



EDITORIAL

The necessary coordination of pancreas, islet cells and kidney transplantation in Spain

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Talking about diabetes is speaking about one of the major causes of concern for physicians, patients and in general whoever has any responsibility in the health care setting. The figures are really stunning: 190 million of diabetics worldwide with a forecast of reaching 330 million in 2025. It causes 3.2 million deaths per year, or similarly 6 deaths per minute. About 2 million affected people only in Spain, between 5% and 6% of the population. It is the leading cause of blindness in developed countries and chronic renal failure in the World. Who suffers from the disease has a very increased probability of having myocardial infarction (the major cause of death: 50% in type 2 diabetes) and/or cerebral hemorrhage (50% of deaths), and also of having amputated limbs (between 15 and 40 fold than the general population, affecting up to 25% of diabetics).

As a matter of fact, the economic consequences of this 21st Century epidemic are similarly impressive. It is estimated that between 6.3% and 7.4% of the Spanish healthcare expenditures is dedicated to this disease (being the percentages similar to other neighbor countries) that annually consumes between €2.4 and €2.675 billions, which is to say figures around half a trillion pesetas. Diabetic patients have a threefold probability of hospital admission than the remaining population and the cost per patient and year was €1,289-1,476 in 2003, versus €865 in the non-diabetic patient.

Modern treatment standards for type 1 diabetes were established after the *DCCT* (Diabetes Control and Complications Trial Research Group) publication, in 1993. In this paper it was perfectly established that intensive insulin treatment of these patients leads to evident advantage over conventional treatment, poin-

ting out at the same time that the indication for pancreas transplantation was the therapeutic option in particular selected patients. When transplant is successful a better control and/or evolution of glycosylated hemoglobin levels, nephropathy, neuropathy, great vessels complications, and quality of life are achieved. These evidences were consolidated throughout the 1990s, as surgical and immunosuppression advances in this therapy were improving the results.

Pancreas transplantation has had a more torpid historic evolution than the remaining solid organs. It was initiated as with the other extrarenal great organs in the 1960 decade, being the pioneer work from Richard Lillehei, in 1966, in Minneapolis (Minnesota). Eight years later, in 1974 it was initiated in Spain by Professor Laureano Fernández Cruz at Clinic i Provincial Hospital of Barcelona. The initial difficulties of this technique are illustrated by the fact that in that center were performed up to 75% of transplantations done in Spain in the following 20 years, something unthinkable with any other organ.

Some how conditioned by surgical difficulties derived from exocrine pancreas transplantation, it was early hypothesized that the ideal would be to transplant only the endocrine part previously isolated from an organ extracted from a corpse or the patient himself in the case of auto-transplantation for pancreatic pathology. The first islet cells transplantation was done in 1974, whereas in Spain it was done in 1992 at Hospital Clínico de Madrid. The results did not accompany the estimates: less than 10% of patients were free from insulin one year after the islet cells implant. The publication, in July 2000, from James Shapiro of the firsts results of the so-called Edmonton protocol with an immunosuppression regimen without steroids based on tacrolimus, sirolimus and dacliximab and with 80% of patients free from insulin one year after was a milestone in this therapeutic approach. The new interest in a great part of the medical and non-medical community was focused on islet cells and worldwide everybody started working hard on this field.

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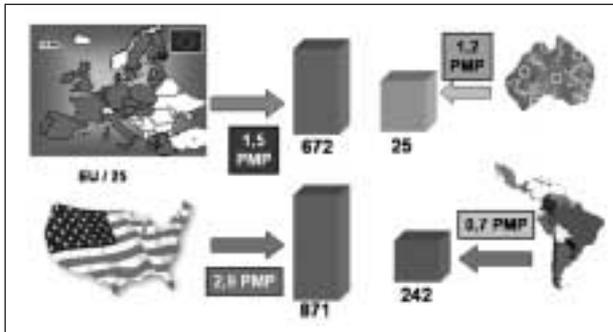


Fig. 1.—Pancreas transplantation activity in several areas of the world in 2003 in absolute terms and per million population (pmp). Data from the European Council.

