Innovative therapies: some ethical considerations

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SUMMARY
The purpose of this text is to try to understand why certain innovations are not permitted, although they are possible. Our guiding thread will be the four principles of biomedical ethics defined by Beauchamp and Childress: beneficence, non-maleficence, justice and autonomy. We shall show how they can guide the ethical inquiry in the field of pancreas or islet transplantation, leading to an analysis of the risks and benefits of the innovations epistemologically taking into account their historical context.

Key-words: Innovative therapies • Four principles of ethics • Pancreas transplantation • Islet transplantation • Beta cell engineering • Review.

ÉTÉ VÉRITÉ

Thérapeutiques innovantes : considérations éthiques.
Le but de ce texte est d’essayer de comprendre pourquoi certaines innovations, qui sont possibles, ne sont pas permises. Nous prendrons comme fil directeur les quatre principes de l’éthique médicale, définis par Beauchamp et Childres : les principes de bienfaisance, de non-malfaisance, de justice et d’autonomie. Nous montrerons comment ils peuvent guider la réflexion éthique dans le domaine de la transplantation de pancréas ou de cellules insulinosécrétrices, conduisant à une analyse des bénéfices et des risques qui doit prendre en compte de manière épistémologique le contexte historique.

Mots-clés : Thérapeutiques innovantes • Quatre principes de l’éthique • Transplantation de pancréas • Transplantation d’îlots • Ingénierie des cellules β • Revue générale.
Medical progress proceeds by steps that are sometimes innovations where we observe a break from the previous practices. The purpose of this text is to try to show how these innovations must be described in the framework of a historical context and how the very meaning of the word possible must be considered: the aim is to understand what makes it that certain things, while they are possible, are not permitted. This question of the “possible” and the “permitted” represents an essential part of the ethical inquiry. We shall take as our guide the four principles of the biomedical ethics defined by Beauchamp and Childress [1]: be beneficent (principle of beneficence), do not harm the patient (principle of non-maleficence), guarantee equity in the allocation of health care resources (principle of justice), and respect the autonomous choices of the patient (principle of autonomy). We shall take as an example the history of the treatment of diabetes (figure 1), a disease that today is treated by several daily injections of insulin, by trying to describe, from an epistemological point of view, the place of the transplantation of pancreatic tissue in the treatment of this disorder.

In 1894, i.e. 5 years after the discovery of the diabetogenic effect of total pancreatectomy performed on a dog by Minkowski, Williams in England tried to transplant fragments of sheep pancreas onto a diabetic patient [2]. At that time insulin had not yet been discovered and diabetes was a rapidly fatal disease: the question of the possible and the permitted was irrelevant. In 1966, insulin therapy was available. However, diabetes remained a disease with frightening complications, due to the lack of understanding of the role of glycaemic control in the occurrence of these complications, since it would be necessary to wait for the work of Pirart and Tchobroutsky at the end of the 1970s. That year, the first pancreas transplant was performed by Najarian in Minneapolis. Since that time, approximately 25,000 pancreatic transplants have been performed, with success in more than 80% of the cases, patients being able to stop insulin, but at the price of a heavy immunosuppressive treatment. The justification of this practice was challenged in the late 1980s [3], at a moment marked by significant progress in the conventional treatment of diabetes. Only recently, studies provided compelling evidence of the beneficent character of the procedure, i.e. the improvement in the life expectancy and the quality of life of the transplanted patients [4, 5]. By the way, a potential “innovative therapy”, the transplant of half a pancreas in the absence of immunosuppression between twins led to a double failure:
it was not beneficial to the recipient: the grafted pancreas was rejected by the diabetogenic autoimmunity; it was harmful to the donor: their glycaemia was altered by the hemipancreatectomy [6, 7].

The transplantation of islets of Langerhans was made possible by the development of methods of isolation of islets of Langerhans from the human pancreas by Ricordi et al in 1989 [8]. Between 1990 and 2000, approximately 400 islet transplantations were performed. Nevertheless, it was not beneficial: their rate of success (i.e. patients off insulin) was around 5%. The analysis of the causes of this failure – diabetogenic effect of corticoids and ciclosporin, role of microangiopathy (the patients had end stage renal failure), role of an insufficient number of transplanted islets -, led Shapiro and his colleagues in Edmonton to propose a triple innovation: immunosuppressive therapy containing neither corticoids nor ciclosporin, change in the indications (patients not presenting an end stage renal failure, but brittle diabetes and recurrent severe hypoglycaemic episodes), increase in the number of transplanted islets requiring their isolation from two to three pancreas per patient. This led to the spectacular first publication of a rate of 100% success in seven consecutive patients [9]. Thus, it seems now that islet transplantation is both technically possible and beneficial. However, considering the criterion of brittle diabetes and recurrent severe hyperglycaemia, further studies are clearly needed to provide the evidence that the prescription of a long term immunosuppressive therapy, which may be harmful (risk of cancer and lymphomas), is permitted. It is necessary to consider the context of the treatment of the diabetes, the comfort and the efficiency of which continue to improve (figure 1). Furthermore, the fact of having to use three pancreas by recipient brings up the question of justice in the allocation of organs which could be used for a whole organ pancreas transplantation in several patients.

