molecules: they must also be more effective and/or less toxic than the present ones.

If we take a close look at the history of biotechnologies and of tissue engineering, the great successes have consisted in reproducing or imitating nature. What we are talking about today, with stem cells and tissue engineering, indeed consists in reproducing or imitating nature. Substitution didn't start just today, whether it be a matter of blood platelet derivatives, various transplantations, marrow grafts, and also monoclonal and polyclonal antibodies, recombinant proteins or else vaccines. All of this represents more than 70% of the turnover of present biotechnologies. It is therefore easy to bet that tissue engineering will enjoy considerable development over the next thirty years. We can quote 'estimated' figures, by basing ourselves on medical needs and patients with liver, heart, kidney, or pancreas insufficiencies, or suffering from diabetes, or we can even make projections regarding organ transplants: in 2020 or 2030, these technologies will represent a turnover of between 5 and 50 billion euros - provided technological progress continues and regulations are adapted.

There is an enormous amount of fundamental research to be performed and for this type of technologies to reach the market the effort cannot be made solely by pharmaceutical groups, investors or biotechnology companies. We have often discussed this topic: if States do not make upstream a very great funding effort for the necessary research for this type of innovation, companies and private investments will not be able to take over. They can take over only if the upstream work has been done.

Where is France situated in this field?

It is situated at roughly the same level as it occupies in the other fields of biotechnologies or life sciences. We find the same chronic problems of life sciences academic research which is under-dimensioned in France. Bearing in mind its financial means and its quality – compared with countries that have taken more intiatives such as England or the United States –, France is perhaps third in Europe. It has a high potential provided the means are implemented and on condition that there is the determination.

What are the challenges for France?

In this field, research is completely globalised and researchers go where universities offer them the best research means, both in terms of salaries, personnel, research teams, and colleagues of the same level. Worldwide, there are approximately 200 biotechnology companies with major activity in the tissue engineering and stem cells field. As there are approximately 3,500 biotechnology companies working in all fields, that represents 5 to 7% of world biotechnology activity. Most of these companies work upstream, lose money of course and consume a lot of capital. The number of companies and their relatively low size

could considerably increase once upstream research will have made progress and once the indications and the products developed will not simply be skin grafts or the most simple tissue engineering applications.

Mr Alain Claeys: How many biotechnology companies are there in France?

Mr Philippe Pouletty: In France there are two or three biotechnology companies whose activity is dominant and which are correctly funded. I'm not sure that there are more than three that are clearly visible.

Mr Alain Claeys: What relations are there with research organisms and laboratories? How does collaboration arise and how is the issue of intellectual property addressed?

Mr Philippe Pouletty: Roughly speaking there are two ways of creating a biotechnologies company. First, it may be a matter of a spin-off from a research organism or from a university, with in general one or two researchers who have had enough of stagnating or who have excellent ideas and want to take the leap by creating a company. Second, it may be a matter of a spin-off from pharmaceutical groups where this activity is not central to their activity. There are no spin-offs in cell therapy and tissue engineering as pharmaceutical groups have very little activity in these fields.

Mr Alain Claeys: So pharmaceutical groups are currently not interested in these fields?

Mr Philippe Pouletty: No, apart perhaps from some large biotechnologies companies like Genzyme, historically Baxter with its blood transfusion and blood derivatives activity, and GlaxoSmithKlein a little bit. There isn't a company more anti-biotechnologies than Sanofi-Aventis, our national pharmaceutical group which is remarkable in other respects, as it considers that there still remains a lot to be done in classical pharmaceutics and in small molecules, and that biotechnologies pose very many problems.

This field is not very attractive for a pharmaceutical group or for a biotechnologies company as tissue engineering poses enormous problems regarding logistics, production costs, traceability, quality control, and quality assurance, as it is often individualised. A small Swiss company, Symetis, is trying to produce heart valves from umbilical cord cells from foetuses with a heart pathology. This means that it takes 6 to 8 weeks to produce a heart valve individualised for each patient. Logistics and production costs therefore weigh very heavily.

For a pharmaceutical company accustomed to producing a molecule in tons or millions of copies, with quite simple packaging and quality control and ten production batches per year, tissue engineering is awfully complicated.

Simplification consists in considering so-called 'universal' cells to allow a product to be produced for various patients. Nevertheless, this sequence requires a considerable transition for the managers of a group.

This transition is more easily made by some biotechnology companies like Genzyme, which has been a pioneer in treating rare and therefore expensive diseases for a small number of patients. A company like Genzyme can therefore integrate much better the idea of developing extremely expensive drugs for a small number of patients with heavy logistics – Philippe Ménasché perhaps spoke of this previously. If we project ourselves ahead 20 or 30 years, the risk for pharmaceutical companies of not launching into this field in time is that they will experience difficulties in carrying out at the last moment all the upstream work others will have done. The production units of these biotechnologies have strictly nothing to do with those of classical pharmaceutical products.

Mr Alain Claeys: When you say that it's a market worth several billion dollars, is the stem cells topic 'stupid'?

Mr Philippe Pouletty: No. I quoted a range from 5 to 50 million euros. If we base ourselves on present examples like heart, kidney or liver insufficiencies, or else marrow grafts, there are approximately 25,000 organ transplants and 50,000 marrow grafts between North America, and Western Europe. The number of patients on the recorded waiting lists is approximately ten times higher than the annual number of transplants or grafts. Those on the waiting lists are very advanced patients. The more therapeutic approaches will be accessible, the greater the number of patients on waiting lists.

Today, the heart transplant candidate is a patient 'near the breaking point' who is under 70. If Philippe Ménasché succeeds, as we hope, in treating more easily heart insufficiencies using cell therapies, a larger number of patients, today not on waiting lists as candidates for transplants and who are receiving more classical therapies, will benefit from these treatments. There are several million patients per year worldwide with an organ insufficiency among those I have quoted. It will remain to be seen if the treatments developed are sufficiently simple, effective and lowly toxic for them to concern 5% or 80% of these potential candidates. For sure, the more research is undertaken in this field, the more chance we have of developing treatments broadly benefiting these patients.

Mr deputy, I am always alarmed by the fact that we are very good at organising roundtables but that, year in year out, we continue to ask ourselves questions that should however have had an obvious answer for 10 or 20 years! When Arnold Schwarzenegger, who is not a great scientist but who has a simple view of the future, decided to allocate 3 billion dollars over 10 years in State funds for Californian research in Silicon Valley where biotechnologies are already advanced, he had not conducted umpteen roundtables!

Mr Alain Claeys: Thank you for your advice, but I don't think it is my model.

Mr Philippe Pouletty: I nevertheless wanted us to speak of it again.

Mr Alain Claeys: Philippe Ménasché, do you work with biotechnologies companies? How does this collaboration take place?

Mr Philippe Ménasché, thoracic and cardiovascular surgery professor at Université Paris V, heart surgeon at Hôpital Georges-Pompidou, unit director at Inserm:

Jean-Thomas Vilquin is certainly more competent than me to speak of this. As he is very modest, I am however going to briefly tell you a story illustrating my previous remarks on this country's potential, provided we don't spend our time being obstructive.

When we began working on the use of muscle stem cells to treat heart-insufficient patients, an important phase was conducted on animals, then we reached so-called translational research. With AFSSAPS, we discussed the way we could adapt our procedures to a human use. Jean-Thomas Vilquin and Jean-Pierre Marolleau of Hôpital Saint-Louis brought this translational research to a successful conclusion and filed a patent specifically concerning the technique used to graft these human muscle cells in a human heart. It was Genzyme, a large American biotechnologies company, which came to meet Jean-Thomas Vilquin! When we grafted the first patients and this gave rise to a certain amount of interest, Genzyme immediately spotted an interesting opening here. Whereas the process is generally in the France / United States direction, Americans turned up at Hôpital Saint-Louis to meet Jean-Thomas Vilquin and Jean-Pierre Marolleau, the holders of the Assistance Publique Hôpitaux de Paris (APHP) and Inserm patent.

The lady technicians from Hôpital Saint-Louis and from APHP and Jean-Thomas Vilquin's team went to Boston to present their techniques to their American colleagues. In the international trial that is taking place there are two production sites with perfectly harmonised and standardised techniques: one at Hôpital Saint-Louis and the other in Boston. There really is a potential, provided people are left to work!

Mr Alain Claeys: This story is very interesting. Can you explain the obstacles you met? What doesn't work in France for this process to reach fruition and develop?

Mr Jean-Thomas Vilquin, founder of the company Myosix: Thank you Philippe Ménasché for having told this story. When we successfully grew these cells we realised there could be a potential and our institutions urged us to apply for a patent, which we did.

Mr Alain Claeys: What have you patented?

Mr Jean-Thomas Vilquin: We have patented the production of muscle cells – and possibly their use in countries where that's possible – and the populations of cells that can be extracted from muscle in quite a short time. This was quite new and to my knowledge had not been undertaken elsewhere in the world.

Mr Alain Claeys: You have patented the production process or something broader?

Mr Jean-Thomas Vilquin: We have mainly patented the process and populations. We therefore created a small company to catalyse all this. There were four of us at the beginning. Genzyme came to see us after a few months: we didn't conclude an agreement with them straight away because we were looking for investors on the spot. We encountered difficulties, perhaps because our company was not sufficiently large, but also because the market was really large. At the time, we were told that there was a 12 billion dollar market per year in the United States for the treatment of post-ischemic heart insufficiency. We therefore needed a large structure immediately, which frightened the capital riskers and investors we had met. On studying the Genzyme file, we realised that this company had a tradition of cell growth, logistics, and the preparation of products, and that it knew how to receive biopsies and send back good quality cells with a good quality assurance approach. We therefore associated with them, for heart developments, while trying however to remain independent for the other developments we could achieve from muscle cells.

Originally, Philippe Ménasché came to find us at the laboratory because he needed myoblasts; I work on myopathies with the Association française contre les myopathies. We greatly benefited from the knowledge we had on myopathies, on the production of cells and on injections. We allowed Philippe Ménasché to benefit from this knowledge. This cell production platform was created and we presently use it with Myosix to try and return to other clinical trials, not towards frequent diseases but rare and even orphan diseases.

Mr Alain Claeys: What difficulties have you met in France? Are they of a legislative, a legal nature?

Mr Jean-Thomas Vilquin: It has mainly been a matter of administrative type difficulties. Between the filing of the application and the reception of the document, it took us nearly a year to obtain an exclusive licence for this patent, for reasons unknown to me. This was an obstacle in the face of investors who regretted we did not have a patent. At the time, some funds were lacking like the Assistance Publique seed funds which now exist and which would have allowed us to undertake a few trials more rapidly. We above all came up against a question of

scale, passing from 10 to 300 patients worldwide. This trial cost 15 to 20 million euros.

Mr Alain Claeys: You have raised a first administrative problem to obtain the exclusive licence and a second problem related to the pool. Today, in 2005, is it more difficult with the stem cells topic to put pools together and mobilise risk capital?

Mr Jean-Thomas Vilquin: I lack experience now. I think it's perhaps a bit more difficult, because in 2000 it was the time of speculative bubbles which rapidly burst afterwards. At a given moment, it was very difficult to find money.

Mr Alain Claeys: The movement is starting anew today. You didn't experience what the data processing field experienced for instance?

Mr Jean-Thomas Vilquin: No, we didn't have the time to experience that.

Mr Philippe Pouletty: As for risk capital, there is currently 150 to 200 million euros invested in France in biotechnologies. This is not very high and the cell therapy field will be deemed a high risk and long term field. If the mass of risk capital is low, the percentage ending up in the stem cells field will also be low as most funds share their investments between short term projects with already identified products and long term seed projects. For there to be sufficient money heading to stem cells or to other upstream technologies, the Gauss curve is not sufficiently developed for the moment.

I would rapidly like to review the decision of this finance Act to place a ceiling of 8,000 €. It can be announced with certainty that, if the decision is maintained, it will reduce the raising of innovation mutual funds (FCPI) from 2007. These funds were created with a tax advantage for the subscriber who can deduct from his income tax 25% of his investment up to a maximum of 12,000 €. These funds represent 50% of French risk capital: without them, the latter would collapse. The placing of an 8,000 € ceiling will make people opt instead for a domestic employee, and FCPI fund raisers say that from 2007 there will be a 50 to 75% amputation of FCPI which is very worrying for all French biotechnology, and of course for stem cells.

Mr Alain Claeys: You mentioned the amount devoted to biotechnologies in France. By way of comparison, can you tell us about the amounts in other countries?

Mr Philippe Pouletty: Today, in risk capital, in initial public offering and in secondary offering (in other words in all the funding chain of the first fifteen years of a biotechnology company), Europe in the broad sense represented, in 2004, 17% of the United States, i.e. 1/6th, which is very low. In Europe, England is situated far ahead, Germany is in second position and France comes third.

Germany, which started well in 1995, has suffered a great deal since 2000. England weighs 4 to 5 times France in size, number of companies and risk capital investments. Europe is lagging very much behind, whereas it has the means. In effect, savings and pension funds feed capital worldwide, and it is known that Europeans are big savers. Very little of French savings or life insurance goes to investments in SMEs, and even less to technological SMEs because of the culture and perception of the risk of investment diversification. If risk capital investments were pushed to all the funding chain, we would see enormous progress in France and in Europe, as the grey matter, management and entrepreneurs exist, as well as the needs!

Mr Christian Pinset, founder and chief executive officer of the company Celogos: As for the funding issue, there are practically no seed funds in France, especially for cell therapy companies, as it is difficult to see what the product is. When autologous cell therapy is performed, the cells of a patient are taken, a process is carried out and they are then reinjected. For many people, it is difficult to know where the product is. This forces them to totally change their outlook as the pharmaceutical industry works to have a product that can treat millions of people. The image of cell therapy is totally the opposite: one product treats a single person.

As for the licences spoken of by Jean-Thomas Vilquin, it is relatively difficult to obtain licences in France when you talk to the CNRS or any university. In a university which I will not mention we had a collaboration agreement with a partner and we worked together. We finally had to give up after one and a half years owing to a change in our management. The situation was no longer manageable.

Mr Alain Claeys: I have been told that in large research organisms, these matters are mutualised.

Mr Christian Pinset: Perhaps there is a determination to mutualise but much time goes by between the moment this approach is chosen and the time when this kind of practice is actually implemented. We are faced with completely grotesque administrative problems. In the previous case, we almost signed, but the management changed and everything had to be started again. We therefore gave up and changed project.