PANCREAS TRANSPLANTATION

But let us return to pancreas transplantation, alone or in combination with kidney. From the Registry of the Commission for Transplantations of the European Council database, 1,800 operations are done every year in the main areas of the World with a clear leadership in absolute and relative terms in the United States (something also exclusive of pancreas and that does not occur with other organs). During 2003, North American physicians did 871 transplantations (2.9 pmp) versus 672 (1.5 pmp) in the European Union countries, far from 242 (0.7 pmp) of Latin America and 25 (1.2 pmp) of Australia. During 2003, there were done 74 in Spain (and while writing these lines it can be foreseen a similar figure for 2004), which means 1.7 pmp, higher than the European mean but clearly lower than the USA in spite of having 50% more donors in relation to the population. Therefore, here we have the first datum that does not suit.

As compared with the steadily, but firm, increasing line in the USA, the progression of pancreas transplantation activity in the rest of the World during the 1980s and the first part of the 1990s describes disrupted lines with a series of ups and downs in Spain and in the rest of the World. This is an unequivocal sign that it is not an easy business and that many of who initiate one of these programs interrupted it soon after or maintained it in a testimonial fashion due to the poor outcomes obtained. In fact, the INTERNATIONAL PANCREAS TRANSPLANTATION REGISTRY (IPTR) shows how in the early 1990s, and in spite of progressively increasing the number of registered centers in the World, the global activity was clearly stagnant with a plateau line.

The 1990s represented, however, a milestone for this technique with the outcomes clearly superior because of the advances introduced in the surgical

techniques and immunosuppression (fig. 2). The 5-year graft functional survival recorded in the IPTR of about 70% overlapped with those of other solid organs and has increased in all possible modalities (simultaneous pancreas –kidney, kidney followed by pancreas or only pancreas).

In Spain, there are 12 hospitals that have performed at any time pancreas transplantation although 3 of them are nowadays inactive, thus remaining 9 centers with the geographic distribution that is shown in figure 3. This map has an interest more than merely anecdotic to know where these transplantations are performed because the distance in kilometers, in ischemia time and/or economic resources between the place where donation is done and the hospital where the surgical procedure must be performed has greatly conditioned the development of this therapy and is still doing so currently. This is the second important fact to consider in our environment.

Acceptation criteria currently used in the document of the European Council are specified in Table I. These criteria are currently discussed and, thus, are considered reasonable internationally, although this does not mean that they are universally used. In fact, most of the Spanish surgical teams do not consider yet these ischemia times or the acceptance of organs with risk factors that we would consider between mild and moderate.

The rationale is or has been clear although it is less clear day by day. Until recently, pancreas transplantation has been moving in a vicious circle in which all the number of diabetic patients in dialysis has been increasing progressively from many years ago, physicians (nephrologists-endocrinologists) have been indicating pancreas-kidney transplantation with a dropper greatly influenced by the technique difficulties and the historical outcomes, not especially

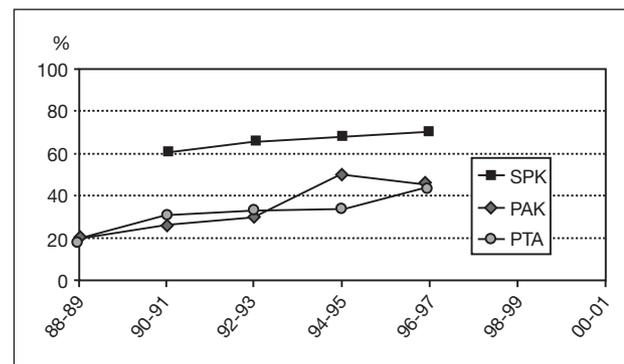


Fig. 2.—Pancreas transplantation in the USA. Five-year graft survival according to time of performance. Data IPTR/UNOS. SPK: Simultaneous transplant pancreas-kidney, PAK: Pancreas after kidney, PTA: Pancreas isolated.

