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# Educator's guide on "The biotechnology revolution"

## (Background information)

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# 1. Introduction

These teacher guidelines will give you information on the Xplore Health module “The biotechnology revolution”. It will first introduce the topic to enable you to prepare your lesson using the different multimedia tools that you will find on the website. The guidelines provide information on the state of the art in this research field and on the ethical, legal and social aspects surrounding this topic.

# 2. State of the art

## 2.1. Definitions

It was a famous British biologist, JBS Haldane, who said at the beginning of the 20th century that if something could be done by a microbe, why to do it ourselves. He was anticipating the modern concept of **Biotechnology**, which according to the OECD (www.oecd.org) introduces a new element in the value chain: living organisms. Nowadays the science and the industry behind the general concept of biotechnology is becoming one of the most important economic driving forces of advanced societies, adding never-ending improvements to the health and quality of life of the population and also triggering profound ethical debates on the limits of life as it has been understood so far. Biotechnology seeks to understand the mechanisms behind biological processes, and tries to adapt those mechanisms to a human need. Thus, knowing the basic mechanisms that control the synthesis and replication of DNA has led to **Genomics**, and the ability to mimic nature’s role in generating biological diversity has allowed the emergence of a research field called **Gene Therapy** (trying to replace defective genes with functional genes in order to cure a genetic disease). It has also led to the creation of organisms with new functions: from the genetically modified bacteria of the ’70s, which were able to synthesise insulin or growth hormone from small pieces of DNA added to the main host DNA by **genetic engineering** (cutting and pasting pieces of DNA using enzymes already existing in nature called “restriction enzymes”), to Craig Venter’s entirely synthetic Mycoplasma, a fully functional bacterium whose whole DNA was made in a machine, the most recent milestone of **synthetic biology** (the discipline and industry that seeks to engineer new organisms with functions that cannot be found in nature, focusing mainly on energy production, bioremediation and healthcare).

In the middle ground between the easy **transformation** of a bacterium and the really complex synthesis of a full new organism, bacteria, cells, plants, animals and even humans (through gene therapy) can be **genetically modified**. Genetically Modified Organisms, or

**GMOs**, are used in the pharmaceutical and food industries and are the subject of intense debate (mainly in Europe) concerning their widespread introduction into the food chain. But there is no debate concerning their use as tools for looking for new drugs and even producing them, since the transformation of living cells is now fully established, accepted and well regulated (plants and cattle can be used as **Biofactories**, cells or bacteria producing therapeutic or industrial proteins are grown in **Bioreactors**, etc.). The study of the molecular basis of life has also led to **cloning** (generating exact copies of a living organism or cell without using the natural reproductive pathway). Cloning bacteria and eukaryotic cells has been routine laboratory practice over the last 30 years. However, moving into full organisms has been more of a challenge, but the cloning of Dolly the sheep in the '90s put this technology at the service of industrial and commercial applications, ranging from the almost routine cloning of mice for research to the "a la carte" cloning of a beloved pet for "only" 100 thousand dollars (with prices going down as we speak).

Moving aside from genetics, understanding the molecular biology of life has allowed scientists to better understand disease, so that almost all gross mechanistic aspects of a living cell, tissue or organ are known, as is the relationship between them. So we have the code (we have all the genes already sequenced), we know how the code translates into function, and we know most of the relationships between the different parts of cells. We understand immunology, we understand cell death, and we understand brain function. We understand our own biology reasonably well enough to transform our knowledge in useful tools, or to design appropriate research to fill in the gaps still unknown within a reasonable time. So we can identify molecular **targets** (pieces of the cell, usually proteins, which, with the appropriate manipulation, can improve a non desirable condition, such as a disease or poor quality of life, in a given individual). Nowadays, the obstacles to finding solutions to the wide range of diseases and other health issues for which there is not yet a cure or even a treatment are mostly economic and are conditioned only by whether a certain solution is considered a priority. Once the disease is seen as a priority, it is only a matter of time before a treatment and even its cure is found. It is not possible to say that we know everything, but our knowledge in biotechnology has a degree of maturity that allows us to feel moderately optimistic about helping to Heal, Fuel and Feed the World, the motto used in the Bio association meetings in the US over the last two years.