Let us suppose now that we find an effective and safe means to avoid immune rejection of the transplanted cells, for example by encapsulating them within an artificial protective membrane: this dream of the bio-artificial pancreas has been pursued by numerous teams for more than twenty years. The problem of the source of the transplantable tissue would then arise, because we would want to treat a large number of patients, which would exceed the resources of human pancreas. These considerations led to the concept of xenograft - transplantation of animal tissues -, for example from a pig. This appears to be technically possible: the method for isolating porcine islets of Langerhans is established, the physiology of the porcine islet is close to that of the human, porcine insulin has been used in humans since 1923, the breeding of pigs exempt from specific pathogens is feasible. It is even possible to create transgenic pigs, in order to avoid acute immune rejection. In fact, porcine cell transplants in humans were already performed by a Swedish team at the beginning of the 1990s: for several weeks it was possible to observe evidence of small amounts of porcine C-peptide in the urine of the patients, proving the survival of transplanted porcine cells [10]. In other words, xenograft is possible.

However, it is no longer permitted, ever since the demonstration of a possible in vitro infection, by porcine endogenous retrovirus, of human kidney cells, fibroblasts and human B and T lymphocytes under culture conditions [11]. Some raised the question of the possibility of a nightmare scenario involving the creation of a new viral disease in humans. It is true that it was possible to show in 160 recipients having had a porcine xenograft (extracorporeal bio-artificial liver and kidney, islets, skin), that there was no argument in favour of any infection by a porcine retrovirus [12]. However, these negative results do not completely reassure concerning the complete absence of risk: the extension of the technique to a large number of subjects might allow the possibility of the appearance of this rare occurrence. Therefore, currently there is a moratorium forbidding xenograft, a moratorium which was requested by some of the pioneers in this domain [13]. Thus, the case of xenograft seems ethically complex. Without even evoking the question of ethics considered from the point of view of the animal, it remains to be proven from the point of view of the human beings, first that it will be beneficial to the patients: to this day, there is not a single case where the real benefit of a xenograft was demonstrated; second, that it does not present the risk of being harmful, neither to the recipient, nor to the society in general. Furthermore, its practice brings us to consider the principle of autonomy: The recommendations to limit the risk of infection require an intensive follow-up of the recipients, and the list of the prohibitions with which they will have to comply with may be not compatible with this principle [14]. Thus, in the case of a disease like diabetes, which already has a treatment - insulin -, the legitimacy of this strategy is really difficult to defend.

We saw that therapeutic innovation often arises from a necessity, or from a new possibility, opened by technical progress. Now, as the legitimacy of the xenograft became questionable, other ways of obtaining insulin secreting tissue appeared. The progress of molecular biology makes it possible to create insulin secreting cells [15], by introducing, for example in pituitary cell lines, the genes which contain the code for the proteins of the insulin secretion machinery: the genes of insulin, of the glucose transporter, of the gluokinase. Or we introduce, for example, the insulin gene into hepatocytes under the control of a promoter sensitive to glucose. But will these cells, capable of producing some insulin in answer to glucose, have the fine-tuning of the genuine β-cell, where the control of insulin is regulated at the level of the secretion, not at the level of the synthesis? It will be necessary to make sure that these cells are capable of controlling diabetes, at least as well as the conventional treatment by insulin. Certainly, they represent what is made possible by the exploits of the molecular biology, but will their use be really beneficial to the patients?

Other procedures are emerging: it is possible in the case of a mouse to transform hepatic cells into insulin secreting...
cells by intravenous injections of a virus carrying the gene of PDX-1, a factor of transcription which intervenes in the differentiation of the islets of Langerhans [16]. Will this be applied one day to humans? Finally, this domain, as the entire field of medicine, risks to be made obsolete by the recent discovery of the potential of cell plasticity. It is possible to obtain insulin secreting cells from stem cells either from adult tissues [17], or from embryos [18, 19]. We know that the use of human embryonic cells represents itself an ethical issue which goes far beyond the mere domain of its application, the innovative therapies, but once it will have been accepted that it is ethical under some conditions to use this kind of material, we will have to justify its use in term of beneficence/maleficence balance, just as for the other innovations which have been described previously. And it will be always necessary to consider the context: for instance, in the same period of time when we will be waiting for the successful development of novel insulin secreting cells, the possibility of closing the glucose-insulin loop may have become a reality (figure 1). Incidentally, the same ethical discussion concerning the development of these technologies is needed. For instance, a closed-loop insulin delivery system will represent as well an exploit of technology, but its performance should be critically examined in terms of its true benefits: real normalization of blood glucose profile without hypoglycaemia, improvement in glycated hemoglobin, and, last but not least, prevention of diabetic complications and improvement in the quality of life.