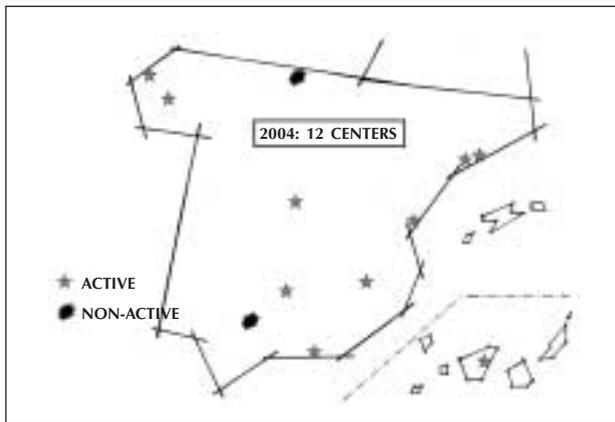


Fig. 3.—Geographic location of Spanish hospitals with active or inactive programs for pancreas transplantations during the year 2004.

brilliant but in very specific centers. Few patients in the waiting list, with not always uniform inclusion criteria and sometimes conditioned by the special knowledge of the technique in particular centers or even by the patient himself have raised the perception that the necessity for optimizing pancreas harvesting from corpse donor has been rather scarce.

Contrary to what occurs with other organs, with pancreas the supply/demand disproportion has historically become the opposite: a relative demand/supply disproportion with very particular exceptions in certain teams. In most cases, pancreases have been locally obtained, something that stopped occurring long ago with other transplantations, and the team or the organ have not travel but in very particular circumstances. Neither the teams have perceived that they had to do so, nor the administrations that they had to finance it, nor the coordinators away from the transplantations centers that they had to optimize organ harvesting if finally organs were not to be extracted. There has never existed, and it does not exist, the mutual commitment that characterizes the donation and transplantation process for liver, heart, kidney or lung in which the whole system does its utmost for optimizing harvesting and utilization.

This adds to the fact that renal transplantation teams that do not do pancreas are very critical with the «deviation» of a considerable percentage of kidneys with better characteristics to the diabetic patient that, in this way, would be submitted to a presumed «positive discrimination» in relation to the young non-diabetic recipient that, with the increasing aging of the donor population, would have in many cases a compromised probability of receiving an «optimal» kidney and might be consigned to dialysis. It is true that the main critic that was clai-

med in the 1990s to the prioritization of certain diabetic patients: the poor results that could be expected with them, has no longer any meaning because of the better survival that we have previously discussed. In any case, prioritization criteria for these patients have been and still are ill defined and worse followed in most of the communities, especially when there is more than one renal transplantation team. In this respect (and in many others related to the topic we are discussing) we outline the Andalusian example where these criteria are perfectly defined and followed with the ONT support without any problem.

More is to say, surgical extraction of the pancreas is not simple, it requires certain expertise, it considerably extends the process time for organ explantation and, according to other surgical teams (particularly lung and intestines), it interferes with the extraction or is a hazard for other organs viability. Finally, and although in Spain it still is a futurable, the real overlap of pancreas-islet cells donation criteria (table I) makes that in certain cases and in particular areas, there could be some competition between one destination or another. A really complicated panorama.

In spite of all this, as long as the outcomes were not good, the indications were scarce and in the entire Country there were less than 30 pancreas transplantations, most of them in Barcelona, the situation

Table I. Utilization criteria of islets/pancreas

| Donors criteria | Pancreas transplantation | Islets transplantation |
|--|--------------------------------|--------------------------------|
| Age | 5-45 (50) years | 20-65 years |
| History of: alcohol abuse/ chronic pancreatitis/diabetes | No | No |
| Glycemia | | < 16.7 mmol/L (3 G/L) |
| Body mass index (BMI) (kg/m ²) | < 25 (30) | > 22 |
| Protracted hypotension/cardiac arrest (> 30 minutes) | No | No |
| High dosis of vasopressor drugs | Acceptable | No |
| Hospital admission (ICU) | | < 7 days |
| Criteria or splachnic hypoperfusion: (elevated liver enzymes o serum creatinine) | | < 2 x upper normal limit |
| Serum amylase and lipase | < 2 x upper normal limit | < 2 x upper normal limit |
| Maximum total ischemia time | 18 hours | 8 hours |