Advances in crystallography, the science that determines the structure of molecules, and also in molecular design and imaging allow us to design new molecules that act on the target (**rational drug design**), but we can also use biological tools like **antibodies** (proteins

naturally used to fight infection, which are very specific, almost magic bullets that only recognise the target, which have been routinely produced in the laboratory since 1976 and are now a therapeutic and commercial reality). As we now know how the molecular machinery of a living cell works, we can interfere with the process almost at will; for example, blocking the **expression** of target proteins using **antisense** or **interference** RNA. By doing so we are just copying natural control processes and adapting them to combat diseases. We can also "invent" new molecules by taking the parts that interest us and putting them together to form a useful drug. This is the case of Etanercept, known as Enbrel, a drug that is widely used for treating autoimmune diseases, which is built from an antibody and the soluble **receptor** for the target molecule. The resulting protein is able to recognise and block its target with great affinity and also with very good stability in the blood thanks to the antibody part. This kind of molecule in general is called a **chimera**, and in this particular case, as it is built from two proteins, it is called a **fusion protein**.

But biotechnology is not alone in this game. Advances in nanotechnology are now allowing new tools, reagents and drugs to be developed, which are based on taking drugs to the "nanoscale". There is a full open and promised field called "**nanomedicine**", which, according to the European Platform of Nanomedicine (www.etp-nanomedicine.eu), uses the new or improved physical, chemical and biological properties of materials and molecules at the nanometric (i.e., less that a millionth of a metre) scale. It is expected that nanomedicine will lead to new diagnostic tools and drug delivery systems. The European project Nanotest (www.nanotestfp7.eu) addresses safety issues concerning nanoparticles used in diagnostics, for example.

Going further into the complexity of the biotechnological tools available, we now understand what it takes for a cell to become a specialised cell or a tissue or an organ, or even a full individual. We have learned how to find **stem cells** (cells that can differentiate into different kinds of cells, some of which are **pluripotent** and some are committed to a specific lineage, for example **haematopoietic stem cells**, which only give rise to blood cell types). All tissues have stem cells that allow for their continuous renewal. Some of them are particularly abundant in the body, like fat tissue, which is a very rich source of **mesenchymal stem cells**. But there are stem cells everywhere, even in the brain. The more undifferentiated a stem cell is, the closer it is to a cell that is able to give rise to a full organism. Thirty years ago this knowledge enabled the genetic manipulation of **embryonic stem cells** (cells from the reproductive lineage that are able to generate a full organism without the need for fertilisation) to obtain full mice containing the desired genes. But it also enabled scientists to

block or introduce genes in a full organism to better understand its function. So we have transgenic animals or plants (animals with foreign genes), or **knockout** animals (animals with a gene that has been genetically inactivated). Going back to stem cells, we can now use these cells as therapeutic agents. This is not exactly new, since for a long time haematopoietic stem cells have been used in leukaemia treatments, but it is now becoming a great priority and using stem cells to treat diseases is just about to become a commercial reality. As developing a drug based on a living cell is very different to developing a chemical entity, the full regulatory pathway had to be adapted and now we have a special category called **advanced therapies**, which deals with the challenges posed by the safety and efficacy criteria of this new type of drugs. Stem cells are being developed particularly in **regenerative medicine** with the idea of restoring a lost function to an individual. The use of cells in combination with **biomaterials** (materials that are well tolerated by the body) for better **tissue engineering** is of particular interest. In the long term **cell therapies** can lead to curative rather than palliative approaches, in conditions such as myocardial infarction, spinal cord regeneration, diabetes or Parkinson's. At the moment they are used in clinical practice for bone and cartilage regeneration, implantology and wound healing (and even in cosmetic applications as fillers). Their use is generally restricted to **autologous** procedures (using cells from the same individual, like an autotransplant), making it difficult to generalise about its applications. However, the field is advancing a lot and there is general consensus that in the end the use of **heterologous** procedures will become widespread. This will make it possible to have stocks of stem cells ready to be used everywhere in the world, just like any other kind of drug. The natural candidates to be used in heterologous procedures are **human embryonic stem cells**. However, there intense ethic debate surrounds their use, since it involves the manipulation of human embryos to obtain the cells. The solution to the dilemma is to use **adult stem cells**, and recent findings indicate that we can set the differentiation clock back, obtaining "**induced stem cells**" or **iES** from almost every adult cell (including skin cells, for example).