Thus, the preceding arguments show that therapeutic innovations, prompted by necessity when we are faced with a rapidly fatal disease (Williams and his sheep pancreas fragments), or by the analysis of a failure (Shapiro’s success in 2000), or on the contrary arisen from the consequences of success (the need to develop mass production of islets), appear generally when they become possible. We saw also that they can be stopped by the occurrence of unexpected events, even to be made obsolete by the advent of competitive innovative therapies. And still, they are necessary, and from there, it is advisable to wonder what makes it so that certain things, while they are possible, are not permitted. This question should be asked by the researchers, if they do not want to expose themselves to the criticism beautifully expressed by R. Weiss at the time of the demand for a moratorium on xenografts: “I’m not telling you that it would be better not to realize clinical trials, but I ask you the question: did you stop thinking?”

Fundamental research tries to develop pure knowledge, épistéme. The object of knowledge, nature, is eternal: only our understanding of nature changes, not nature. Thus, the method of fundamental research is to interrogate nature without modifying it. Therapeutic innovation does not belong to the field of fundamental research, but to applied research. Applied research aims to develop techné. Its aim is to dominate, to force nature. Its method is to create tools. Thus, it tries to modify nature, its domain of investigation. Therefore, it has to integrate the notion of future, which is by definition contingent. This is why therapeutic innovation is at the same time necessary for progress and presents intrinsic risks. Let us remind the readers that the word “risk” comes from the Latin risicare, to double a cape. What is behind the cape, or rather after the cape? The unknown, the danger!

We are thus driven to justify risk-taking. As pointed out by Evandro Agazzi [20], risk represents an essentially anthropological category: nature does not know the categories of choice and decision; God does not take risks; only we, humans, are capable of taking risks, of deciding to realize a project. It is this possibility of risk-taking that made possible all exploration, all investigation, all progress. But it is not justifiable to defend any risk. Agazzi distinguishes between the “sectorial”, individual risk, at the level of the patient, requiring a decision on a case by case basis, depending on the context, risk which can be possibly taken, and the total risk, the collective risk which puts in danger the future of humanity. The latter kind of risk cannot be taken. It is this last type of risk that Hans Jonas evokes in his Responsibility Principle [21], with his concept of fear heuristics. We understand that the most real anxieties concern the risks of modification of the nature of humanity: infectious risk of the xenograft, which imposes a moratorium as long as it is not proved that it exists, problem of the embryonic cells, where some people see a risk of drift towards reproductive cloning.

If we come back to the more common sectorial risk, involving only the individual patient to whom the innovative therapy is proposed, it is important to recognize that risk is a relative concept. 1) The respective risks of action and of inaction must be taken into account in the deliberation: let’s remember that diabetes remains nowadays a severe and distressing disease and that any efficient and safe method to improve the quality of metabolic control and the quality of life will be welcome. 2) The ethical inquiry has to consider the severity of the disease and the availability of conventional therapies. The fact that type 1 diabetes has already a treatment, relatively efficient, is obviously a brake to the implementation of novel techniques, which will have to prove that they are at least as efficient (similarly in clinical trials aimed to prove the interest of a novel drug, it will not be compared to a placebo, but to a competitor, if available). 3) Therefore, as shown in this paper, the evaluation of the risk/benefit of a novel therapy cannot be definitive, and has to take into account the appearance of new “competitors”. 4) It is also important to consider the risks linked to rare events, which may not be detected in small scale clinical trials. This, points out the importance of registries reporting for each individual patient the outcome of novel therapies.

An ethics of caution is thus necessary. Indeed, according to Aristotle in the Nichomachean Ethics [22], what characterizes the cautious man, it is the “good consideration”, that allows him to avoid immoderation, to appreciate the obstacles, to take into account particular cases, to choose the convenient
moment, to foresee even the unpredictable. To take into account particular cases: the ethical answers can be only casuistic. To choose the convenient moment is to take into account the context, which, as we saw in the example of the history of the treatment of the diabetes, is evolving. To appreciate the obstacles is to be capable of being able to by-pass them, thus to take the risk of going beyond the cape. But also to avoid immoderation, the *hybris* of the Greek philosophers, and this will protect us against the temptation of unjustified risks. The Latin word *caute* (“be cautious”) was written on Spinoza’s seal.

References