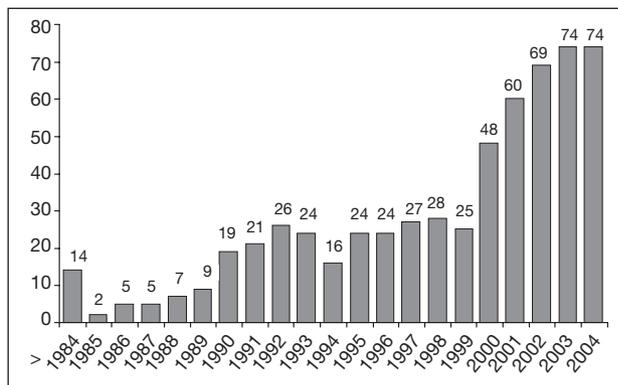


Fig. 4.—Pancreas transplantation activity in Spain.

showed a deficit but was quiet and stable. The 21st Century has come to change this merry «arcadia»: better outcomes, more indications, more centers, more transplantations (fig. 4), waiting lists emerge or grow (between 70 and 80 patients in Spain), the Edmonton protocol, the isolation of the islet, the media phenomenon of stem cells, the confounding or intentionally mixing of cellular therapy with basic research...Definitely everything becomes complicated.

Which is the real situation with a pancreas donation in Spain? If we analyze the 1,443 solid organ donors registered in Spain during 2003 and we consecutively exclude those that share the standard exclusion criteria mentioned above (age, history of diabetes, cardiac arrest, etc), we find that we could have used the pancreas for transplantation in 264 donors, 18.3% of the total. Probably, this is an overestimation because we are doing a retrospective analysis in which not all donors had for example amylase levels or other data that would have excluded them from a clinical point of view, without considering the restrictive criteria of some Spanish teams that we have mentioned above. In any case, it gives us an idea that we are talking about a «difficult» donor that occurs in less than 1 in 5 cases.

As finally there were performed 74 pancreas transplantations during 2003, we find out that only 28% of the theoretical valid, or which is the same 5.1% of all donors, were used. Only one of every 20 donors in Spain generated a pancreas transplantation during 2003, a ratio that has remained stable in 2004.

In figure 5 we can appreciate the utilization level by the autonomous communities of the 264 theoretical valid donors. Only in 5 autonomous communities the 30% utilization rate is exceeded (Catalonia, Andalusia, Galicia, Madrid and the Canary Islands, in decreasing order) while in the remaining autonomous communities that did not have a pan-

creas transplantation team none of these organs were obtained because the extraction teams did not travel. Very few conjectures are necessary to point out another key point, which is that the situation can be overtly ameliorated.

And however, nobody seriously discussed the usefulness of pancreas transplantation in its different modalities. In 2000 and 2003, the AMERICAN DIABETES ASSOCIATION recommendations established that one must consider the possibility of a combined kidney and pancreas transplantation as the first option treatment for the diabetic patient in dialysis, whereas the isolated pancreas transplantation must be considered in patients with unacceptable poor metabolic control and quality of life. In both cases, islet cells transplantation was still considered as an experimental treatment.

ISLET CELLS TRANSPLANTATION

As we discussed before, pancreatic islet cells infusion for hydrocarbon metabolism regulation in diabetic patients is a panacea hoped for a long time that has only recently begun to be a reality in clinical practice since the historical publication by Shapiro et al. in 2000, with the now famous Edmonton protocol.