## 2.2. Summary of the State of the Art

### Nucleic acid-based therapies

- Gene therapy
- Gene knockdown (RNA interference, antisense therapies)

### Protein-based therapies

- Antibodies
- Hybrid molecules

### Nanomedicines

- Drug delivery tools
- Biopolymers
- Therapeutic nanoparticles

### Cell-based therapies

- Autologous adult stem cells
    - As a stand-alone therapy
    - In regenerative medicine
- Heterologous stem cells
    - Embryonic stem cells
    - Reprogrammed adult stem cells

## 2.3. Targeted therapies: towards Ehrlich's classic "magic bullet"

Our deep and increasing understanding of normal and pathological mechanisms and the wide range of molecular tools available to manipulate living cells is helping us design more discriminating, more focused therapeutic strategies. We are referring to the classic "magic bullet" envisioned by Paul Ehrlich, and we call this "targeted therapy". A targeted therapy seeks to act in a non normal condition only on the cells that are relevant for the disease. Oncology is leading the way, with more than 70 drugs under development that are clearly targeted therapies. The combination of a targeted therapy with personalised medicine is the new paradigm of the biotech and pharmaceutical industries (which are experiencing a process of convergence, with the boundaries between them being more on the business model side than the technical side). The old "one drug fits all" paradigm is being replaced by "a customised treatment for each patient". Biotechnology, as a science and as an industry, is leading the change and enabling us to create safer and more efficacious treatments.

## 3. Ethical, Legal and Social Aspects (ELSA)

In this section you will find a number of opinions and incentives for discussion in class on ethical, legal and social aspects (ELSA) related to biotechnology:

### 3.1. Ethical aspects of Biotechnology: an overview.

Biotechnology, in its broadest sense (technologies based on biology), is one of the most striking technologies derived from knowledge that appeared in the mid 20th and early 21st century. The development of Biotechnology has offered us the chance to improve our knowledge of the most intimate characteristics of a living being: its *genetic code,* and even, once we have this knowledge, going a step forward and altering it. The discipline that has prompted these transformations is *genetics* and all the technologies based on it. As mentioned, the capacity to develop these technologies comes first through simple knowledge (**genetic information**) and then through changing the genetic characteristics of individuals (**genetic manipulation**). Depending on the species involved in the biotechnological process, we refer to this manipulation as **genetic engineering** (in species other than humans) or as **gene therapy** (in humans). All these technologies have ethical issues that need to be addressed, which have profoundly changed the concept of the place that humankind occupies in the universe and even the concept of humanity itself.

### 3.2. General ethical aspects

There are some general aspects to be considered when talking about the ethics related to Biotechnology; concerns that can be applied to almost all the biotechnological procedures we will discuss later. These ethical aspects are: **availability** and the **precautionary principle** (also referred to as the *slippery-slope principle*).

- **Availability**

In general, Biotechnology is a high-technology field, so it is time-consuming and expensive, making it available only to well-developed countries or to economically powerful people. These economic implications lead to a bias in the way Biotechnology evolves, often leaving some interesting research aside due to profitability criteria instead of criteria of general well-being. This is the case of research into malaria vaccines or the development of transgenic rice that produces vitamin A precursors (golden rice). Therefore, we have to be aware that although *distributive justice* applied to Biotechnology is generally accepted, it is not always practised.

- **Precautionary principle**

Although the precautionary principle could be applied to any new technology, it has been especially invoked in Biotechnology.

The precautionary principle states that no new technology should be used (or even developed) until enough guarantees that it is harmless are obtained. This principle, although sound, can impair scientific progress if applied to its extreme. Most technologies have dual aspects and their misuse in the pursuit of undue or perverse objectives should not impair their development. Emmanuel Kant (1784) already consecrated the necessity of scientific improvement in his essay “An answer to the Question: What is Enlightenment?” when he wrote “An epoch cannot avert or commit itself to put the following one in a situation that will be impossible to expand its skills (in particular those of maximum urgency), purify them of errors and, in general, further progress in the Enlightenment. That would be a crime against human nature, the original destination of which lies precisely in this progress...”, meaning that present knowledge and technologies are based on the knowledge developed by preceding generations of scientists, while today’s science becomes the groundwork for future knowledge; banning some research can cause delays and undesired effects on future generations. For instance, transgenic technology or somatic cell nuclear transfer (cloning) in humans have evolved much more slowly due to this prevention.