Mr Alain Claeys: Mr Ménasché, do you confirm this?

Mr Philippe Ménasché: I wasn't directly involved in these problems, because I am not part of a company, but it's true that the multiple partners in question, in this case the Assistance publique, the university and research organisms (Inserm and CNRS), makes the situation terribly complex. Everyone wants his share and that makes matters difficult.

Mr Alain Claeys: Everyone also wants his share in the United States today! The university exception is over. Administrative complexity is another point.

Mr Philippe Ménasché: The fact that work like that we are speaking of can be of benefit both to a research organism like Inserm and also to a treatment organism like the Assistance publique appears completely normal. Once again, it's the 'setting to music' which poses a problem, because it takes one year.

Mr Alain Claeys: We will return to these various subjects later. Hervé Chneiweiss, as a researcher, how do you view the economic aspect of the subject at hand?

What questions should the public authorities ask themselves? In other terms, is the intellectual property system that exists today internationally adapted to this type of research? Does this intellectual property allow innovation or, as some believe, does it serve to constitute situations of economic rent and slow down research?

Mr Hervé Chneiweiss, research director at Inserm, professor at Collège de France and member of the steering committee: I first wish to thank you for allowing me to participate in this roundtable. I will not speak directly about the questions of company creation, but I feel that when addressing the issue of the patentability of living organisms, to which Mrs Yeats will also refer later, we are faced with difficulties already encountered with the patentability of genes, and which are even more serious. We indeed recalled previously the low number of differentiated cells (235 for adult tissue), which is even lower for embryonic stem cells on which I am going to insist more. Patentability, when it concerns a product patent, can produce an instability effect, or even jeopardise existing companies and lead to difficulties in the creation of new companies, including in the provision of risk capital.

Mr Alain Claeys: So that everyone clearly understands, what do filings of patents on stem cell lines represent at the European and American level? Are they a potential risk or a reality?

Mr Hervé Chneiweiss: I don't have European figures but Mrs Yeats certainly knows them.

As for USPTO (the American patent office), a database search finds 2,000 patents for which the word 'stem cell' appears. I wish to insist in particular on two patents concerning, for their part, embryonic stem cells, filed by the University of Wisconsin following the characterisation work on human embryonic stem cells by James Thomson's team, and which in a sense grant a full monopoly to the triangle formed by the University of Wisconsin (represented by its subsidiary WARF), the

biotechnology firm Geron and the NIH which participate in this triangle regarding the regulation aspect.

Two patents have been granted to the University of Wisconsin. They are held and developed by WARF: these patents, 780 and 806, concern the preparation, purification, characterisation and production, of primate stem cells for the former, and of human embryonic stem cells for the latter. On this basis, the University of Wisconsin issued a procedure to WARF which fits in with the 2001 regulations set in place by the American administration at the level of the NIH, with a list of approved human stem cells that can be funded by American federal funds, and a list of unapproved stem cells that can be used and developed by private funders but are not eligible. All of this is therefore based on a Human Embryonic Stem Cells Register at the NIH.

The company Geron, which had partly funded the work by James Thomson, is the owner of the exclusive licence of the first three stem cell lines concerning in particular possible differentiations towards neural lines, pancreatic island lines to treat diabetes, and towards cardiomyocytes. The agreement between WARF and Geron also concerns other lines, but in a non-exclusive manner. All of this is completed by a memorandum of understanding between Wicell and NIH to agree on the regulations and distribution worldwide of licences authorising or not authorising teams to work on human embryonic stem cells. Other international companies have joined the agreement: Bresagen, ES Cell International (a Singapore company) and the Regents of the University of California. We will refer back to the question of Arnold Schwarzenegger and proposal 71 as Californian citizens themselves voted this 3 billion dollar fund. Today, the implementation of proposal 71 is experiencing difficulties owing to this system of patents obtained by WARF.

Two categories of use can be distinguished.

First, not-for-profit scientific uses: 132 licences have been granted by WARF to various teams worldwide to use human embryonic stem cells. All these licences are granted to a laboratory or to a precise team for a series of uses and all the commercial rights are retained by WARF. Then, a certain number of agreements have been signed with private companies. It is known that there are at least seven private for-profit companies which have signed these agreements, but their exact content is not known. In any case, exclusive commercial rights to human embryonic cells remain theoretically covered by these two patents 780 and 806.

The problem is the same as that we have already encountered with genes. These patents, through their claims, cover the product, the patented matter. In this case, it is a matter of human embryonic stem cells. In particular, patent 806 claims as products mesodermal, endodermal and ectodermal human stem cells, in other words all the human body's basic cells. What's more, product patents automatically cover all products derived from the initial product and all the ways of obtaining these products derived from the initial product.

Mr Alain Claeys: Were these claims accepted?

Mr Hervé Chneiweiss: Yes, by the USPTO for these two patents, especially for patent 806. The problem will be the same as that encountered for genes, in other words the possibility of disputing in the very field of patent law the validity of these claims. The patent can be disputed: regarding novelty if a publication prior to that of the Thomson group can be found relating the same thing; regarding its inventiveness if the method used to produce them can be demonstrated as obvious for someone of the field; regarding feasibility; and especially regarding the extension of the claims. One of the weaknesses of patent 806 is the broadness of its claims: it is not clearly proved in these claims that all the claimed cells have really been produced or whether it was really possible to produce them at the time the patent was claimed.

I think we should be aware that there is a heavy threat over all a biotechnologies field of which we have stated the importance. The fact that a certain number of product patents have been taken out on the most basic cells by the WARF-Geron-NIH triangle must make us question ourselves on the manner of envisaging intellectual property to develop biotechnologies and not to give such or such a group a pure economic rent.

Mr Alain Claeys: I think we must stop a few moments on this subject, one of the central subjects of our debate. Today, is the product patent, as defined, adapted to living organisms, and especially to research on stem cells? Or else can product patents form an obstacle, including for research and development? We know very well what will happen: if product patents continue to be accepted, the dispute will be settled by justice. If the legislator wishes to reduce the product patent notion to application patents, will the latter be a major handicap for research and development? How can a product patent be an element of the development of research today? Isn't it rather a pure economic rent?

Mr Philippe Pouletty: On what date was this patent filed?

Mr Hervé Chneiweiss: It was published in 2001.

Mr Philippe Pouletty: It will therefore expire in 15 years. Whenever we are on the wrong side of the barrier we find it is inadmissible to have patents that are so broad. When we're on the right side, we're proud of the discoveries of our organisms, like the discovery of HIV by Institut Pasteur. It should be remembered that the length of these patents is limited. Mrs Yeats will correct me if I'm wrong: in Europe, we are entitled to conduct research and development during the length of the patent, whereas in the United States, case-law can allow people who do so to be attacked. For technologies requiring many years development, I'm not certain that it forms such an obstacle against the marketing of products, which will take a fair amount of time. To justify massive investments by investors, the absence of

very broad patents represents an obstacle against investment risk-taking. I'm not one of those who criticise very broad patents when they exist.

Mr Alain Claeys: Are there many product patents in Europe?

Mr Philippe Pouletty: There are certainly less than in the United States. There are many European patents but they are often narrower. Big patents exist like that on HIV: this example of an extremely broad product patent has allowed Institut Pasteur to collect more than 100 million euros in royalties.

Mr Alain Claeys: Mrs Yeats, the European Directive has been transposed into French law. Long before that took place, it was incorporated in the Implementing Regulations of the European Patent Office. You therefore have a certain amount of hindsight with respect to this subject: what thinking is going on at the European Patent Office regarding living organisms and what changes can be expected as a result?

Mrs Siobhán Yeats: Thank you.

I don't think it's up to the European Patent Office to attack or defend patents. Some have attacked them, others have defended them. The role of the Office is to represent the law as it is. European patent legislation stipulates that human elements, including cells can be patented, in accordance with certain conditions of course, and within the limits of ethics. This means that stem cells can theoretically be patented if there are no special ethical considerations. The various types of stem cells must therefore be distinguished.

Adult and foetal cells can be obtained from blood or from spinal cord donated for research by volunteers. There is therefore no ethical problem. These cells can be patented without limitation.

The situation is different concerning embryonic cells.

Their use is controversial for the same reasons as research is controversial in Europe as they are derived from human embryos. Determining if these cells can be patented is of course the subject of a very vigorous debate in Europe. A new development regarding the WARF patent took place last week, concerning patent 780 on primate cells.

A specific provision in European legislation stipulates that the use of human embryos for industrial or commercial purposes is excluded from patentability as it is unmoral. The reason for this exclusion is not entirely clear. The Directive was drafted in 1998, and even before. At that time, human stem cells had not yet been isolated, unlike primate cells. It is difficult to know why the European Commission included this provision in the rule. This is a problem for European Patent Office examiners at it must be interpreted. Public opinion is divided, which does not make the task easy for the EPO examiners. One of the positions would be

that the use of human embryos as such would be excluded from patentability. This would correspond for instance to the sale of human embryos intended for reproduction or cloning. A statement by the Commission's Ethics Committee seems to say that the people who wrote the text had these ideas in mind. In this first interpretation, it could be considered that embryos as such cannot be patented, but that cells derived from embryos are not embryos as such and would therefore be patentable. The second interpretation would of course be broader: any research involving human embryonic stem cells implies at one moment or another the destruction of human embryos. It can therefore be alleged that this research on embryonic cells is based on the use of human embryos for commercial purposes, and that the result of this research is not patentable. A consensus must be sought on the subject, even if there isn't one: must these cells be patented or not?

Till now, when faced with this type of decision the highest bodies of the European Patent Office have considered that human embryonic stem cells could not be patented. Not only the cells themselves, whether derived or not from cell lines, but also all their uses as well as the methods to isolate them and grow them would not be patentable.

Mr Alain Claeys: Therefore today, at the European Patent Office, cells themselves and the processes to grow them are not patentable.

Mrs Siobhán Yeats: That's what the examiners decided in the three cases addressed till now, including the WARF case. The three applicants appealed against the decision of first instance and last Friday we had oral proceedings. The appeal chamber decided to refer the question to EPO's Enlarged Board of Appeal which takes decisions on fundamental matters to interpret the law.We are going to ask how we should interpret the stipulation according to which the use of embryos is not patentable and if we can patent these cells or not.

Mr Alain Claeys: For the moment, this issue has therefore been transmitted to your highest jurisdictional body for arbitration. That therefore makes you different from the American patent office. What is the position of the Japanese patent office?

Mrs Siobhán Yeats: I think they are also quite strict but the issue of embryos is slightly different in Japan.

Mr Alain Claeys: Is there a difference between the position of the European Patent Office and the English patent office?

Mrs Siobhán Yeats: The English patent office issues patents for cells and their use, but neither for the methods to isolate them from the embryo nor for embryos as such.

Mr Alain Claeys: But do they issue patents for cell lines?

Mrs Siobhán Yeats: They have quite a narrow interpretation; they state that use itself is not patentable. Cells isolated later are not a use as such and can be patented. Each company can therefore apply in Great Britain for a patent, obtain an English patent and file at the same time an application in Europe. Several companies follow this strategy. We will have to wait one to two years to obtain the answer of the Enlarged Board of Appeal. Till then, we will stop dealing with cases related to embryonic cells; we will wait for this decision.

Mr Alain Claeys: For the moment, all patent applications sent to you are not analysed, pending the decision?

Mrs Siobhán Yeats: We are going to wait for this decision. This event was very recent, since it took place four days ago. Till now, we continued to deal with them, but we took a decision only in three cases.

Mr Alain Claeys: Do you have any questions on this subject?

Mr Jacques Hatzfeld: At the CNRS, we filed an application for a patent and we indeed received that answer. It is rather a matter of a line producing a factor allowing ES cells to be differentiated. Isn't this patentable in Europe? It is not a matter of an ES line but of a line which is a factor, which we wish to analyse. If what you say is true, no more private companies will invest in this kind of research!

Mrs Siobhán Yeats: You're right, it's a problem we clearly understand at EPO. But we are stuck between two positions. Some tell us we are jeopardising all the European industry as we are not issuing patents, whereas others consider it is totally unethical to issue patents as this research is unmoral. We still haven't found a consensus in Europe: we are seeking the opinion of the majority.

Mr Jacques Hatzfeld: You therefore confirm that for this type of patent application, there is no answer for the moment?

Mrs Siobhán Yeats: For the moment, there is no answer.

Mr Jacques Hatzfeld: EPO told me that the answer by Brussels was negative.

Mrs Siobhán Yeats: Brussels makes the law. Brussels doesn't have an answer because I personally asked them what they wanted to obtain with this legislation and they told me they didn't know.

Mr Alain Claeys: The European Directive which has been adopted doesn't in practice answer the question you asked.

Mrs Siobhán Yeats: That's right.

Mrs Marina Cavazzana-Calvo: I am at last discovering at the level of legislation the relation between a European State and the European Patent Office. Can States take out patents individually and then file them at EPO? Wouldn't this be a way of circumventing this legislation?

Mrs Siobhán Yeats: No, but each patent application can be filed separately in all the countries of Europe – in Great Britain, in France, in Germany, in Denmark, etc. – and you can obtain patents that are valid solely in the country concerned.

Mr Daniel Aberdam: We have patented the production of skin from murine ES cells, and the patent concerned mammal cells. The term 'mammals' chosen by the French patents body has been visibly rejected by the European community and accepted by the American community. This means that a patent that can hold in the United States, and possibly in Belgium and in France, cannot probably hold in Europe. It doesn't make sense.

Mr Alain Claeys: Parliament was therefore right in questioning itself about the transposal of the European Directive. What was addressed with genes is being raised very concretely at present with stem cells. It has been decided at the level of the European Patent Office that EPO's highest authority would be referred to in order to adopt a position concerning the patentability of stem cells or stem cell lines, since Brussels could not give an interpretation. Four days ago it was decided that this type of claim could not be examined by the European Patent Office.

Mrs Siobhán Yeats: That's rather good news since it means that we will at last have a final decision, even it takes a year or two. I feel this is progress. Till now, the examiner was forced to seek what to do almost on his own.

Mr Jacques Hatzfeld: It's a good thing in the sense that we will be able to use all American inventions in Europe: does this mean that we couldn't care less about their patents?

Mrs Siobhán Yeats: It's not that we couldn't care less about their patents, but an American patent is not valid in Europe.

Mr Jacques Hatzfeld: We will therefore be able to apply these patents without having to pay royalties?

Mrs Siobhán Yeats: That's your interpretation, not mine.

Mr Jacques Hatzfeld: It's a question.