Although simple in theory, the achievement of a proper isolation of islet cells in adequate facilities is one of the critical steps of the process. Islet cells are dissociated from the exocrine tissue by enzymes (collagenase, liberase) and are visualized with dyes. Then, they are separated from the exocrine tissue by density gradients until obtaining them with the hig-

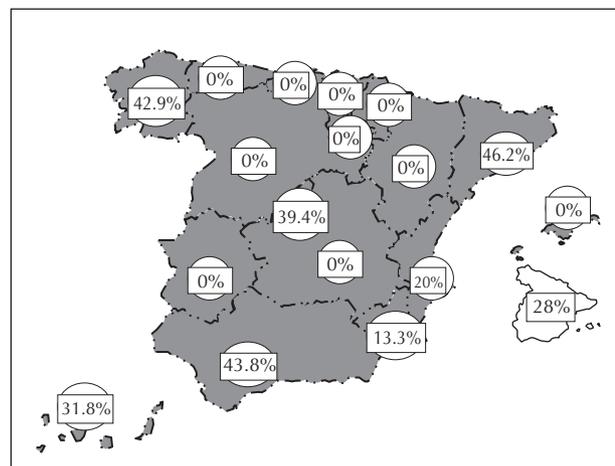


Fig. 5.—Utilization level of potential pancreas donors in Spain by autonomous community. The figures are expressed in percentages of utilization.

hest possible degree of purity. The more the age of the donor the more delineated the islets are, which makes the isolation complicated in young and almost impossible in children.

Once isolated and purified, the islets are injected in the portal vein by interventional radiology until its deposition in the periphery of the liver in a maneuver that does not require general anesthesia, the potential complications being hemorrhagic or local thrombotic phenomena (table II). Although early outcomes were really encouraging, there are several clouds on the horizon for this procedure that make it cannot be considered a consolidated therapy but one in clinical trial phase. In the first place, the early one-year survival rates of 80% of patients free from insulin dropped to 50% three years later, a figure clearly lower than the one achieved with pancreas transplantation. On the other hand, the center effect is evident with success rates very different from one hospital to another, making that the current 50% estimation of primary malfunction has varied between 0 and 100%. Moreover, most of the patients require two or up to three islet infusions, which complicates, burdens the cost and restricts the procedure.

Although there exists the more or less spread idea that pancreas and islets compete with regards to deviation of pancreas to one or the other procedure or to the adscription of patients to one or the other therapy, in Tables I-III it can be observed that overlap is very limited, at least from the time being. However, it does not preclude that we could foresee a series of potential conflicts already present in some areas of Europe and the USA that, as it many times occurs, the outcome may vary depending on the

Table II. Pancreas versus islet transplantation

| | Pancreas transplantation | Islets transplantation |
|-----------------------|--|--|
| First transplantation | 1966 | 1974 |
| Worldwide experience | 20,000 cases | 900 cases |
| Surgery | Laparotomy-Major surgery | Intervention radiology-minimally invasive |
| Number of donors | 1 | ≤ 3 |
| Free from insulin: | | |
| At one year | 85% | 80% |
| At three years | 80% | 50% |
| Complications | <i>Frequent-severe:</i> Graft thrombosis Peritonitis Graft pancreatitis | <i>Infrequent-mild:</i> Portal thrombosis Hemorrhage |
| Mortality | Low (less than 4%) | Exceptional |

Table III. Contraindications and exclusion criteria for pancreas and islets transplantation

| Recipient criteria | Pancreas transplantation | Islets transplantation |
|---|--------------------------|----------------------------------|
| Age | < 50 years | < 65 years |
| severe cardiac or respiratory disease | X | |
| Ilio-femoral and mesenteric severe angiopathy | X | |
| Daily insulin requirements | No limits | < 50 U/day < 0.7 U/kg/day |
| Body weight | No limits | < 70 kg (woman) < 75 kg (man) |
| Body mass index (BMI) (kg/m ²) | No limits | < 26 |
| Thrombophilia | | X |
| Hepatopathy, chronic hepatitis | | X |

local preferences, capabilities or likings for which the sooner the solution the better the outcome.