Therefore, it seems clear that, although not everything that can be done should actually be done, invoking the precautionary principle may impair the development of new technologies that might offer better living conditions for future human generations. Seeking a balance between the benefits and risks (principle of proportionality) seems to be the soundest approach to this apparent conflict.

### 3.3. Genetic information

As regards humans, Biotechnology offers the possibility of developing personalised medicine (pharmacogenomics, toxicogenomics) that provides genetic information about individuals. Use can be made of this information by the individual him or herself (self genetic information) or by others.

In general, the ethical aspects of using self genetic information are seen as less relevant because it is assumed that having this information can be regarded as a right that people can exercise. The main questions to determine are to what extent people have the right to gain this self-knowledge, which is expensive and difficult to obtain (at least at present), and who should assume the cost of providing this information. Availability is thus the key point to be

addressed in this topic. Although knowledge (and especially self knowledge) is generally viewed as something positive, it can also have negative aspects arising from the right not to know. This situation occurs when the person is at risk of suffering a genetic disease for which no cure is available. Under these circumstances, revealing the information without appropriate consent should be considered ethically unacceptable.

By contrast, it is generally accepted that the use of personal genetic information by third parties (other persons, companies or institutions) has important ethical and social implications. Ethical concerns in this field are mainly derived either from its commercial use (exchanging personal genetic data between companies) or from discrimination exerted due to this knowledge (for instance, people losing their jobs because a genetic predisposition to some kind of cancers or paying extra to insurance companies for the same reason). All these preventions are considered in Article 10, Private life and right to information, of the Oviedo Convention[1] (Council of Europe, Convention on Human Rights and Biomedicine, 1997).

Finally, some people fear that obtaining genetic information specific to certain human populations may bring back old concepts such as human race, thus acting as an intellectual support for new forms of racism.

### 3.4. Genetic manipulation

- **Genetic engineering**

Genetic engineering refers to the modification of the genetic characteristics of species other than humans (either bacteria, plants or animals; generically referred to as GMO - *genetically modified organisms*- or transgenics) to adapt them to the interest of human beings. In fact, it can be considered a sophisticated form of domestication that has the advantage of being faster and more straightforward. However, concerns have arisen regarding the use of this technology. Ethical concerns are mainly related to the general aspects already mentioned, such as availability and, especially, the precautionary principle. While a direct influence of transgenic technologies on human health has almost been ruled out, the precautionary principle has mainly been invoked because of the *threat GMOs may pose to environment*. Although this is a long debate in which scientists and environmentalists argue that no direct

[1] *The Oviedo Convention (Council of Europe, Convention on Human Rights and Biomedicine, 1997).*
*Article 10 – Private life and right to information*
*1. Everyone has the right to respect for private life in relation to information about his or her health.*
*2. Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed.*
*3. In exceptional cases, restrictions may be placed by law on the exercise of the rights contained in paragraph 2 in the interests of the patient.*

proof has been reported of detrimental effects of GMOs on nature, the contrary (proof of the innocuousness of GMOs to the environment) still seems to be true. The main worries stem from the reduction of biodiversity and substitution of natural organisms by uncontrolled GMOs which, in the end, may threaten other fragile ecosystems. The responsibility for leaving a safer world, free from environmental catastrophes to future generations is at the centre of this debate. Transgenics have been proposed either to be used as bioreactors, to generate products through biochemical pathways in organisms that do not normally produce them, or to act as a source for xenotransplants by producing organs (*xenoorgans*) in animals that can be transplanted to humans. While no particular concerns have arisen regarding the first aforementioned application, the production of xenoorgans does give rise to ethical concerns. The *production of chimeras* (organisms with cells from two or more different origins, especially from different species) poses ethical preventions, mainly when these species are very close. Worries appear when the possibility of generating hybrids between humans and closely related species, such as apes, may become true. The consideration of these chimeras and even their own self-consideration, if they could have any kind of self consciousness, is undoubtedly one of the most frightening aspects Biotechnology could offer. Recently Biotechnology has moved one step further after the reporting of what has been called *synthetic biology*, which refers to the creation of a completely new organism (a bacterium) having designed its whole genetic code. Such an approach could currently be considered a sort of "global transgenic", since it has been conceived as a combination of different genes from different organisms. Claims have arisen against this possibility, using arguments such as scientists *playing God* or going against the *natural order of things*. Although worthy of respect, all these arguments do not seem to have a solid scientific grounding and should be kept within the realm of religious belief. The playing God concern can be considered a variant of the precautionary principle, since supporters of this argument maintain that, unlike God, we are not omnipotent and omniscient, and therefore unforeseen and uncontrollable effects may occur when such technologies are developed. In fact though, the precautionary principle we have already discussed is the main argument that can be proposed besides the religious ones. With respect to "going against the natural order of things", namely going against natural evolution, this is also an argument that can be asserted against any medical intervention, which obviously makes it unacceptable.