Mrs Siobhán Yeats: It depends on the situation.

Mr Philippe Ménasché: Let's take the following example: if tomorrow the long-awaited implementing decrees finish by appearing, and once the Biomedicine

Agency has given its go-ahead, even if it is undoubtedly not tomorrow, and once a French laboratory derives a 'French' embryonic stem cells line and proposes a new process, for instance of the predifferentiation of cells or the selection of predifferentiated cells, in short something that has nothing to do with the line strictly speaking, but with preparation processes in a clinical perspective. For the company in question, is the process patentable?

Mrs Siobhán Yeats: Unfortunately, I cannot give you an exact answer: we really will have to wait for the decision of EPO's board of appeal on the scope of this Directive. Law evolves with consensus in society. I feel that it is not unimaginable that by continuing to reflect on these matters, discuss, hold roundtables, and develop European opinion, we will finish by deciding that we cannot at all patent the results of this important research.

Mr Hervé Chneiweiss: I would like to make a few small clarification points.

First, to date, WARF has granted research institutions exclusive licences for a given use, but always free of charge. This is part of the research agreement. From the moment it is a matter of a not-for-profit laboratory, the agreement with the NIH stipulates that there is no entitlement: there must be a material transfer agreement, and all the commercial rights are retained by WARF. A licence is granted to a not-for-profit institution without royalties and without any costs. From this viewpoint, NIH and WARF have established an agreement in which the 'research' specificity is granted.

Second, in the United States, jurists have already addressed the following question. If, after having derived a European human embryonic stem cells line, a European company tried to sell a product from them in the United States, it would then come within the ambit of the two WARF patents and would have to find a licence agreement or a secondary patent agreement to sell its product. In the American territory and in countries like Canada which recognise American patents, the company would have to find a consent agreement with Geron and WARF to be able to sell its products. In the American territory, the two WARF patents apply until the scope of the claim is possibly disputed before the USPTO chamber of appeal. As I stated, patent 806 covers the three embryonic germ layers and so it appears difficult in the present state of matters to imagine a product derived from a human embryonic stem cell not coming in one way or another within the ambit of this patent.

In response to Philippe Pouletty's remark, we are certainly pleased when we have broad patents – and the royalties on AIDS tests have been high – but Institut Pasteur has not taken out intellectual property protection on all sexually transmissible diseases involving a retrovirus, or else for all diagnosis test means involving the use of lymphocytes! We are here at levels of extension that do not take account of the multiplicity of genes. To return to human embryonic stem cells,

I feel it is not a moral problem related to the origin of these cells - we discussed that at length this morning - but a problem arising from the fact that, by taking out this patent, WARF grants itself a right to all embryonic stem cells whatever and wherever they come from, and for the next 15 years! If that's not a major limitation on all biotechnological development...

Mrs Siobhán Yeats: It's a bit more complicated than that, as we still have patent system principles, with very broad patents, then patents that become progressively narrower as a matter is developed. The same applies when you peel an onion which grows smaller as the layers are removed. In the genes example, we had in Europe a patent on the expression of any gene in a mammal cell. This does not mean that everyone has stopped working on genes expression. A second patent was then filed on for instance the expression of growth factors, then afterwards on other genes and other promoters. We continue to develop the general principle contained in the first broad patent. Even if it is a broad patent covering, as a rule, the isolation of embryonic stem cells, it is indeed WARF which performed this pioneering work, which obtained this patent and which has also applied for a patent in Europe. If you have a big innovation, you'll have a broad patent. Then, if you isolate specific stem cells, which are not specifically covered by this patent and which are not expressed in this patent, you'll obtain a second patent. The process will continue. Of course, you are in a way dependent on WARF or others, but you nevertheless have something to offer. If the various parties each possess their cells, they can decide to work together and make a licence agreement. As a rule, this system has always worked in the pharmaceutical industry and already operates in the biotechnology industry. Theoretically WARF controls everyone but finally it is not very much in its interest to do so as it will also suffer in the process by not being able to use the discoveries of its competitors. An agreement will be found: that's how the system works.

Mr Alain Claeys: There are two possible practices. Either a judge arbitrates on the basis of broad patents, which will progressively allow a point of balance to be reached, or else there is another approach according to which the legislator takes a stance on this type of patent by considering that product patents are not accepted and that we must stick with application patents. This is the debate which must be held. The European Patent Office needs to think things over, including in the framework of its rules of procedure. This proves that, in terms of its interpretation, the European Directive, has its own limits.

Mr David Sourdive, delegate general director of Cellectis, also has his point of view to give. We will then give the floor to Mr Christian Pinset of the company Celogos.

Mr David Sourdive, delegate director general of Cellectis: Thank you.

I would like to add a bit of optimism to the debate: since this morning, I have heard a lot of remarks about the problems that are arising, about the difficulties encountered, and on the fact that questioning is going on worldwide.

I will center my remarks on two things. First, it's a matter of trying to give you a feeling of the very great potential of stem cells and the major challenge they represent, in particular in the engineering of living organisms. Second, I will bear witness to the special opportunity we have today in France of adopting a strong and perennial position in this field and of seeing how important it can be for us to head in this direction.

The company Cellectis was created at the beginning of 2000 as an industrial spin-off from Institut Pasteur. In response to the question posed previously 'is it difficult to obtain licences from academic institutes in France?', the answer is yes, but there are nevertheless methods that work.

We happen to be the holders of extremely strong intellectual property and of very broad patents on knock-in and knock-out genome engineering. This represents 6 families of patents and 75 patents worldwide, which is enormous. It took several months for us to negotiate with Institut Pasteur, which is co-owner with Institut Curie, CNRS and Inserm. How do we proceed? We appoint a single spokesman and we give ourselves 14 days to answer any proposal and counter-proposal. These are simple methods which work, and which lead to a ratification. I'll close this digression by answering that it is difficult to obtain licences from academic institutes but that methods exist. You simply have to agree. Admittedly too many co-ownerships can make things extremely difficult.

Cellectis was founded on the basis of the following vision: in the 20th century chemistry experienced a revolution. In the 1920s, we passed from empiricism and a few isolated reactions to something far more systematic. We became capable of working on carbon, hydrogen, nitrogen, and oxygen in a very skilful and systematic manner. Chemistry invaded all compartments: life, textiles, pharmacy, fertilisers, etc. Living organisms will experience the same evolution in the 21st century. We have therefore positioned ourselves from the outset in this genomic engineering approach, and especially in the engineering of cells in general and tissues in particular.

Why is it a strategic field? Because it will be one of the main sources of growth in the years ahead. It's entirely strategic for therapy, I won't refer back to this as we have spoken a lot about it, since it is a matter of being capable of repairing diseased sequences in cells isolated from patients, whether the cells have inherited or acquired genetic defects, like viruses. It has been demonstrated that cells could be cured of viral infection, which is a rare approach. This field is also strategic as it has an enormous application in industry: I will focus my remarks on this point.

There are very many bio-industries in Europe and living organisms are present in a very great number of fields. However, a very great number of processes are needed to obtain a stem. Everything that takes place downstream (purification…) is quite well mastered. However, obtaining an industrial stem is a nightmare, whether for people doing screening to validate molecules, or for people who make animal models or produce recombinant molecules (antibodies...) or complexes (antibiotics). I am of course not speaking of persons working on plants, who are today condemned to perform transgenesis and who would like to do something else. There is today an enormous challenge in the engineering of living organisms and in particular in genomic engineering. We are positioned in this specific sector and have become an industrial reality and, since then, a sectoral reality.

Where is the challenge situated?

The opportunity comes from the fact that the moment is right: genomics have come onto the scene. We have the means to know the content of the genome sequences of a certain number of organisms and micro-organisms which are of immediate interest for industry or therapy. Second, technological leaps have been made. Today we know how to target very precisely a place in a genome and rewrite it. We do not know how to go to the very base, but we are not far off. It's a matter of months or a few years. The technological leap has been made and concept proofs are already under way. We therefore benefit from anteriority. Third, we have the players: as has been said and repeated, we have very great researchers and great clinicians in France, and a capacity to act with existing industrial players. We also have the tools, like the competitiveness poles such as Méditech in which Cellectis is involved. We have demonstrated that we know how to work together and organise ourselves. I can testify that a certain number of my partners are around this table and that we succeed in developing collaborative and structuring projects producing research and highly effective applications.

Today, how can we seize this opportunity and reach a strong, dominant and perennial position in this field? Patents are indeed merely a banning instrument. They don't allow you to do something but ban others from doing so. They are a 'trading currency', and it's not because someone has taken out a very broad patent that you no longer stand a chance. I can testify to this in my daily work: we are ourselves the holders of a very broad patent, and I can see what is happening around us and how we must pursue competition in the face of people who have understood very well that they could block downstream such or such an application and have a 'trading currency' with us.

Mr Alain Claeys: I agree with you, but in addition to that, through these patents, we are nevertheless moving on to knowledge patents.

Mr David Sourdive: I'm going to speak of that immediately.

In our case, it's a matter of a process patent. We're not in the case of a product patent. We must be clear. We control the entirely artificial use of mechanisms whose bases are indeed natural, like induced homologous recombination, targeting a specific place in a genome (whether a mammal or not, depending on the territories). We control the use of these extremely precise molecular scissors, which are also natural, allowing that recombination to be triggered. These patents with extremely broad claims today do not concern knowledge as such. We do not patent knowledge but a material process involving the implementation of very precise and well-documented molecules.

This morning we have spoken a lot about normative power and the difficulty resulting from the stacking of rules, whether in the law, regulations, or procedures, to obtain such or such an authorisation.

There is a second important aspect on which I would like to question you: that of your aptitude to release funds. Budget lines must be opened on these topics and especially for the engineering of living organisms – a field where we are quite good in France. We are going to reach a stage where the management of complexity will make the difference.

Complexity results from the mountain of information coming from genomics and all the biochips: traditionally, France has good mathematicians and good information theorists to manage to extract meaning from all this. I'm not certain that we have won or even waged this first battle on biochips and genomics: on the other hand, we will be present for the next battle, and really stand to win it or at least reach a very dominant position in this field. I feel that the first thing you can do is to open budget lines in this field and recognise these topics of living organism engineering and genomic engineering, if only by making it appear in the nomenclature. This action may appear symbolic but it isn't as it induces extremely important budgetary consequences. It is a leverage phenomenon.

Secondly, support must be strong and perennial. A certain number of structural measures aimed at promoting investment in our society are essential. What has been said is unfortunately very true: today the fuel of biotechnology companies is indeed capital. We are in the field of long-term risk projects requiring highly intense investment for a period of time in keeping with the clinical trials. Everything that can promote the mobilisation of savings – France has the second savings rate after the Japanese – will be favourable. But today these savings are not heading to innovative French SMEs. I can quote a certain number of examples: our main competitor – for once, the French are ahead and the Americans are following us – is raising money to catch up with us. This money comes inter alia from French life insurance! Our competitor therefore comes to Europe, buys up companies, destroys them, and delocalises them in California. We will resist but a certain number of European players are experiencing this: savers from their countries prefer to give money to Americans who are going to delocalise the industries of these countries.

We must question ourselves on the means of mobilising these savings. A few years ago, a formal commitment was given before the minister for industry and finance of the time (Mr Sarkozy) by life insurers that they would invest 4% in innovative SMEs. That's not at all the case today and yet these people enjoy an enormous tax privilege, which is mainly to the advantage of American and Chinese producers – statistics will back up these remarks better than me. From the viewpoint of the producer who I am today, I must tell you that you have an opportunity before you, that we have a quantity of assets, and that we are in a position to wage some - not all - of the important battles that will arise. We need this support to be strong, effective and above all perennial. You have two levers in your hands: that of the budget line and the possibility of mobilising savings.

Mr Alain Claeys: Have you contacted the Agency for Industrial Innovation (A2I)?

Mr David Sourdive: I am going to be frank with you. A2I is today composed of three persons who find it very hard answering the phone, who state that the agency is in the process of being set up, and who, observing that we are an SME, state that that is just fine insofar as the agency has committed to setting aside a few % fractions of its money for SMEs, but that we should come forward with a very large group. As Mr Pouletty said previously, there is no longer more than one very large health group in France, which is not very much in favour of biotechnologies. We are trying to find a means of structuring something of the dimension that would suit A2I through the competitiveness poles. That's the instrument we are going to use.

Mr Alain Claeys: Are you part of a competitiveness pole?

Mr David Sourdive: Cellectis is not only part of one but is one of the founders of Meditech, of which it is the administrator and member of the executive bureau. Yet interactions with A2I are complex today. The arrangements which A2I wants to set in place are not yet even approved by Brussels, where they have been merely tabled for examination. If I have correctly understood, it is a matter of very big projects. However whenever there is more than 25 million euros on the table, files are treated on a case per case basis and you have to return to Brussels. We are therefore being sent extremely confused signals and not very positive today for innovative SMEs. I wish to recall that innovation in health mainly takes place in biotechnology companies. A very large share of drugs today under clinical development result from biotechnologies – not to say the majority. So, to say that A2I reserves a 'small share' of its money for SMEs is paradoxical.

Mr Alain Claeys: Thank you Mr Sourdive. I'll now give the floor to Mr Christian Pinset.

Mr Christian Pinset: Thank you for having invited me and I wish to thank Mr Sourdive for having tried to introduce some enthusiasm which I shall try to illustrate.

Mr Alain Claeys: I didn't find the researchers were pessimistic this morning.

Mr Christian Pinset: These views are 'variable' like the weather forecast! I'm going to tell you the story of a scientist who felt unmotivated in his job and decided to create a biotechnology company with the underlying idea of trying to find the best means of proving the concept that cell therapy is not only something possible but that it can be possible industrially. In a sense, this forces different thinking than that going on in academic research, and which consists in trying to find the association between a pathology for which a cell therapy could be glimpsed, a product which might treat this pathology and an alternative to the already existing product. This is relatively tricky.

I am going to try and show you that cell therapy products can be built for indications that don't spring immediately to mind. Cell therapy often brings to mind rare or life-threatening diseases. What interests us is to develop cell therapy for non-life-threatening diseases but which lessen the human being's dignity. We are in the process of launching a product for which we started the clinical trial in May with four patients treated against urinary incontinence. Why have we chosen this pathology? When we approached investors, all were frightened by our proposals and surprised that we were proposing an innovative and very expensive therapy for a non-life-threatening indication. We met with surprise and sometimes disdain on the part of these investors.