The islets would be preferably indicated at the current time in the labile diabetic with normal renal function, limited weight and without excessive insulin requirements that greatly limit the indications. With regards to donors (table I), although there is a real overlap, especially with age, the evident tendency is to derive the younger patients to pancreas and the older ones to islets. However, everything indicates that, as the outcomes will be more established, these criteria will be extended.

Making a similar estimation as described for pancreas transplantation, and excluding donors included among potential donors for complete organ, the number of susceptible donors for pancreas extraction for islets was 228 in 2003, 15.8% of the total, also an increasing estimate. Linked to 18% of pancreas, we would be talking about 33.8% of donors, the third part of registered donors in our Country, which is the same to an annual figure of approximately 500 being potential pancreas or islet cells donors.

However, the real number that we could use and especially the number of patients to treat will be much lower even if the process is fully optimized. Distances and ischemia times do exist, the donor and recipients distribution by blood type makes that they are difficult to fit in small lists and, on the other hand, considering an organ inadequate for a transplantation depends on local criteria or decisions, sometimes totally unpredictable but always lower than the «maximal» consideration that we have done here. In the case of islet cells, the already mentio-

ned use of two or three pancreases by patient and the fact that performance of the pancreas used for isolation is not greater than 50%, together with logistic factors even more demanding than for the whole organ, drastically reduce the number of susceptible, treatable patients. A simple and rapid estimation of these figures and taking into account the huge number of diabetic patients show us in a clear and unequivocal way that, in case this procedure would consolidate, it could only benefit a minimal proportion of patients. The big scale solutions would have to wait for the possibility of obtaining endocrine pancreatic cells from stem cells, a many times pointed out possibility but still today aloof in clinical practice.

THE SPANISH AND EUROPEAN SITUATION

Following the Edmonton protocol, in Spain only 2 islet cells implants have been performed at Hospital Carlos Haya of Malaga, in 2002. The ones performed at Hospital Clínico of Madrid in the 1990s were done with old protocols of isolation and immunosuppression, previous to 2000. In spite of this, pancreases are already being processed with research goals and eventual future implant in at least 7 Spanish cities (and in some of these cities in more than one center), with incipient local interests in some others.

A simple categorization of potential pancreases by autonomous communities or areas of influence, of the necessary organs to transplant a single patient and of their temporal cadency highlights that the way undertaken of diversifying efforts is not precisely the more indicated and that certain rationalization of this therapy in the early phases would be more welcome. Moreover, the publication in recent years of up to three European Union directives oriented in a clear way to the consecution of the maximal quality standards for product and citizen safety has made necessary to reconsider in a radical way procedures such as islet infusion, classifiable under the concept of «somatic cellular therapy». According to the 2003/63 EC directive, somatic cellular therapy is defined as «the use in humans of autologous somatic (of the patient himself), allogenic (from another human being) or xenogenic (from animals) living cells whose biological characteristics have been substantially altered as a consequence of manipulation for obtaining a diagnostic, preventive or therapeutic effect by means of metabolic, pharmacological or immunological procedures».

The inclusion of islets implants in this section, although questionable from a theoretical point of view

and discussed in several European settings, seems an irreversible process. It basically implies two things: on the one hand, as with any other cellular therapy, it *turns to be considered a medication* and its use is regulated by similar criteria that the ones used for high standards (GMP rules) with regards to facilities, equipment, staff and methodology. On the other hand, its consideration as a medication obliges to initiate its use as a clinical trial, according to 2001/20 EC Directive. To close the circle, the recently approved 2004/23 EC directive on quality and safety of cells and tissues, not yet transposed to our regulations, establishes the correspondent standards that will have to be accomplished in donation harvesting, assessment, processing, preservation, storage and distribution of every type of cell and tissue.