## 3.5. Gene therapy

When genetic manipulation is applied to human beings, it is referred to as gene therapy since, in general but not always, the main objective of this procedure is to try and remedy a disease. We will later discuss how gene modifications in humans can also be used to improve human individuals, thus constituting a sort of active *eugenics*. Gene therapy can be used on cells (**cell therapy**, which includes **regenerative medicine**) or on **embryos**. The latter use derives from the availability of human embryos offered by **reproductive medicine**, a biotechnological process with a wide variety of ethical implications to be discussed.

- **Cell therapy – Regenerative medicine**

Cell therapy is based on the use, manipulation and genetic modification of cells. Cell therapy does not have ethical implications, except when it is performed on a special type of cells known as *stem cells*. These cells are in an undifferentiated state (they are *pluripotent*), so they can be derived into any kind of cells of an organism to regenerate damaged tissues and organs from individuals (*regenerative medicine*). Stem cells can be obtained from adult cells either directly (*adult stem cells*) or by inducing their pluripotentiality (*induced Pluripotent Stem Cells iPS*).

The use of both types of cells does not present any ethical concern but they have some biological characteristics that might make them unsuitable for certain regenerative processes. By contrast, stem cells derived from spare human embryos (*embryonic stem cells ESCs*) do have the capacity to be derived to any kind of cells and seem to be suitable for regenerative medicine; nevertheless, they pose serious ethical concerns since their production implies embryo destruction. Worries about their use arise from the consideration a human embryo deserves; however, we will discuss this topic later in the Reproductive Medicine section. One of the most serious drawbacks that regenerative medicine must face is immunological rejection. To solve this problem self transplantation is proposed, which involves the use of cells derived from the same adult organism (iPS) or the use of cloning technologies to produce genetically identical ESCs, which has been called *therapeutic cloning*. Cloning technology, initially developed for transgenic animal production, has been widely criticised because it has been considered, according to the slippery-slope principle, an open gate to reproductive cloning (which will later be discussed in the Reproductive Medicine section).

- **Gene therapy in embryos**

The modification of the genetic characteristics of a whole human organism sets forth a deep ethical concern: assuming that genetic characteristics are what ultimately define an individual, is it ethically acceptable to modify them and thus produce a "new individual"? Should we consider such a procedure as a sort of assassination of the old, original individual? Moreover, to what extend should we apply this technology? Should we use it merely to modify abnormal characteristics (merely *healing*) or should we go one step forward and modify some behavioural traits (*biological enhancement*)? Insofar as some traits that are considered valuable to offer greater all-round capacities for better living (intelligence, memory, self discipline, patience, empathy, optimism, etc.) have some genetic basis, genetic manipulation could alter them, thus benefiting individuals. Traditionally all these characteristics are modified by environmental enhancement (education and cultural refinement); biological enhancement could be considered another way to address the same objective: increasing people's chances of leading a better life. According to the *beneficence principle* (all actions must be to the benefit of individuals), we could consider we have a moral obligation to do so. As stated by J. Savulescu (2007) "Biological manipulation to increase opportunities is ethical. If we have an obligation to treat and prevent disease, we have an obligation to try to manipulate these characteristics to give an individual the best opportunity of the best life". In fact, biological enhancement, while increasing people's well-being, could be considered equivalent to treating diseases, since health is not only the absence of pain, but also achieving the maximum well-being.

However, against biological enhancement it has been argued that, as already mentioned, it could be considered to be altering identity, since it would mean altering the genetic characteristics of individuals. It could be reasoned that this is true only if significant alterations of mental capacity have been performed, but what does "significant alterations" mean? Again, the extent of changes occupies the centre of the debate.