We remained steadfast, especially thanks to aids from the State which I wish to thank on this occasion, in our goal to develop proof of this concept. The urinary incontinence market is extremely large - there are approximately 3 million urinary incontinents in France, and the seriousness of this incontinence is highly variable. It is a disorder for which there are few therapeutic alternatives, especially in men. In men, this frequent pathology represents 20% of the after-effects of prostate cancer. When I examined the clinical histories of our first four patients, I was myself surprised by the fact that they were persons who were relatively fit till then and who suddenly became incontinent. For these patients, the only alternatives are diapers or an artificial sphincter: not much in the way of therapies. In this context, we thought that we could repair the sphincter in a relatively simple manner. An autologous therapy is involved: a piece of the patient's muscle is taken from the shoulder, treated in culture in accordance with a process similar to Myosix's, characterised and reinjected. It is relatively easy to set in place and can work. I hope it can be profitable for our company.

Regarding your question on the areas where we have encountered difficulties, my answer is that we were expecting some problems of a technical

nature: that's part of our job as scientists. I thought I would come across regulatory difficulties, and in that respect I was very surprised. I think it's Mr Pouletty who said that things went smoothly with AFSSAPS. In effect, by discussing and advancing together, we make the regulations with AFSSAPS. This agency is a good specifically French body because, while it forms an obstacle, it imposes standards on us which are very important in marketing a product afterwards. We above all met economic type difficulties. It is relatively difficult to find investments in France, especially in the first round of financing. We succeeded a miraculous operation. If today's meeting had been held a year ago, I would not have been present because we were in an extremely tricky situation and I was wondering whether we weren't going to have to dismiss the personnel. We had the authorisations and could begin clinical trials but we absolutely didn't have the means to implement the project. It was tragic because people working with me were likely to lose their jobs and because that would be catastrophic to putting the project together.

As we were close to a clinical trial, and as we were beginning to believe there could be a product and that the urinary incontinence market was big, we managed to make some contacts, and made in particular an alliance with a small French company very interested in innovation and which is our partner, HRA Pharma. This company has marketed the day-after pill (Norlevo). This alliance allowed us to obtain funds and also all the technical wealth (medical management, construction of clinical trials) allowing us to view this trial from another angle and with another type of competences. We are much happier now.

We are in a situation in which we must combine two dimensions, economic aspects, which I will not refer back to, and the clinical trial. Performing a clinical trial consists in wishing to be audacious by proposing things which have not been done and at the same time being vigilant. Managing these two capacities is not necessarily easy. I 'took the plunge' without having any industrial experience. I serenely pursued my career as a scientist until I became unmotivated as research director. It's this experience I'm trying to share with you: if you are given the means to be audacious while remaining vigilant, there really is a future, and not simply in France, for cell therapy. I very sincerely believe we have one of the best models to show that we can prove a concept in an extremely widespread and handicapping pathology. Since we have entered into this industrial alliance we are in satisfactory conditions to view the future not only in terms of autologous therapy but also in terms of a reflection on cell therapies of the future, in particular to obtain allogeneic cell therapy products.

Mr Alain Claeys: Mr Vilquin ?

Mr Jean-Thomas Vilquin: My first remark does not directly concern patents but the fact that patent conceptions must be harmonised. It is also necessary to harmonise regulations on cell therapy at the European level. We are presently fortunate in France to have AFSSAPS, one of the agencies carrying out the most

extensive and in-depth work. When you have obtained AFSSAPS validation, it is much easier to obtain validation in other European countries. Nevertheless, every time we want to go into another country, we must pass via a regulatory agency. Harmonisation is therefore necessary: perhaps it is taking place. In our case, with Philippe Ménasché, we have an on-going international trial. We were able to make cells immediately in France because this was filed at AFSSAPS, but we have had to pass again via all the agencies of other European countries.

In another respect, it's the lack of short term visibility which makes investors flinch. They have little information on reliability and efficacy and don't know what the return on the product will be. It would be important to hold a debate on the means of reimbursement of the use of cell therapy products, whether alone or in conjunction with prostheses or tissue engineering products. That will encourage them to invest.

My third remark is optimistic: what interests Philippe Ménasché is to be able to inject cells into the heart using a syringe. Ultimately, the content of the syringe clinically does not interest him: he is interested scientifically to know what these cells correspond to. All the peripheral developments are common to ES cells and adult cells. A catheter will be made to inject cells the same way, whether it is a matter of modified ES cells, that have become adult or differentiated, or adult stem cells directly. There is a complementarity. The developments to do with ES cells or adult stem cells are the same for cell types. What is advantageous to one is advantageous to the other. That also applies between us, doesn't it?

Mr Philippe Ménasché: I nevertheless know what is in the syringe.

Mr David Sourdive: One aspect should be clearly insisted on: cell engineering technologies and living organism engineering have long-term applications in regenerative therapy, but they don't have just these market outlets. This has enabled investors to get involved in projects where there is an immediate market. The opportunity I mentioned to you is to be found in industrial applications: Marc Peschanski will be able to give you a concrete example of what can be done today in this field. We must not limit ourselves by considering that the problem will arise in 10 to 20 years time: the problem exists today. We have large shares of this growth potential to seize immediately! Living organisms are present in many compartments! Following the example of the chemical revolution in the 20th century, we aren't going to wait for opportunities to go by before deciding to use living organisms in order to stop doing chemistry or doing something which chemistry doesn't know how to do. There is an immediate application and investors can go ahead and invest. Cellectis corresponds to 16 millions euros having been raised with Danish and French investors. In this matter, the field must be broadened and we should not limit ourselves to the sole vision of regenerative medicine.

Mrs Siobhán Yeats: I merely wish to say that the patents system is not there to please the officials at the European Patent Office! It has been created as a

service to the public and to companies and to find a balance between public demands and corporate demands. We listen to you: if there are problems with legislation, we of course hold a debate. If I may say so, it's also the duty of politicians to make clear laws acceptable to all. Analysing fundamental society issues should not be the work of the European Patent Office. Legislation should be made and then these issues should be included in it. We are going to pursue these debates at the Office and outside the Office, and we will listen to all those discussing these matters with us. This work is difficult; we are trying to work with the legislation available to us. If it's not right, it should be modified, but that's not the role of the Office. It's better to keep a quite general law: we have a general patents law dating back more than 100 years and which has well served the community.

Mr Alain Claeys: We're not going to make you bear the hesitations politicians sometime have regarding legislative texts. If there are no more remarks, I propose we move on to the last roundtable. Before doing so, for those joining us now, I would like to summarise in a few words the debates since this morning, which have been pleasingly rich.

First, there is an understandably unanimous demand for the decrees implementing the legislation to be published as rapidly as possible, all the more so since I learnt yesterday that changes were taking place at the Biomedicine Agency. The director of the agency was to be present today but she told me yesterday that, as she was on the point of leaving, she couldn't attend the debates. As the *ad hoc* Committee is finishing its work, it will no longer appraise dossiers. The Biomedicine Agency should therefore be operational as rapidly as possible. You all agree on that.

The second thing mentioned concerns the possible ambiguity in the drafting of Article 25 of the bioethics Act. I heard this without giving a substantive judgment: ban on research on the embryo, five year moratorium, analysis of research programmes on the basis of their therapeutic purpose 'provided other techniques do not allow this.' Clarifications are necessary, and I think the implementing decrees will have to be as clear as possible. Through your remarks, the legislator has understood what falls today within the field of fundamental research and what offers therapeutic prospects. I think there is a sometimes dramatic confusion for our fellow citizens, as they are led to believe incorrect things. It's the legislator's role to avoid the sensational and to be very scrupulous regarding advances made by research. Your successive remarks have allowed us to understand this matter much more clearly. The other thing which has been said, and which I think was at the heart of the discussion at the end of the morning, is not to oppose a research centre working on adult stem cells and a centre working on embryonic stem cells. All the parties were very clear on that point.

One point which does not directly concern today's debate, but which is important in mobilising means, is the complexity of procedures in this field. The

director general of Inserm and the director of the living organisms department at CNRS, who were present this morning, explained to us what their budget was in the stem cells field. They clearly told us that it was necessary to find a working relationship with the new agency which has just been created: this is a subject of debate and concern which must be examined by the public authorities. This also applies with the Institut du Cancer: if, through the canceropoles, the latter invests in such or such a team, there must be coordination as this team is very certainly linked to Inserm or CNRS.

The European aspect has also been mentioned, and I wish to insist a great deal on the difficulty encountered today by our teams to participate actively or usefully in European invitations to tender. We must bear that in mind. As the rapporteur of this study, I will not fail to mention this strongly.

We have also addressed as a main theme what some call scientific cloning, therapeutic cloning, or, to take up Mr Claude Sureau's expression, nuclear transposition. What are the prospects? The dominant picture this morning, for the various speakers, was to say, while explaining – and I think that's important – what is really taking place in the world and not fantasising about such or such a discovery which would take place, that this technique will have to be authorised some time in France. You did the right thing mentioning, as researchers, that the condemning in the present legislation of so-called 'therapeutic' cloning, placed almost on the same plane as so-called 'reproductive cloning', poses a certain number of difficulties.

We are going to devote the last roundtable to scientific cloning (or to therapeutic cloning), by mentioning a topical subject that several speakers have addressed, namely ovocyte donation.

Roundtable no. 5
Scientific cloning: what prospects?

Mr Alain Claeys: I'm going to present the last speakers: Messrs. Daniel Aberdam, research director at Inserm; Alain Fischer, professor of medicine, director of Unité 429 at Inserm (Hôpital Necker-Enfants malades), member of Académie des sciences; Bertrand Jordan, research director at CNRS, adviser at Marseille-Nice Génopole; Axel Kahn, research director at Inserm and member of the steering committee of this study; Marc Peschanski, research director at Inserm; Didier Sicard, chair of the National Consultative Ethics Committee; and Claude Sureau, honorary chair of Académie nationale de médecine, member of the National Consultative Ethics Committee.

I'll give the floor to Daniel Aberdam.

Mr Daniel Aberdam, research director at Inserm: I have already mentioned a few notions I consider important, and I am going to take up those that have been spoken of during the day. It is absolutely necessary not to fall further behind, as we have done in the past. We must not have prior conceptions: techniques which are impossible today will not necessarily be so in the future. This must not be a reason to slow down a legislative decision. We saw this clearly when in the years 2001-2002 somatic cells were opposed to embryonic stem cells. Some considered that adult stem cells could do at least as well as embryonic stem cells and that the latter could be left aside. Delay has been incurred in the decision to legislate and the decrees have still not been applied for the derivation of new lines. I think that Jacques Hatzfeld sufficiently insisted on the non-reasons to further delay the derivation of lines from PGDs. As René Frydman said, it is a matter of operative waste and, on the face of it, the discussion is very different from the status of the embryo.

The debate on the status of the embryo is still taking place and we will not speak of it. Everything related to cloning or what is presently called nuclear transposition – I think this term is more correct – will of course be extremely useful as a cell model. We have sufficiently insisted today about systematically avoiding giving false therapy hopes in the short or medium term. Nuclear transposition is essential to have cell models allowing us to understand mechanisms and to have models of pathologies of which we do not know the molecular and genetic bases and the causes of dysfunctionings. I am more concerned by autoimmune diseases directly related to skin biology for which skin models would be very important using nuclear transposition. This of course applies even more for neurodegenerative

or other diseases. I think specialists will speak on this subject. I prefer to leave the floor to those who are directly concerned by this evolution of legislation.

Mr Alain Fischer, professor of medicine, director of Unité 429 at Inserm (Hôpital Necker-Enfants malades), member of Académie des sciences: I'm not sure there still remains a lot to be said. You have broadly addressed the issues of nuclear transplantation – which is my personal term: I agree not to use the term therapeutic cloning. Today, we can reasonably say that there is potential interest in this technique. Daniel Aberdam has just recalled the generation of stem cells using nuclear transfer and coming from pathological cell material. A skin fibroblast of any individual has the potential to be used.

Mr Alain Claeys: Can you give us your vision of what is taking place internationally, with respect to countries where 'therapeutic cloning' is authorised?

Mr Alain Fischer: I'm not sure I'm in the best position to give such a view. May I not directly answer your question. I am sure other speakers know better than me about the international situation in the nuclear transplantation research field.

There is a major interest in the generation of embryonic pathological cells using which absolutely fundamental work - in the literal as well as figurative sense - can be undertaken as it is a matter of subsequent therapy development models. We need this material in enormous fields of the medicine of genetic diseases and not only in the medicine mentioned above. There is also the possibility that these cells may one day present a therapeutic interest, even if it is necessary to be honest by saying that is more than uncertain and very remote. There is nevertheless the notion of compatibility for major histocompatibility antigenes.

The question on which we must spend time is not 'why did you finally reach the conclusion that it will have to be authorised?' but 'insofar as it will be necessary to authorise it in the future, what prevents us from authorising it today?' Are there objective obstacles?

One of the long-standing obstacles – which in my opinion was partially acceptable – was considering that on the whole it was not feasible. In this case, why authorise something which is not feasible? Today we know that it can be clearly performed, in conditions that are still difficult and with a relatively low efficacy but which has apparently considerably improved in the space of a few years and which is probably going to improve still more. That argument therefore vanishes to my mind.

The second argument consists in saying that we are generating cells that have the potential to live, which brings us back to the old debate which is not specific to nuclear transfers. This same debate has taken place regarding embryos therefore I don't think it should be specifically mentioned at this level.

The third argument is that this technique is potentially dangerous for, alongside the possible benefits of a scientific or medical nature, it may be used for reproductive cloning. This argument can be debated for I feel that, from the scientific viewpoint, there are today known notions as regards imprint problems which mean that this is far from obvious. Even if this argument was accepted, I feel that it is unreasonable to put it forward. Per se, a scientific development is neutral: it is neither positive, nor negative. It is then necessary to regulate so as to promote socially 'useful' development, while avoiding a development which society rightly does not want. I feel it is a matter of a discussion at another level.

The fourth argument, mentioned this morning, and which in my opinion is the only one worth serious attention regarding this issue, concerns ovocyte donation. There is a real problem that deserves debate and regulation. Insofar as there are already medical circumstances today where ovocyte donation is authorised, a strict regulatory framework is to be found, while avoiding, at least in our country, the risks of slippage towards unacceptable practices, financial pressure, trade... I feel this question is the only one that is really worth special attention but it does not appear unsolvable. I therefore want to say that nuclear transfer is to be authorised, and as quickly as possible, but of course in very strictly framed conditions.