On the other hand, the practical aspect of the implementation of these directives is the necessity, on the one hand, to *conceive islet cells implant as a clinical trial*, with all that it implies with regards to controls, authorizations, etc. and, on the other hand, having the facilities in agreement with the GMP requisites. In the European document mentioned above, the estimated cost for these facilities is between €1 and €2 million. Isolation costs from pancreases have to be summed up and they range from €10,000 and €20,000, and taking into account that only 50% of processed pancreases supply valid islets and that most of the patients need at least 2 infusions, the isolation cost per patient can be estimated to be between €40,000 and €50,000. From an administrative point of view, the authorization to initiate one of these trials corresponds to the AGENCIA ESPAÑOLA DEL MEDICAMENTO (Spanish Medication Agency) with the previous ONT report, as the technical body in charge of the clinical application of cellular therapy in Spain.

Considering the costs of the necessary facilities to fulfill these quality requirements, the necessary, sufficient and maintained expertise in isolation, with a protracted learning curve as one of the factors that explain the main differences between centers, and the need for a good selection of patients, the option of working in a national or supranational network of the kind of the already existing (NICE; GRAGIL, etc.) is suggested. This scheme derives from the convenience for regrouping isolation centers, always considering the distance criteria to donor hospitals, ischemia time and costs in order to optimize the existing resources. In Central Europe, with demographic and distance characteristics clearly different from the Spanish ones, it has been evaluated the convenience for having one isolation and islet preservation center every 10-20 million inhabitants,

which would offer the possibility of isolating 100-200 islets/year/center. Some experts consider that at least two pancreases must be processed every week to maintain an adequate training degree for the team, without considering the basic cost for maintaining in alert the whole structure for harvesting and processing.

SUMMARY: ACTIONS TO UNDERTAKE

As it can be noticed, the situation is as complex as fascinating and, of course, it is a clear example of the need for a coordinated action at a national and international level, especially in view to anticipate to the changes and the supply/demand disproportion that inevitably will occur in an intermediate term. Because the European Council has already started to work on the topic, there is a good reason for confronting the situation at a national level with no delay.

For all these reasons, the Organización Nacional de Trasplantes (National Transplantation Organization) has wanted to open an information and reflection process with all the implicated agents on the topic: surgeons, endocrinologists, nephrologists, coordinators, investigators, people responsible for islet cells extraction and manipulation processes, and eventually any other interested group on these transplantations. The goal is first to gather all the available information (which is not easy to summarize given the very different aspects that intervene in the topic), for later creating a multidisciplinary working group that will elaborate a document where all of these key points will be considered. Later on, a consensus would be initiated on the recommendations elaborated by all the implicated parties.

For the first time this working group got together in December 10th 2004 and it included representatives of:

- National Transplantation Organization
- Autonomic Coordinators (Transplant Commission of the Inter-territorial Council)
- Spanish Society of Nephrology
- Spanish Association of Surgeons
- Spanish Association of Urology
- Spanish Society of Endocrinology
- Spanish Society of Diabetes
- Spanish Network of Pancreatic Islets
- Spanish Network of Cellular Therapy
- Spanish Society of Immunology

In this meeting, after broadly setting out all of the aspects here referred, all of the attendees expressed the convenience and need for this process and the will of the corresponding represented societies to reach a global agreement about the topic. The correspondent working group was established, which has already started to elaborate the proposal document. The points to tackle are many and correspond to the presentation that we have done in these lines through all the process. Criteria for indication of one or the other therapy, prioritization criteria, organ distribution, teams traveling, pancreas extraction for transplant or for islets, planning criteria for islet centers and a large etcetera.

The existence of this group is not an impediment for not making a detailed presentation of the problem to all the different implicated groups throughout the first months of 2005 with the goal that the initiative will be widely known and that future outcomes will benefit from a broad consensus. The idea is to pursue these processes throughout the next months to end up in a consensus meeting to which all interested people will be invited and of which an ample broadcast will be done.

An Arab proverb says that «the easy is already done, the difficult will be done and the impossible will be overcome». Although there are many and different actors that intervene in this problem, there exists a good will of getting along that with any doubt will lead us to find out the better solutions in a reasonable term. There are many diabetic patients that can benefit from the optimization of the process.

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