Moreover, M. Sandel (2004) proposed that designing children leads to mastering the mystery of birth, alters parent-child relationships and deprives parents of humility by banishing the appreciation of life as a gift, leaving them with nothing to affirm or behold outside their own will.

For all these reasons, Article 13 of the Oviedo Convention reads: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants", completely banning gene therapy in embryos.

The alternative to embryonic genetic manipulation is embryo selection using *pre-implantation genetic diagnosis*. This is a procedure for identifying genetically abnormal embryos before implantation, aiming to transfer only those that are normal, while discarding the rest. Since technology cannot currently offer a complete screening of the whole genome of the embryo, it was initially developed to detect abnormal embryos in couples with a high risk of presenting a certain genetic disease. However, it has been evolving since it was first developed in 1992 and new applications have been proposed: detection of predisposition to certain diseases (some forms of breast and colon cancers), selection of embryos that are immunologically compatible with severely ill elder siblings to generate individuals that can act as donors of cord blood stem cells (called *HLA matching*), or even selection of embryos of the desired sex without any medical indication (which is commonly referred to as *social sexing*).

Complaints against pre-implantation genetic diagnosis have been put forward in the sense that it can be regarded as a sort of *eugenics*. Eugenics is defined as “a science that deals with the improvement (as by control of human mating) of hereditary qualities of a race or breed” (Merriam-Webster dictionary); however, in this case no improvement of a human group is pursued apart from avoiding the birth of a children affected by a severe genetic disease.

*The instrumentalisation* of embryos and therefore the children derived from them is another criticism that pre-implantation genetic diagnosis must face, especially with regard to HLA matching or social sex procedures. *Kant’s categorical imperative* (Groundwork of the Metaphysic of Morals, 1785) states that any rational individual can never be used merely as a means to our ends, but always as an end in him or herself. This argument can be considered absolutely true for children but may not be so for embryos, since pre-implantation embryos are often not regarded as persons with a moral status (see Reproductive Medicine section). With regard to the instrumentalisation of children, it is in fact quite a common situation (for instance, children partly being conceived as heir a fortune or to continue a constitutional monarchy or simply to solve relationship problems in the couple). Therefore, would saving an already existing life (HLA matching) not be a “good reason” to partially instrumentalise a child?

Fears on demographic unbalancing of the undesired sex, an argument often used against sex selection, seems to be excessive when applied to pre-implantation diagnosis since this is not, and probably never will be, a widespread technology. Moreover, much more dramatic systems of exerting sex selection, such as selective abortion or even assassination, have been and are still being used.

The strongest complaints appear again when trying to decide to what extent these procedures could be used; will we accept HLA matching for the embryo's siblings? But what about for cousins or people who are not related? Will we accept social sexing only to balance the genres in a family? Or only if pre-implantation diagnosis has been performed for medical reasons and during this process the embryo's sex is collaterally obtained? Will it be acceptable if embryos of the undesired sex are donated for adoption to couples with reproductive problems? Guidelines and the law are extremely variable in this matter, depending on the cultural and religious tradition of different countries and societies.

### 3.6. Reproductive medicine

Reproductive medicine makes human embryos available for the first time in history, thus leading to a profound debate on the moral and legal considerations of the human embryo. There are two main positions that can be adopted on this debate: human embryos should be considered as persons from the moment of conception onwards or they should be considered as potential but not actual persons in such early stages of development.

The first position is supported by non-reductionist (religious) beliefs. According to the Catholic Declaration of the Pontifical Academy for Life "On the basis of a complete biological analysis, the living human embryo is - from the moment of the union of the gametes - a human subject with a well defined identity, which from that point begins its own coordinated, continuous and gradual development, such that at no later stage can it be considered as a simple mass of cells". However, a hydatidiform mole (a kind of abnormal pregnancy that can develop into some embryonic cancers), naturally-occurring twinning or the Siamese phenomena threatens this idea, since none, one, two or even something between one and two individuals can be derived from the same embryo. Under the first point of view, a human embryo has a full *moral status* since it is considered a person; under the second, it does not have a moral status, although it can posses a *moral value*, meaning that there are moral reasons to treat it in certain ways and not in others. According to the report issued by the NIH Human Embryo Research Panel, while the pre-implantation human embryo "does not have the same moral status as infants and children … it deserves special interest and serious moral consideration as a developing form of human life". This special interest and respect (something similar to the respect offered to human remains and corpses) is expressed by restricting their use to morally significant purposes only. This latter position is the one mainly adopted by legislation on human embryo research in most developed countries.