As regards your question on the international situation, I am certainly not the best placed to answer. Apart from what is happening in Korea with the present uncertainties that are certainly casting a shadow over this situation, I am referring to the ethical questions relating to ovocyte donation, on which I don't have any specific information. I believe research activity is advancing in Great Britain. American teams – especially in Boston – are working on these subjects with private funds and are advancing quite seriously. I'm unable to give an exhaustive list, but research teams are working on this subject and have or will have the knowhow in the short term to develop lines of various types which will be very useful in a very large number of research.

Mr Bertrand Jordan, research director at CNRS, adviser at Marseille-Nice Génopole

Thank you for giving me the opportunity to express myself. I am not a participator in the nuclear transposition or scientific cloning field, but rather an observer and adviser. I shall try to adopt a slightly broader perspective.

Two things appear striking to me in this field.

First the rapid progression and yet unforeseeable nature of research. Ten years ago, if we had been asked whether the reproductive cloning of mammals was possible, we would have probably nearly all answered no. A year later, Dolly was born! Two or three years ago, after the reproductive cloning of a certain number of animals, a few excellent journals published some of our results which demonstrated

that the cloning of primates would apparently be much more difficult than the cloning of other mammals and that, in all likelihood, the spectre of reproductive cloning or possibly 'therapeutic' human cloning was growing more remote, or that in any case we had more time to think about it.

Slightly one year after these articles, the first article by Hwang's team showed that it had indeed managed by nuclear transfer or transposition to obtain human blastocysts and in one case to derive ES cell lines. A year later, far more advanced work was published: this team had this time started from diseased cells and had obtained 11 lines from blastocysts.

We have therefore been contradicted several times regarding advances which appeared excluded and which have taken place. That does not mean that everything we consider as impossible today will become possible tomorrow. There are counter examples: medical advances have appeared within reach but have taken far longer to achieve than believed. This is the case with gene therapy which we imagined to be within reach 20 years ago. It has taken far longer than believed to lead to tangible results and for the moment still merely concerns a few cases. All this field is highly moving and this of course has many implications on legislative aspects and on the need for legislation to react rapidly to advances in research. This is a point that appears striking to me in this field.

The other point, which we have seen all day long, is the very great interconnection between research, ethics, politics and industry, which are extraordinarily entwined in this sector, far more than in others. For instance, the issue of the origin of ovocytes is real. I feel that, in all probability, the scandal created around the origin of the ovocytes used by the Korean team is not solely motivated by the ethical questions it can raise. It appears that this team used the ovocytes of at least one person participating in the research team and a signatory of the article. This appears morally wrong as this person may have been placed under pressure to participate in the research work. But if that's all the case boils down to, then there are no grounds for a full-blown scientific and moral scandal justifying the pillorying of Mr Hwang. Behind all this, there are apparently economic, political and scientific competition aspects that undoubtedly mean this affair has been given more importance than it actually has.

Another example is that of the issue of adult stem cells. We discussed this this morning in a rather heated but all the same quite balanced manner, while listening to one another and understanding each other. If we examine the American press, the issue of adult stem cells has become completely political. In the present state of affairs, the affirmation that they can be made to do everything that can be hoped to be done with embryonic stem cells is incorrect. It is nevertheless widely taken up in political debates on the discussion of such or such a law in the House of Representatives or the Senate.

In this sector of nuclear transposition, I feel it is extremely important to try to clearly separate what comes within the field of scientific reality and what comes within the field of politics and industry. We must try to have legislation and regulations that take account of the state of opinion at a given moment, that may possibly restrict research possibilities, and that, at the same time, should be capable of taking account of developments and adapting to advances in research.

Mr Axel Kahn, research director at Inserm, member of the steering committee: According to the old principle that it is better first to recall the state of affairs before making an ethical or moral judgment on what is to be done, I am going to recall the state of affairs internationally and scientifically.

First, in a therapeutic perspective, I feel there is no doubt that regenerative medicine based on a transfer of cells will progress and will definitely have a future, that may be brilliant, whether these cells are derived from somatic stem cells or else from embryonic stem cells. Presently, clinical trials concerning no less than a thousand patients, or in any case several hundred, are taking place with various populations of progenitor cells or somatic stem cells. Apart from what has been presented to you on the heart, trials are currently being undertaken in Japan on liver cirrhosis, in the United States, Japan and Korea, on the neurological consequences of cardiovascular accidents, and on what Christian Pinset presented to you… The interest of all this is that these results will be analysed and that in one or two years we will know what to think of them and what progress in the therapeutic field can be obtained from them in man.

Strictly speaking there have not yet been any therapeutic trials using embryonic stem cells but some will be taking place quite soon I hope, in the perspective presented to you by Philippe Ménasché this morning. Bearing in mind the extraordinarily broad number of types of cells that can be obtained, there is no reason to believe that cells derived from embryonic stem cells will not reach a level of safety such that major clinical trials can be reasonably launched.

The problems to be overcome are of three types, some already being solved.

Among these persistent difficulties, a few 'good surprises' can in a sense be found. It is first of all a matter of making sure of the non-tumorigenicty of these cells – as when they are not differentiated they are tumorigenic – or possibly of being able to protect oneself against them by introducing a gene that would allow cells that would become tumoral to be destroyed (this is one of the perspectives developed).

Then, it is a matter of comparing in the long term the function of these cells, derived *in vitro* from embryonic stem cells, with cells differentiated in a morphogenic field *in vivo.* Even if they often seem equivalent, this is worth being checked. Their durability after transfer should also be examined.

Lastly, the third element to be taken into account is that of immunological tolerance: it is generally a matter here of allotransplantation when stem cells derived from spare embryos are being spoken of. Here there are rather good surprises. We were expecting quite classical graft rejection reactions. We can't yet say that knowledge has stabilised but the good surprises are that, highly singularly, embryonic stem cells apparently have a certain immune privilege. Several experimental results show so, including those of Philippe Ménasché, and in the most amazing manner. Against all expectation, and even in xenotransplantation conditions, there is a quite singular tolerance to these cells.

That's roughly where we stand at present concerning therapeutic aims.

Where do we stand as regards nuclear transplantations and the obtaining of embryonic stem cells from embryos obtained by nuclear transfer?

You know the results obtained by the Koreans. The important questions arising concern first of all the origin of ovocytes. Ultimately, it is imagined that ovocytes will be able to be used that would not be collected after hormonal hyperstimulation of women and endovaginal ovarian puncture which is usually performed to collect ovocytes, but which could be obtained after *in vitro* mastered differentiation of embryonic stem cells. This would supply ovocytes in a theoretically unlimited number. In fact, three years ago it was shown that, in specific conditions, embryonic stem cells could differentiate into cells having many characteristics of ovocytes. One year after, we managed to obtain cells having many characteristics of spermatozoons, by *in vitro* mastered differentiation of embryonic stem cells. This material must be further tested and cannot be used today – and I don't know when it will be – as the spermatozoons are not fertilising and as the ovocyte type cells obtained do not need to be fertilised or activated to begin to divide. They undergo spontaneous parthenogenetic development. Complementary work must therefore be performed. There is a possibility that tomorrow these cells may be obtained in very large quantities, which would remove a major difficulty today. That's not the case to date.

Today, the production of embryos by somatic nucleus transfer continues to be based on the obtaining of ovocytes. Whatever developments take place, it is obvious that very close attention must be paid to the conditions in which this material is obtained. Even if the Korean colleagues have considerably improved the technique and while they show that we have a chance to obtain a line from ten or so ova, it nevertheless remains true that for many and major research studies there will be an enormous need for ova and the conditions in which they are obtained are of considerable interest and must be clarified.

The obtaining of embryonic stem cells from cloned embryos has obvious scientific interest. This interest has already been presented and is mainly of two types.

The first interest is to be able to work on 'reprogramming': this is the phenomenon by which there is a reprogramming of a somatic nucleus, initially programmed to do something entirely different from embryonic development and whose programme is erased and reprogrammed in man. It is an interesting scientific subject: bearing in mind the specific characteristics of species, this can be carried out in various species of mammals including primates and man.

The second type of interest consists in obtaining embryonic stem cells from which differentiated cells can be developed which will be characteristic of various pathological states. The day we master them, we can imagine obtaining pancreatic cells for a disease like diabetes. Today, we do not know how to do this yet but we will probably know how to when the techniques improve. Similarly, it will be possible to obtain nerve cells to follow the evolution of the characteristic disorders of a nerve degenerative disease. When all this will be mastered, perhaps the most interesting point will be to use such cells for molecular screening purposes, in other words for pharmacological purposes.

As has been said, I totally confirm that the prospects of using such cells directly for therapeutic purposes are to date uncertain and remote. That's why we ought to hesitate before speaking of somatic nucleus transfer – even if it is a good term – or else of scientific cloning. The term therapeutic cloning is certainly a bad term which must be abandoned as it bamboozles. In a sense there is no need to advance the therapeutic interest to justify the interest in authorising this.

The main doubt which means that this method is uncertain results from the fact that it is not a matter here of treating rare diseases. It is not a matter of genetic diseases, even of the type which Alain Fischer has successfully treated. We are speaking here of diseases affecting tens or hundreds of millions of people: myocardial infarction, Alzheimer's disease…. If every time a patient is treated, even with the best techniques, it is necessary to begin by obtaining ovocytes, creating a cloned embryo, isolating cells, characterising them and checking that they are not pathogenic,... this will certainly be difficult. It is to be hoped that other methods will be developed and be easier to use from this viewpoint. No doubt the most probable and realistic methods consist in deriving embryonic stem cells, even if a real problem of immune intolerance persists, but perhaps we will have a real good surprise, in other words that these cells are so well tolerated that we won't have to pay too much attention to the incompatibility of allogeneic lines.

Insofar as there are very many spare embryos, we will be able, as we do so with marrow grafts, to obtain very large quantities of embryonic stem cells characterised for histocompatibility antigenes in group HLA and use them as the basic material for any patient with equivalent tissue groups. The advantage of this is that this method is similar to a drug: products are placed in ampoules and sent from one place of the world to another. Depending on the most frequent diseases to be treated, it is even possible to begin deriving, the day when we know how to, a whole series of pancreas, liver, heart, dopaminergic cells... which will be

characterised for their functions, typed for HLA groups, and placed in sealed and sterile ampoules ready for use, meaning that we can draw closer to cell drug concepts. That's what can be hoped if we want this therapy to be really accessible to a growing number of persons.

To finish, what's my personal position as regards developments in legislation?

I was one of the very rare persons who were not initially in favour of legislation authorising this experiment involving the production of cloned embryos, for two main reasons. I have explained myself many times in this respect, so there is no secret in this respect.

First, I was shocked by the lobbying strategy presenting therapy possibilities as an obvious fact we had no choice but to agree with, possibly mobilising patients' associations. For the debate to be able to develop, I felt it was important to re-establish the situation from this viewpoint. On the other hand I have never denied the scientific interest of this method. However, the issue of ovocytes and the fear that I had that the development of this technique of obtaining embryos by somatic nucleus transfer would give the recipe to all those wishing to clone children (reproductive cloning which I am entirely opposed to), meant that, for me, the scales tipped to the side of non-authorisation of research.

There is no doubt that things have changed in a sense, not because my analysis was wrong but because things are developing the way they had to develop. A really remarkable Korean team has developed this technique and published it worldwide: this technique is now accessible to all those wishing to use it, for whatever reason, and in whatever country, whatever its legislation. I certainly do not suspect my colleagues in France of producing embryos by somatic transfer to clone babies. This situation is really new and entirely justifies that the debate be relaunched.

Mr Marc Peschanski, research director at Inserm: It is amazing that I work in tandem with Axel Kahn and that I state that I perfectly agree with him, whereas for years we have quarrelled bitterly over this legislation.

This legislation, finally, bans us from working on nuclear transfer for many years, unless by chance it is reexamined and we can really begin to speak again about sciences and the possibilities of conducting research in the usual conditions of research as regards framing and authorisation, and through the justification of our programmes and control exercised over what we are actually doing. I have defended this principled position since the outset, which guides us in general whatever activities we are undertaking. There are many other activities which are against the law when we engage in them outside this framework or on the footpath in front of our laboratory! When I had the relevant authorisation, it was possible to

work on cocaine or LSD in our laboratory. If I had gone out onto the footpath with these products in my pocket, I would have been imprisoned like anyone else.

I am pleased that Axel Kahn has become a defender of this position, that we can speak again in a single voice in the scientific community to ask for these rules to be respected, and that society has again given us, at the same time, the regulatory framework and the authorisation for research work where we respect per se the principle of respect for the living human being or the embryo becoming a human being, a being different from the cells with a human genetic heritage but which are destined for nothing but destruction.

Regarding nuclear transfer, I will adopt the viewpoint of the scientist who explains why he needs them and what he is going to try to use them for if ever he has the possibility to do so, in other words if the legislation is amended.

Nuclear transfer is the means to give an embryonic stem cells line a known, but not necessarily entirely known, genetic heritage, but which has genetic characteristics of interest to us. Of interest to us, for instance, because the genetic heritage is that of a patient affected by a disorder related to a genetic mutation (monogenic disease) or by a more widespread disease and heavily influenced by the genetic heritage he bears, for example maniac-depressive psychosis, autism, and other diseases related significantly to the genetic heritage but which are not related to a specific gene. The possibility of creating a line of embryonic stem cells having this identified genetic heritage would also allow us to have – at least theoretically – an infinite quantity of cells of any phenotype at any moment of their development or their differentiation, on which we could study the mechanisms of the disease in question and possibly try to combat them.

Through this means we would have a pathological model on which, like industry does so with chemical targets, we could use a biological target which would be a real pathological target reproducing entirely per se the genetic heritage leading to the disease in question. This would allow use of the hundreds or thousands or millions of molecules that are in the cupboards of the pharmaceutical industry, and which are brought out of them when the industry finds targets on which to test them, and the results of which are ultimately important. For instance, the anti-retroviral treatments used today to combat the AIDS virus result from this screening, in other words from the systematic testing of hundreds of thousands of molecules on an identified target, in other words one of the targets from the retrovirus.