Another field of debate on the consideration human embryos deserve is *Kantian respect*, directly derived from the categorical imperative already mentioned. Kantian respect encourages us to treat others (including embryos, it could be argued) as ends in themselves. To treat others as ends in themselves we must take their ends (their interests, projects and goals) seriously and not just our own. It has been argued that since embryos do not have interests or ends they cannot be considered as ends in themselves, and therefore Kantian respect cannot be applied to pre-implantation embryos. But which argument supports the idea that embryos do not have interests? This idea derives from the fact that embryos in such early stages do not have sentience. In this sense B. Steinbock (2007) proposes “”Without experiences of any kind,” (pre-implantation embryos do not have any nerve cells) “embryos cannot have wants. Without wants they cannot have a stake in anything, including their health or continued existence…My claim is…they do not have an interest in being healthy or in continuing to exist”. She adds “Sentience is a condition, not of having interests, since temporarily non-sentience beings can continue to have interests in the dispositional sense, but of acquiring interests”. To have interests in the dispositional sense means to have inherent interests in one’s own welfare, despite not being aware of it.

The second ethical hot spot of reproductive medicine is *reproductive cloning*. In fact, this is a misleading term since clones cannot be considered as the offspring of the original individuals but their asynchronous twins; therefore, they would be better considered as siblings. This procedure is based on the *somatic cell nuclear transfer* technology that was developed to produce transgenic animals, which allowed the birth of the first mammalian clone, Dolly the sheep, in 1996. Although it has not yet been performed in humans or apes, and some authors even believe that it will never be possible to carry it out, it has given rise to long and heated debates.

Human cloning has been proposed to be acceptable in terms of *reproductive freedom* but has been considered as unethical for many other reasons, the most widespread of which is that it is contrary to *human dignity*. Article 11 of UNESCO’s Universal Declaration on the Human Genome and Human Rights reads: “Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted” and the Preamble of the Oviedo Convention on the Prohibition of Cloning Human Beings reads: “Considering … that the instrumentalisation of human beings through the deliberate creation of genetically identical human beings is contrary to human dignity and thus constitutes a misuse of biology and medicine…”. However, human dignity is a very blurry concept that is not well defined in either of these declarations, as they do not clarify whose dignity is threatened by cloning: the

embryo's dignity, that of the individuals to be cloned, that of the individuals that perform the cloning process, mankind's dignity? All of this uncertainty makes both declarations susceptible to severe counter-arguments (Birnbacher, 2005). Another argument against reproductive cloning is that it will decrease the genetic diversity of humankind; this is a true argument but it would only have a noticeable effect if it were widely used, which will probably never be the case. It has also been argued that it can deprive clones of an open future, which is obviously a weak argument since genetics cannot predetermine a whole human life. Finally, the only sound and well-founded argument against reproductive cloning is that it yields an extremely negative balance between benefits and risks (*negative proportionality principle*). At present, cloning technology poses a serious threat to the clone's health and well-being since clones suffer from high spontaneous abortion rates, increased perinatal death rates and fetal malformations; moreover, there are no reproductive problems that can be solved exclusively by cloning, thus making it useless. According to this, even developing human cloning technologies would imply an unacceptably large amount of children with severe health problems just to fulfil the odd desire of some people.

Reproductive medicine is a fast evolving field that is constantly raising new ethical concerns ready for debate. Recently it has been reported that, in animals, ESCs can be derived into cells resembling gametes, which will probably soon have reproductive capacities. This possibility raises two new ethical worries. The first one has already been referred to as *ultimate incest* because it could offer the possibility of self sexual reproduction (which is clearly different from cloning) since both male and female gametes might be derived from the same cells. The second one appears if ESCs are used to produce gametes to solve the shortage of gamete donors in most countries: by doing so we would allow individuals that have never existed to reproduce; will we consider it ethically acceptable?

We have given a very quick overview of some ethical aspects biotechnology has presented us with, but new ones will surely continue to arise as new technologies appear; is our duty as democratic and well-developed societies to think and argue about them on the basis of true information without apriorisms.

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