As for embryonic stem cells that thus bear a mutation, it can be objected to us that preimplantation diagnosis exists, of which we have spoken this morning. In effect, embryonic stem cell lines derived from embryos discarded at the time of the preimplantation diagnosis can be available in laboratories – we are working in Evry on such lines thanks to a first authorisation and then a second one which has just apparently been given to us by the *ad hoc* Committee – and allow us to start

working. Preimplantation diagnosis today covers thirty or so monogenic diseases. Specialists tell us that this figure may evolve to forty or fifty diseases. There are today several thousand identified diseases – 6,000 are spoken of – related to a genetic defect of this type. We will therefore still have roughly 5,950 diseases for which we will not have access to an embryo by preimplantation diagnosis. But we can have access to an embryonic stem cells line by nuclear transposition from a patient identified as carrying the disease.

There is therefore a genuine research benefit here and possibly at a future date something which is high risk and which cannot be promised today – all we can do being to promise we will work on it –, in other words the development of a therapy.

In addition there is also another but obvious industrial use of this type of stem cells and of nuclear transposition: I am referring to the issue of predictive toxicology mentioned by David Sourdive. Today, pharmaceutical manufacturers test their drugs and cosmetic manufacturers their products on models that are more or less distant from the human situation. For various reasons, it is extremely difficult for pharmaceutical manufacturers to test their molecules on all the cells of all the tissues of the human organism. The same applies in cosmetology, as it is relatively difficult to examine in the long run the effect of creams on the skin and especially in well organised systems. It is all the more difficult to envisage this in non-pathological but different genetic heritage conditions. For instance, a person particularly sensitive to the sun, even if he is not an albino, will possibly have a reaction to a given cream. In this case, this could have been foreseen in a predictive toxicology test which today does not have any model. By means of nuclear transposition from someone presenting these characteristics in a stem cells line, with afterwards differentiation to a certain number of cells forming the skin, a model could have been tested by cosmetics manufacturers. This is obviously a matter of considerable markets. The modelisation market and the predictive toxicology market are presently genuine obstacles for the pharmaceutical and cosmetics industries, blocking the development of a large number of products. It is of capital importance to have models that are real human models on which to test these drugs or these cosmetics.

These models are also highly important for us too. The fact that the pharmaceutical industry can correctly test these drugs before putting them on the market or the fact that creams you apply to your skin do not necessarily lead to a gigantic urticaria has a therapeutic interest, even if that cannot be included as such in legislation.

I wanted to present a few examples so as to situate things as they actually are, so that, as said by Axel Kahn about science, we can consider them as application prospects. Of course I am not promising this for tomorrow. Simply, applied research, which heads towards this type of use, must be considered from now on. There isn't a fundamental research on mechanisms that should be done

immediately, and an applied research that would be postponed by legislation in order to think afterwards of the applications. These two aspects of research go together, operate parallelly and in fact feed on one another. By imposing a therapeutic goal for a serious pathology on authorisation applications for imports or for an embryonic stem cell line derivation, the legislation commits an obvious error which runs counter to the need for fundamental research. Conversely it should not be said that there is first of all fundamental research before there can be applied research: that would be equally wrong.

Mr Alain Claeys : Before giving the floor to Messrs. Sicard and Sureau, I wish to emphasise that we have spoken to one another very directly since this morning. You quite rightly sometimes levelled relevant reproaches at Parliament. These criticisms were especially judicious - and I agree with them - on a point of Article 25 of the Act, in other words the fact that research protocols are accepted if they have therapeutic applications. Let me return the question to you. Why, to justify nuclear transposition, do some members of the scientific community - including professors of medicine who are receiving great publicity -, always speak of therapeutic cloning? As a parliamentarian, I find it scandalous to say that there will be therapeutic applications tomorrow. I have often discussed this with Axel Kahn: this was one of the reasons which made me question myself about nuclear transposition. Why was the the scientific community so lax as to announce that therapeutic applications were for tomorrow? I perfectly agree with what Marc Peschanski has just said. As researchers, when you heard of therapeutic cloning, didn't that bother you?

Mr Philippe Ménasché: Of course it did. Unfortunately the term of therapeutic cloning came into being a few years ago to set reproductive cloning in opposition with cloning that would not have a reproductive purpose. The unfortunate term of therapeutic cloning was found. All those who really work in the stem cells field have since the beginning said that it was absurd to add the epithet 'therapeutic' which to date has not been validated by any experimental work. Unfortunately it sounds good and it must be admitted that the media have amplified this phenomenon because it is the stuff of dreams.

Mr Alain Claeys: The media should not be blamed for transcribing what they hear from the mouths of acknowledged researchers and doctors who no later than this weekend published texts in mass publication newspapers!

Mr Philippe Ménasché: I'm not blaming the media. I'm simply saying that as this term fosters hope, it is more easily amplified and it is then extremely difficult – Axel Kahn, Marc Peschanski and Alain Fischer know this well – to backtrack and permanently explain what we are doing. To date, no serious preclinical experiment has validated the fact that cloning would really have therapeutic effects. Once again, I don't think that the poeple working in this field have ever claimed that cloning would have therapeutic effects.

Mr Alain Claeys: It is absolutely necessary to educate Parliament and explain to it every day that fundamental research is not shameful!

Mr Axel Kahn: I wish to add a small detail. I am the scientific adviser for biology at Oréal. When it comes to testing products on skin, there is no problem: African, Asian, albino, etc. skin can be created, as skin stem cells are well known. If there is one indication for which we will not need embryonic stem cells, it will be to produce skin Skin rebuilt this way is capable of tanning, presenting inflammatory reactions... I agree with Marc Peschanski for the rest.

To return to your question, since you blamed us for something, I'm going to blame you for something! I was a member of the Ethics Committee until recently, and I remember one day when, as one of the speakers on the rostrum, I happened to be next to the Prime Minister. The latter announced that the legislation was going to authorise these 'so promising cells of hope'... It was at that moment that I felt very shocked, saying to myself that, whatever is decided, everything was justifiable. I am deeply a man of debate: for the debate to take place, the question must be raised. Admittedly, scientists are guilty, but it is a situation involving three players: scientists, politicians and the media.

Mr Hervé Chneiweiss: I cannot but pursue in Axel Kahn's direction.

Unfortunately, a utilitarian approach is prevailing which arose with genomics and large-scale biology, when our American colleagues launched in 1969 the great human genome programme as the new ambition after man had walked on the Moon. They did not sell it as knowledge of the human genome but as a new frontier to cure cancer. From then on there was a kind of snowballing which meant that, in any scientific article, authors have begun or finished by justifying their work by a pathology. There is also a game with respect to the various public representations, the media or politicians, to try and justify the underlying idea crossing through all political parties that pure scientific knowledge is something noble but which is not necessarily worth a fight vis-à-vis moral beliefs deeply rooted in the history of a country. It has sometimes appeared easier to some to defend utilitarian positions. When, with a certain courage, the Prime Minister in question used the appropriate scientific terms, he was 'corrected' by some scientists who advised him to us ordinary language.

Mr Alain Claeys: That's how History is written.

Mr Alain Fischer: I naturally agree on the fact that a certain number of scientific expressions or doctors are not really acceptable and 'sell' in the very short term progress which does not exist. On the other hand, I don't absolutely agree with – if I have understood it well – the interpretation you give of it, consisting in saying that, since we are in a context in which we are told codswallop, there is therefore no reason to take an interest in the subject.

Mr Alain Claeys: Let me stop you straight away. I think that calling nuclear transposition fundamental research is enough to justify it.

Mr Alain Fischer: I have nevertheless heard that for a certain length of time - and I was led to believe that for a moment this was Axel Kahn's position -, some have believed that since they were being sold promises that were not serious, this approach could not be considered seriously. In a sense, this reasoning can be acceptable, but it is absolutely not specific to nuclear transplantation. In a field that I know well, gene therapy, we have heard remarks that are just as scandalous repeated a great number of times, but that hasn't brought about a ban on gene therapy research, fortunately! Our role as scientists is of course to control our remarks but some expressions are diehard. What Hervé Chneiweiss said is fairly correct regarding the trend to want to justify any research in a utilitarian manner. Even if we don't always manage to do so, it is our duty to try and avoid this. It is also your duty as politicians, and the media's duty, to sort matters out and nevertheless consider in a field under discussion what can be interesting.

Mr Didier Sicard, chair of the National Consultative Ethics Committee: I chair the committee but do not represent it here. Moreover, three or four years ago it expressed itself as a majority in favour of cloning.

I would level the same reproach at scientists as you, by referring them to Parliament, as you have enshrined in legislation, and I share Marc Peschanski's opinion, the therapeutic obligation of work on the embryo. Parliament is the first to have laid down a therapeutic obligation to work on the embryo. We are faced with a quality of scientists, with Korean discoveries and with the need of biotechnology companies to receive money and invest. What is ethics in this field? It is a background noise that would like to think of itself as bearing a virtue and a human truth. Ethics obviously merely allow us to question ourselves. Basically, the success of a therapeutic cloning on the industrial plane forms a paradox because even if we manage to circumvent the ovocyte market, it cannot be regulated. Because from the moment it becomes a therapeutic process for diabetics and Parkinson's sufferers, and from the moment that cell therapy becomes an antibiotic and antihypertensive therapy, women will inevitably be the subject of merchandising.

In other words, legislation will not be able to do anything. We can see, worldwide, that the merchandising of living organisms is one thousand times greater than in France which is still one of the few countries to have banned it very formally.

We are aware of this semantic debate. Indeed if we had announced straightaway that nuclear transfer was aimed at better understanding the beginning of some metabolic or genetic diseases and living organisms, I feel there would not be the society obstacles, there would be no debate on ovocytes which we are trying

to frame by means of legislation or by creating stem cells leading to ovocytes so as to avoid the use of women. It is worrisome to note that most countries, especially in Asia, do not consider this subject a problem. However I feel it does remain an existential problem for humanity. Considering that it is not an ethical issue or sweeping it aside legally or opportunistically, continues to be a source of concern.

If we manage to make cloning an industrial process to screen antibiotics, antivirals and antihypertensives, or to test creams, in other words if cell therapy becomes *the* therapy pathway, its success would then be faced with a dead end.

There remains so much work to be done on cell therapy with embryonic and adult stem cells. From the moment that cloning is aimed at repairing one person and not ten, it can be imagined that this therapy, using one's own cells, has a major future. I feel that preimplantation diagnosis is still limited, but it isn't necessary to work on the 4,953 genetic diseases straightaway. We are moreover struck by the haste of some in announcing results at all costs.

Cell therapy must not enclose itself in a universal therapeutic project for most human diseases, which appears frightening to me in its very concept whereas other promising pathways exist. Ethics are indeed derisory in this field. I can't stand José Bové's discourse on GMOs, but the same reproach could be levelled at me by telling me that I am brandishing a kind of human apocalypse via this thinking. My feeling reflects an irreversible distress because it is necessary to act with prudence. Both technologies are not only centered on these issues.

Mr Claude Sureau: First, I am not as distressed as Didier Sicard but rather optimistic by nature.

I am going to recall an event that took place in 2002. A great number of persons present here were participating in a symposium on cell lines organised jointly by the Académies des sciences, represented by Jean-François Bach, and the Académies de médecine, which I represented. This symposium led to both Académies adopting an extremely strong and clear stance in favour of research on embryonic cells obtained from spare embryos left over from *in vitro* fertilisation, but also in favour of nuclear transfer. Why did the Académie de médecine, deemed very conservative, adopt this stance? Apart from the general interest and the therapeutic benefit for some pathologies, which were mentioned this morning, it retained the improvement of the conditions of medically assisted procreation and of embryo medicine.

For, to a certain extent, we have completely forgotten the object of the 1994 Act: improving procreation conditions thanks to medically assisted procreation. This element has disappeared, whereas regarding the freezing of ovocytes major advances remain to be obtained.

Embryo medicine, for its part, has evolved and benefited from the impetus given by Georges David who insists on the need to develop it. It is, according to his terms, a fundamental concept, for us, obstetricians who are aware of a dramatic drift in society. In effect, owing to the ever stronger means of investigation, diagnoses of real or supposed pathologies of the embryo and fœtus are increasingly forcing us to become 'the garbage collectors of society'. That is what we are asked to do and yet we are criticised. It's a dramatic situation which will automatically get worse as the diagnosis methods get better. The sole means of avoiding this dangerous evolution is to strengthen research on the embryo and embryonic cells, a stance we have adopted at the Académie.

Embryo medicine is not just a part of medicine in general applied to the embryo, as it has a specific characteristic which supposes the destruction of embryos for this research to be effective and for it to make progress. Embryos like foetuses are like patients for us but we accept the possibility of destroying them.

Basically, we are in favour of research on embryos, whether they are spare because they do not have a fate, or pathological and must be destroyed.

In this respect, a point remains to be clarified on the philosophical, ideological or even religious planes.

Opinions are quite divergent. A very important person at the Académie pointed out to me that an *in vitro* embryo is no longer more than a red globule. I don't share the opinion of those who believe that *in vitro* embryos are merely masses of cells without consistence or dignity. Contrary to the opinion of the Constitutional Council of 27 July 1994, I personally feel that the *in vitro* embryo possesses an important personal ontological value. I personally think that it is legitimate to disregard the protection which the law grants it in accordance with Article 16 of the Civil Code, for reasons acknowledged as valid, whether individual reasons in the case of extrauterine pregnancies or collective reasons like research.

We are also entirely in favour of nuclear transposition and insist on the need for it. We were not lucky because the evolution to therapeutic nuclear transposition occurred after reproductive cloning. Let's imagine that in 1997 reproductive cloning had not been discovered with Dolly the lamb, that we had to wait ten years and that, in the meanwhile, we discovered nuclear transfer application possibilities. Nobody would then have raised the question of the likening of the two concepts.

Lastly, I don't believe I have found in the legislation an allusion to research on gametes and ovocytes, which is nevertheless necessary to my mind. That would however be extremely useful to us. In that framework we could envisage the modification of the genetic heritage of gametes. Even if Article 13 of the Oviedo Convention opposes this, Article 16.4 of the Civil Code acknowledges the

legitimacy of this research insofar as it would help avoid the appearance of congenital anomalies.

The embryo for research is a thorny subject profoundly disturbing the community of scientists and parliamentarians and jurists as a whole.

Is it legitimate to ban the production of embryos for research?

That is what is envisaged by legislation, in accordance with Article 18 of the Oviedo Convention, and which appears to me to be a major conceptual error, which moreover has been avoided by the English who are more pragmatic. Leaving aside experimental teratology which is to be dismissed, let's suppose that progress is made with the freezing of ovocytes and that we envisage their subsequent fertilisation. We would obtain an embryo which we would not transfer because it could be pathological, but which we would study. What else would we have made but an embryo for research? The legislation contains shortcomings in this sense which the English have avoided. Parallelly, we answered negatively when we were consulted to get our approval on the implementing decrees being drafted for the Act. We indeed deplore the absence of a paragraph on studies that do not jeopardise the embryo but which can lead to a transfer of the embryo. It would be considerably useful, in accordance with a perfectly defined and extremely closely monitored protocol, to encourage progress that would in particular serve to improve *in vitro* fertilisation.

Referring to the rarity of ovocytes, we will sooner or later manage to produce an artificial meiosis and obtain artificial gametes from somatic cells with n chromosomes. The situation will then be profoundly modified as definitive sterilities will be solved and the reproductive cloning quarrel will thus be emptied of its substance.

Mr Hervé Chneiweiss: The scientific and medical community as well as Parliament must squarely face the situation, explaining what has changed to citizens.

A proposal has recently been made by a famous embryologist, Rudolf Jaenisch, and taken up by a member of the President of the United States' Ethics Committee. It is a matter of making the *in vitro* embryo non-implantable by adding to nuclear transposition a siRNA gene making it impossible to implant the embryo. As stated by Marc Peschanski, do we really need this technical artifice to respect legislation and the scientific goal? I hope not and we'll need a lot of courage to pursue our scientific project and the goal of deriving lines.

Mr Alain Claeys: The National Assembly Bureau decided to entrust this study to the POSTA owing to the subjects still unsettled by the August 2004 Act. Referring to this Act which is a necessity for us all, a few urgent matters are to be addressed.

First, the implementing decrees must appear and must not make some Articles of the Act any more complex. Indeed if we tighten up any more the notion of the therapeutic goal of scientific projects, we are likely to give rise to a system where no research protocol would be accepted any longer. We must ensure that the publication of the decrees takes place rapidly and in the best conditions.

I am also concerned by the situation at the Biomedicine Agency, of which I greatly regret the absence despite the presence of a representative, Mrs Ott. She must be able to appraise as quickly as possible these research dossiers as there is no longer any structure capable of doing so presently. It would be a year lost for some teams.

Lastly, it is not the legislative rule but the environment that poses problems for us to participate in European invitation to tenders or set up international stem cell banks. We must therefore provide clarifications as this is essential.

Not only for parliamentarians but also for the press, our exchanges today have allowed us to precisely review the situation of fundamental research and of the therapeutic hopes while replacing the debates in the real situation and not in a fantasy world.

I am convinced that if this debate is not partisan today, Parliament will be able to advance. This must take place in full transparency as there are no oppositions between Parliament and the scientific community, nor with patients' associations. As regards international advances, we must, when the time comes, take our responsibilities in order to cross a new step.

The Office will work as quickly as possible and we hope, thanks to this report, to provide answers and propose some to Parliament because it is Parliament which will decide a certain number of advances by taking into account your experiments and analyses, and the positions of associations, of the Ethics Committee and of the Académies.

Thank you.

Annexes

Annex 1:
Article 25 of Act no. 2004-800 of 6 August 2004 on bioethics

I. - Title V of Book I of the second part of the Public Health Code becomes Title VI and Articles L. 2151-1 to L. 2153-2 become Articles L. 2161-1 to L. 2163-2.

II. - A new Title V of Book I of the second part of said code is drafted as follows:

TITLE V

RESEARCH ON THE EMBRYO AND ON EMBRYONIC CELLS

SINGLE chapter

'Art. L. 2151-1. - As stated in the third paragraph of Article 16-4 of the Civil Code reproduced hereafter:

'Art. 16-4 (third paragraph). - Any intervention having the purpose of causing the birth of a child genetically identical to another person alive or dead is forbidden'.

'Art. L. 2151-2. - The in vitro conception of an embryo or the creation by cloning of a human embryo for research purposes is banned.

'Art. L. 2151-3. - A human embryo cannot be conceived or created by cloning, or used, for commercial or industrial purposes.

'Art. L. 2151-4. - It is also banned to create by cloning a human embryo for therapeutic purposes.

'Art. L. 2151-5. - Research on the human embryo is banned.

'Exceptionally, when the man and woman forming a couple give their consent, studies that do not jeopoardise the embryo can be authorised subject to compliance with the conditions laid down in the fourth, fifth, sixth and seventh paragraphs.

'In derogation from the first paragraph, and for a period limited to five years from the publication of the decree at the State Council as laid down in Article L.

2151-8, research can be authorised on the embryo and on embryonic cells when it is likely to allow major therapeutic progress and provided it cannot be pursued by an alternative method of comparable efficacy in the present state of scientific knowledge. Research whose protocols have been authorised in this five year period and which has not been able to be completed in the framework of said protocol can nevertheless be pursued in compliance with the conditions of this Article, especially regarding its authorisation regime.

'Research can be performed only on embryos conceived in vitro in the framework of medically assisted procreation, which are no longer required for fertility treatment purposes. It can be performed only with the prior written consent of the couple donating them, or of the surviving partner of said couple, who must moreover be duly informed about the possibility of another couple using the embryos or about the possibility of stopping their storage. Except for the situations mentioned in the last paragraph of Article L. 2131-4 and in the third paragraph of Article L. 2141-3, the consent must be confirmed following a three month reflection period. In all cases, consent by both partners of the couple can be rescinded at any time and without justification.

'Research cannot be performed unless its protocol has been authorised by the Biomedicine Agency. The authorisation decision is taken on the basis of the scientific relevance of the research project, the conditions of its implementation with regard to ethical principles and its interest for public health. The agency's decision, along with the opinion of the steering board, is transmitted to the ministers for health and research who, when the decision authorises a protocol, can ban or suspend the execution of said protocol when its scientific relevance is not established or when compliance with ethical principles is not ensured.

'In the event of an infringement of the legislative and regulatory provisions or those laid down by the authorisation, the agency suspends the research authorisation or withdraws it. The ministers for health and research can, in the event of a refusal of a research protocol by the agency, ask the latter, in the interest of public health or of scientific research, to carry out within a thirty day period a new examination of the dossier that served as a basis for the decision.

'Embryos on which research has been performed cannot be transferred for gestation.

'Art. L. 2151-6. - The import of embryonic or foetal tissues or cells for research purposes is subject to the prior authorisation of the Biomedicine Agency. This authorisation cannot be granted unless these tissues or cells have been obtained in compliance with the fundamental principles laid down in Articles 16 to 16-8 of the Civil Code.

'The export of embryonic or foetal tissues or cells for research purposes is subject to the same conditions as their import, as defined in the previous paragraph. It is also conditional on the participation of a French research organism in the international research programme.

'Art. L. 2151-7. - Any organism ensuring the storage, for scientific purposes, of embryonic stem cells must hold an authorisation issued by the Biomedicine Agency.

'Issue of the authorisation is subject to compliance with: the provisions of Title I of Book II of the first part of this code; the rules in force as regards the safety of persons exercising a professional activity on the site; the provisions applying as regards environmental protection; and also health safety rules.

'In the event of non-compliance with the provisions mentioned in the second paragraph, the Biomedicine Agency can, at any moment, suspend or withdraw the authorisation.

'The Agence française de sécurité sanitaire des produits de santé (French Health Products Safety Agency), is informed of stem cell storage activities for scientific purposes carried out at the same site as the activities authorised by it pursuant to Articles L. 1243-2 and L. 1243-5.

'The organisms mentioned in the first paragraph can transfer embryonic stem cells only to an organism holding an authorisation issued pursuant to this Article or Article L. 2151-5. The Biomedicine Agency is previously informed of any transfer.

'Art. L. 2151-8. - The implementing procedures of this chapter are laid down by a State Council decree, especially the conditions for authorising and implementing research on human embryos.'

Annex 2:
Decree no 2006-121 of 6 February 2006 on research on the embryo and on embryonic cells and amending the Public Health Code

The Prime Minister,

Following the report of the minister for health and solidarities,
In the light of the Civil Code, and especially its Articles 16 to 16-8;
In the light of the Public Health Code, and especially its Articles L. 2151-5 to L. 2151-8;
In the light of the Customs Code;
In the light of the amended Act no. 78-17 of 6 January 1978 on data processing, files and freedoms;
In the light of Act no. 2000-321 of 12 April 2000 on citizens' rights in their relations with the administration;
In the light of Act no. 2004-800 of 6 August 2004 on bioethics, especially its Article 37;
The State Council (social section) having been heard,

Decrees:

Article 1

I. - Title V of Book I of the second part of the Public Health Code (regulatory provisions) becomes Title VI.

II. - Title V of Book I of the second part of said code is drafted as follows:

'TITLE V

'RESEARCH ON THE EMBRYO

AND ON EMBRYONIC CELLS

'Single chapter

'Section 1
'Implementation of research

'Art. R. 2151-1. - Are in particular likely to allow major therapeutic progress, in the sense of Article L. 2151-5, research on the embryo and embryonic cells pursuing a therapeutic goal for the treatment of particularly serious or incurable disaeses, as well as for the treatment of disorders of the embryo or foetus.

'Art. R. 2151-2. - The director general of the Biomedicine Agency can authorise a research protoocl on the embryo or embryonic cells, after obtaining the opinion of the steering board, for a given period which cannot exceed five years.

'Apart from checking the conditions laid down in Article L. 2151-5, the Biomedicine Agency makes sure of the feasibility of the protocol and the perenniality of the research organism and team. It takes into consideration the titles, diplomas, and experience and scientific work of the research officer and of the members of the team. In addition, the Biomedicine Agency takes account of the premises, material and equipment, as well as of the processes and techniques implemented by the applicant. It assesses the means and arrangements guaranteeing the safety, quality and traceability of embryos and embryonic cells.

'Art. R. 2151-3. - I. - Only the following can obtain authorisation to perform research on the embryo:

'1° Public health establishments and medical biology analyses laboratories authorised to store embryos pursuant to Article L. 2142-1, as well as establishments authorised to practice biological diagnosis using cells taken from the embryo in vitro pursuant to Article L. 2131-4;

'2° Establishments and organisms having concluded an agreeement with at least one of the establishments or laboratories mentioned in 1°. This agreement lays down the conditions in which the establishments or laboratories mentioned in 1° store embryos and make them available for these establishments or organisms. The authorisation for making embryos available is valid only for the length of the research.

'II. - Only the following can obtain authorisation to perform research on embryonic cells:

'1° Establishments and organisms pursuing a research activity and holders of the authorisation to store embryonic stem cells for scientific purposes as mentioned in Article L. 2151-7 ;

'2° Public and private establishments and organisms pursuing a research activity and having concluded an agreement with an establishment or organism mentioned in 1° in which the latter undertakes to supply and store emrbyonic stem cells for the former to pursue research..

'Art. R. 2151-4. - I. - The consent of the couple, or of the surviving partner of a couple, as laid down in Article L. 2151-5, is obtained in accordance with one of the following procedures:

'1° When the couple no longer has fertility treatment plans, the practitioner authorised pursuant to Article L. 2142-1-1 can propose to both partners of the couple or, in the event of the death of one of them, to the surviving partner, to consent to the stored embryos being used for research, after informing them of the possibilities of these embryos being used by another couple or their storage being stopped. They confirm their consent by writing to this practitioner following a three month reflection period.

'2° If, after performance of the biological diagnosis using cells taken from the embryo in vitro, it turns out that the embryos carry the sought anomaly, the practitioner authorised pursuant to Article L. 2131-4-2 to carry out this diagnosis can propose to both partners of the couple or the surviving partner to consent in writing that these embryos may be subject of research provided they are no longer required for fertility treatment purposes.

'3° When, for the implementation of medically assisted procreation, the couple gives its consent to the practitioner authorised pursuant to Article L. 2142-1-1 to perform in vitro fertilisation, with or without micro-manipulation, it may be asked, pursuant to Article L. 2141-3, to give its consent at the same time in writing to research on embryos that could not be transferred or stored.

'II. - The research officer must be able to justify at any moment during research that he has made sure of the existence of the consent mentioned in I.

'Art. R. 2151-5. - Embryos can be given to the research officer mentioned in Article R. 2151-8 only by practitioners authorised under Article L. 2142-1-1 or Article L. 2131-4-2. This officer must produce the research protocol authorisation. The authorised practitioner hands him the document testifying to the collection of the consents mentioned in Article R. 2151-4.

'Embryonic cells are handed to the research officer by the holder of the import authorisation laid down in Article L. 2151-6 or the storage authorisation laid down in Article L. 2151-7 upon production of the documents mentioned in the previous paragraph.

'The research officer cannot be given any information allowing identification of the couple or surviving partner of the couple donating the embryos that are the subject of the research.

'Art. R. 2151-6. - The authorisation application for a research protocol on an embryo or embryonic cells is sent to the director general of the Biomedicine Agency by return-receipt mail or handed over likewise at the agency against a receipt. This application is accompanied by a dossier whose form and content are fixed by a decision of the agency's director general.

'The director general also fixes the periods during which authorisation application dossiers can be handed in. The closure date of these periods represents the beginning of the four month period mentioned below.

'When items essential to appraise the application are lacking, the return-receipt states the time period during which these items must be supplied.

'In the four month period following the closure date of the period during which the complete dossier has been handed in, the director general of the Biomedicine Agency notifies the applicant establishment or organism

of the authorisation decision or refusal. After this period, the absence of a decision from the director general is tantamount to an implicit refusal of authorisation.

'The director general's decision granting the research authorisation mentions the name of the research officer. This decision is published in the Official Gazette of the French Republic.

'The agency director general can ask by a return-receipt registered letter for any complementary information he feels necessary to appraise the authorisation dossier. He informs the applicant of the period during which he must supply these elements. This request for complementary information suspends the time period mentioned in the fourth paragraph.

'Art. R. 2151-7. - The decision of the director general and the opinion of the steering board are transmitted simultaneously to the ministers for health and research who, if they feel it necessary, have a one month period to:

'1° Suspend or withdraw the authorisation in accordance with proceedings involving the hearing of both parties, pursuant to the fifth paragraph of Article L. 2151-5;

'2° Ask for a new examination of the authorisation application dossier, pursuant to the sixth paragraph of Article L. 2151-5, in the event of a refusal of the Biomedicine Agency.

'Art. R. 2151-8. - Any research authorised under Article L. 2151-5 is placed under the management of a research officer designated by the application and mentioned in Article R. 2151-6.

'The research officer sends the director general of the Biomedicine Agency an annual report. He sends him the final research report as soon the research is completed. These reports contain in particular information on the fate of the embryos and embryonic cells that are the subject of the protocol, and especially on their destruction.

'The agency director general can at any moment ask the research officer to report on work progress.

'Art. R. 2151-9. - Any establishment or organism wishing to modify a substantive element of the protocol authorised pursuant to Article L. 2151-5 must hand in a new authorisation application dossier. The latter is appraised in like manner to the initial application.

'Art. R. 2151-10. - In the event of the infringement of the legislative or regulatory provisions or of requirements laid down by the authorisation, the latter can be suspended at any time for a maximum of three months by the director general of the Biomedicine Agency, who informs the steering board thereof in the shortest lapse of time. The authorisation can also be withdrawn after obtaining the opinion of the steering board. The director general's decision is notified to the holder of the authorisation and transmitted to the ministers for health and research.

'Before any decision to suspend or withdraw the authorisation, the holder of the authorisation is ordered to put an end to his shortcomings or present his remarks in a period stated by the director general.

'Art. R. 2151-11. - I. - Establishments and organisms authorised under the first and third sections of this chapter keep a register of the embryos and embryonic cells they hold.

'This register mentions:

'1° The organism that supplied the embryos or embryonic cells and their identification code after anonymisation;

'2° The heading of the research protocol;

'3° The name of the research officer or of the storage activity;

'4° The number of embryos and embryonic cell lines that are the subject of research;

'5° The number and designation of the embryonic stem cell lines stored or obtained during research;

'6° The results of the analyses concerning infection biological markers;

'7° The place(s) of research and storage;

'8° The fate of the embryos and embryonic cells: research, transfer or destruction.

'The research or storage officer is tasked with keeping this register. He makes sure of the exactness of the information recorded in the register and also ensures it is kept in safety conditions guaranteeing its integrity and confidentiality.

'II. - The Biomedicine Agency keeps a national register of embryos and embryonic cells, comprising in particular:

'1° The authorisation numbers and the names of establishments or organisms authorised to perform research or store embryonic stem cells;

'2° The name of the research or storage officer;

'3° The heading of the research protocol;

'4° The number of embryos and embryonic cell lines that are the subject of research and their identification code;

'5° The number and designation of the embryonic stem cell lines stored or obtained during research;

'6° The results of the analyses concerning infection biological markers;

'7° The place(s) of research and storage;

'8° The fate of the embryos and embryonic cells: research, transfer or destruction.

'At the time of the annual report laid down in Article R. 2151-8 the research or storage officer sends the director general of the Biomedicine Agency the necessary information for him to keep the national register up to date.

'The identification code given to each embryo, listed in the above mentioned registers, and given to each line of embryonic cells derived from them, is established and made anonymous in accordance with a coding system defined by a decision of the director general of the agency following the opinion of the National Data Processing and Liberties Commission (CNIL).

'The anonymisation of the code is reversible so as, where applicable, to have access to the data allowing the persons donating the embryo to be identified when required by medical or health safety reasons.

'Art. R. 2151-12. - Any establishment or organism performing research on embryos or embryonic cells is obliged to keep for ten years from the end of said research the protocol laid down in Article L. 2151-5, the document testifying to compliance with the conditions laid down in Article R. 2151-4 and the final research report and register mentioned in Article R. 2151-11.

'Section 2
'Import and export of embryonic or foetal tissues or cells for research purposes

'Art. R. 2151-13. - By embryonic or foetal tissues or cells the following is meant in the following section:

'- Embryonic or foetal tissues or cells taken or collected after the termination of a pregnancy;

'- Embryonic cells collected from human embryos in vitro which have been conceived in the framework of medically assisted procreation and which are no longer required for fertility treatment purposes.

'Any organism importing or exporting embryonic or foetal tissues or cells mentioned in this Article must be in a position to justify that they have been obtained in compliance with the principles laid down in Articles 16 to 16-8 of the Civil Code, with the prior consent of the woman having undergone a termination of pregnancy or of the parental couple in the case of medically assisted procreation, and without any payment of whatever form being granted to them.

'Art. R. 2151-14. - Only the following organisms can obtain an authorisation to import or export embryonic or foetal tissues or cells for research purposes:

'1° Holders of the authorisation to perform research on the embryo and embryonic cells, as laid down in Article L. 2151-5;

'2° Holders of the authorisation to store embryonic stem cells, as laid down in Article L. 2151-7;

'3° That have filed a research protocol on embryonic or foetal tissues or cells taken or collected after a termination of preganancy pursuant to Article L. 1241-5.

'Art. R. 2151-15. - The director general of the Biomedicine Agency authorises the import and export of embryonic or foetal tissues or cells for research purposes after obtaining the opinion of the steering board. This authorisation is valid for one year.

'This authorisation is issued for each operation envisaged and comprises the information mentioned in Article R. 2151-16.

'The provisions of Articles R. 2151-6, R. 2151-9, R. 2151-10 and R. 2151-12 apply to the authorisations laid down in this section.

'Art. R. 2151-16. - Any import or export operation for research purposes, excluding transit and carriage through the customs territory on the occasion of a transfer between two Member States of the European Community, of embryonic or foetal tissues or cells defined in Article R. 2151-13 is subject to the statement on the external packaging of the following information:

'1° The statement 'embryonic or foetal tissues or cells';

'2° The designation of the tissues or cells concerned;

'3° The use for which these tissues or cells are intended;

'4° For imports, the name and address of the supplier foreign organism, of the organism authorised to import and of the consignee;

'5° For exports, the name and address of the organism authorised to export and of the consignee.

'Art. R. 2151-17. - Any incident occurring during the transport of embryonic or foetal tissues or cells must be the subject of a declaration to the director general of the Biomedicine Agency by the holder of the import or export authorisation.

'In the event of an incident likely to affect health safety, the director general of the Biomedicine Agency immediately informs thereof the director general of the AFSSAPS (French Health Products Safety Agency) and the minister for health.

'Section 3
'Storage of embryonic stem cells for scientific purposes

'Art. R. 2151-18. - Any organism storing embryonic stem cells for scientific purposes must be in a position to justify that they have been obtained in compliance with the fundamenal principles laid down in Articles 16 to 16-8 of the Civil Code and with the prior consent of the parental couple and without any payment of whatever form having been granted to them. It must be able to justify that it has made sure of this.

'Art. R. 2151-19. - The Director General of the Biomedicine Agency authorises the storage of embryonic stem cells, after obtaining the opinion of the steering board, for a determined period which cannot exceed five years. The authorisation mentions the name of the storage officer.

'Prior to the director general's decision, the Biomedicine Agency assesses the storage implementation conditions.

'For this purpose, the agency checks in particular that the supply and storage conditions of embryonic stem cells present sufficient guarantees to ensure compliance with the provisions of Title I of Book II of the first part of this code, with the rules in force as regards the safety of persons engaging in a professional activity on the site, and with the provisions applying with regard to environmental protection.

'The agency makes sure of the competence of the team tasked with storage. It takes into consideration the titles, diplomas, experience and scientific work by the members of the team. In addition, the Biomedicine Agency takes account of the premises, material and equipment, as well as of the processes and techniques implemented by the applicant. It assesses the means and systems implemented to assure the safety, quality and traceability of embryonic stem cells.

'When the organism applying for a storage authorisation exercises simultaneously at the same site activities laid down in Articles L. 1243-2 and L. 1243-5, the director general checks that the organism has planned for procedures guaranteeing against any risk of contamination.

'Art. R. 2151-20. - The provisions of Articles R. 2151-6 and R. 2151-8 to R. 2151-12 apply to the authorisations laid down in this section.

'Art. R. 2151-21. - When he withdraws an embryonic stem cells storage authorisation, the director general of the Biomedicine Agency organises the transfer of these cells to another organism authorised to store them.

'In the event of an incident likely to affect health safety, the director general of the Biomedicine Agency immediately informs thereof the director general of the French Health Products Safety Agency.

Article 2

The authorisations issued pursuant to decree no. 2004-1024 of 28 September 2004 on the import for research purposes of embryonic stem cells, on research protocols and on the storage of these cells and implementing the provisions of Article 37 of Act no. 2004-800 of 6 August 2004 on bioethics are maintained until their expiry. From the date of publication of this decree, these authorisations are governed by the provisions of the latter, except for the provisions of Articles R. 2151-2, R. 2151-6, R. 2151-7 and R. 2151-19 of the Public Health Code.

Article 3

Decree no. 2004-1024 of 28 September 2004 on the import for research purposes of embryonic stem cells, on research protocols and on the storage of these cells and implementing the provisions of Article 37 of Act no. 2004-800 of 6 August 2004 on bioethics is repealed.

However:

- Authorisation applications appraised on the date of publication of this decree by the 'ad hoc committee' laid down by Article 37 of Act no. 2004-800 of 6 August 2004 on bioethics are the subject of a decision by the ministers for health and research in the conditions laid own by this Article and by decree no. 2004-1024 of 28 September 2004 adopted for its implementation;

- Applications filed at the 'ad hoc committee' and not yet appraised on the date of publication of this decree are transmitted to the Biomedicine Agency to be appraised and to be the subject of a decision in accordance with the rules laid down by this decree.

Article 4

The minister for national education, higher education and research, the minister for health and solidarities and the minister delegate for higher education and research are tasked, each to the extent of his responsibility, with the implementation of this decee which will be published in the Offical Gazette of the French Republic.

Done in Paris, 6 February 2006.

Dominique de Villepin

By the Prime Minister:

The minister for health and solidarities,

Xavier Bertrand

The minister for national education, higher education and research,

Gilles de Robien

The minister delegate for higher education and research,

François Goulard

Annex 3:
Article 19 of the bill on bioethics adopted by the National Assembly at first reading on 22 January 2002

Article 19

I. - Title V of Book I of the second part of the Public Health Code becomes Title VI and Articles L. 2151-1 to L. 2153-2 become Articles L. 2161-1 to L. 2163-2.

II. - A new Title V of Book I of the second part of said code is drafted as follows:

'TITLE V

'RESEARCH ON THE EMBRYO AND EMBRYONIC CELLS

'Single chapter

'Art. L. 2151-1. - As stated in the third paragraph of Article 16-4 of the Civil Code reproduced hereafter:

' "*Art. 16-4 (third paragraph)* - Any intervention having the purpose of causing the birth of a child or the development of a human embryo not direclty generated by the gametes of a man and a woman is forbidden."

'Art. L. 2151-2. - The *in vitro* conception of human embryos for research purposes is banned, without prejudice to the provisions laid down in Article L. 2141-1-1.

'Art. L. 2151-3. - Research on the human embryo and embryonic cells is authorised that has a medical purpose, on condition that it cannot be pursued by an alternative method of comparable efficacy in the present state of scientific knowledge.

'Research can be performed only on embryos conceived in vitro in the framework of medically assisted procreation and which are no longer required for fertility treatment purposes. It can be performed, after a three month reflection period, only with the prior written consent of the couple donating them, or of the surviving partner of said couple, who must moreover be duly informed about the possibility of another couple using the embryos or about the possibility of stopping their storage. Embryos on which research has been performed cannot be transferred for gestation. In all cases, consent by both partners of the couple can be rescinded at any time and without justification.

'Research cannot be performed unless its protocol has been authorised by the Procreation, Embryology and Human Genetics Agency (Apegh). The authorisation decision is taken on the basis of the scientific relevance of the research project, the conditions of its implementation with regard to ethical principles and its interest for public health. The agency transmits these protocols to the ministers for health and research who can, jointly, ban or suspend the execution of these protocols when their scientific relevance is not established or when compliance with ethical principles is not ensured.

'In the event of an infringement of the legislative and regulatory provisions or those laid down by the authorisation, the agency suspends the research authorisation or withdraws it. The ministers for health and research can, in the event of a refusal of a research protocol by the agency, ask the latter, in the interest of public health or of scientific research, to carry out within a thirty day period a new examination of the dossier that served as a basis for the decision.

'Art. L. 2151-3-1 (new). - The import of embryonic or foetal tissues or cells is subject to the prior authorisation of the minister for research. This authorisation cannot be granted unless these tissues or cells were obtained in compliance with the fundamental principles laid down by Articles 16 to 16-8 of the Civil Code.

'Art. L. 2151-4. - The implementing procedures of this chapter are laid down by a State Council decree, especially the conditions for authorising and implementing research on human embryos.'

Glossary

Chromatin
Biological substance composed of DNA and proteins, present in the form of granules in the nucleus of cells and organising itself into chromosomes when cells divide.

Chromosome
Threadlike body in the nucleus, visible at the time of cell division and carrying the genes.

DNA
Deoxyribonucleic acid
Macromolecule formed by polynucleotides that appear in the form of a double helix chain of which the two strands are complementary and constituting the genome of most living organisms.

Epithelium
Non-vascularised tissue made up of one or serveral layers of cells adhering to one another and covering and protecting the external surface of the body as well its natural cavities.

Enzyme
Macromolecule of a proteic nature characterised by its catalytic activity governing specific biochemical reactions in the organism.

Eucaryote
Organisms whose cells are composed of a genuine nucleus surrounded by a membrane and whose protoplasm contains mitochondria and ribosomes.

Ex vivo
Is said of treatments, modifications, therapy processes, etc. performed outside the organism, on cells, tissues or organs taken from a subject with a view to their reimplantation in said subject.

Gene
Ordered sequence of nucleotides occupying a precise position on a determined chromosome and forming genetic information whose transmission is hereditary.

Genotype
All of the genetic material carried by an individual and which forms his hereditary heritage.

Histone
Basic protein and major consistuant of the nucleosome.

In vitro
Is said of an experiment or of a reaction taking place in an artificial environment, in the laboratory.

In vivo
Is said of an experiment or of an exploration observed or practiced in a living organism.

Mitosis
Division of the nucleus of a cell into two identical daughter nuclei.

Nucleus
Generally unique constituent of the cell, often spherical, ensuring the transmission of hereditary characteristics and playing an important role in cell metabolism, especially in the regulation of protein synthesis.

Nucleosome
Subunit of chromatin formed by a DNA fragment coiled round histone molecules.

Phenotype
External aspect of an individual conditioned by his genotype and the action of the environment.

Procaryote
Unicellular organism whose nucleus lacks a membrane and consists in a single chromosome.

RNA
Ribonucleic acid
Macromolecule present in the cytoplasm, mitochondria as well as in the cell nucleus and serving as an intermediary in the synthesis of proteins.

Trophoblast
Thin cell envelope of the embryo allowing it to attach to the uterus and draw subsistence from it.

Source:
Grand dictionnaire terminologique (Office québécois de la langue française)