Preservation of Intra-Abdominal Organs for Transplantation

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The history of clinical organ transplantation and its development in routine surgical practice has been packed into the last 40 years and is encompassed by the careers of many of the pioneers of transplantation. Improved immunosuppression, surgical, anesthetic, and postoperative management have transformed results and allowed many new organs to be transplanted. Progress in preserving organs for transplantation has lagged behind the other advances in transplantation. Until the introduction of UW solution, no major progress was made after the introduction of machine perfusion preservation by Dr. Belzer in 1967 and that of simple cold storage by Dr Collins in 1969. This solution was developed at the University of Wisconsin and has allowed extended simple cold storage of the pancreas, liver, kidney, and more recently, the small bowel prior to transplantation. The UW solution represents a good answer to the problem of short-term storage of organs for transportation and early reimplantation, but equally important, it has also stimulated renewed research interest in this area. A more profound understanding of the events occurring during hypothermic storage and subsequent reperfusion is needed if further advances are to be made. It is anticipated that if long-term organ storage is to be achieved this will require a perfusion preservation system that allows the maintenance of essential metabolic processes.

INTRODUCTION

The history of modern transplantation as a useful clinical modality is relatively short, and almost all of the significant developments in clinical practice and application have taken place within the last 40 years. Nonetheless, the rapid advances in clinical application in this recent period are based on the pioneering efforts of earlier workers who developed the techniques and disciplines that formed the foundation on which our modern transplantation edifice is built. Notable contributions were made by Carrel and Guthrie in the early 1900s who developed the techniques of vascular suturing. Alexis Carrel went on to show that removal of organs and their reimplantation was possible, although he failed to recognize the importance of the immune response in the failure of organs transplanted between different individuals. The full recognition of this immune reaction was not defined or explored until Peter Medawar and his coworkers began to explore the new field of immunology in the '40s and '50s. Clinical application of transplants was still not possible in the absence of methods of defeating rejection, except in the rare cases where the problem could be avoided by transplanting tissues between genetically identical individuals as in the special case of identical twins. Successful grafting of organs between nonidentical donor and recipient became possible only with the introduction of drugs that interfered with immune response. The first of these drugs were steroids, followed by the introduction of the anti-metabolite azathioprine, which marked the first major step in chemical immunosuppression. This was followed in turn by the development of newer more potent agents starting with Cyclosporin A and moving on to a host of other new agents, such as FK506, Rapamycin, and many more, developed in the last few years .

As the practice of organ transplantation expanded and extended, it became apparent that there was a need to store organs for variable periods of time before they would be reimplanted in the recipient—thus allowing time for tissue typing and transportation of organs from distant sites to the center where the organ would be transplanted.

Why preserve organs?

Organ preservation refers to the protection of the organ during the period of storage between its removal from the donor and the restoration of its normal blood supply in the recipient.

In living related transplantation, it is possible to carry out screening and tissue typing procedures in advance of organ donation. Thus, the organ ischaemic period can be kept to a minimum in the case of living related renal transplantation where it is possible to perform the donor and recipient transplant procedures in adjacent operating theaters allowing the organ to be transferred from one patient to the other directly. This fact probably contributes significantly to the advantages of living related transplantation over cadaveric transplantation with one-year graft survival rates in the order of 95 percent being commonplace in the former. This favorable opportunity to minimize ischaemia does not apply in transplantation where the organs are obtained from a cadaver. Not all patients have a suitable, appropriately motivated living related organ donor, and the majority of kidney patients receive a cadaveric organ. In the case of other solid organ transplants, living donor donation is not an option. The heart is an obvious example, and using this option in the case of liver, pancreas or lung transplantation is experimental at best, with what many feel are unacceptable risks to the donor.

In cadaveric organ donation, many organs may be removed from a single donor; simultaneous removal of heart, lungs, liver, pancreas and kidneys are routine with each organ going to a separate recipient. Complex logistical arrangements are involved, and safe storage and preservation techniques are needed for each graft to allow for transfer to the recipient hospital and implantation. It is important to minimize the damage incurred by the organ during this period so that an immediate life-sustaining function is established when the organ is revascularized. Only in the case of the kidney is there the option of a "safety net" provided by the availability of dialysis to tide the patient over until a damaged graft recovers. But even here, the establishment of good early function increases the chances of long-term graft success and minimizes hospital stay and cost.

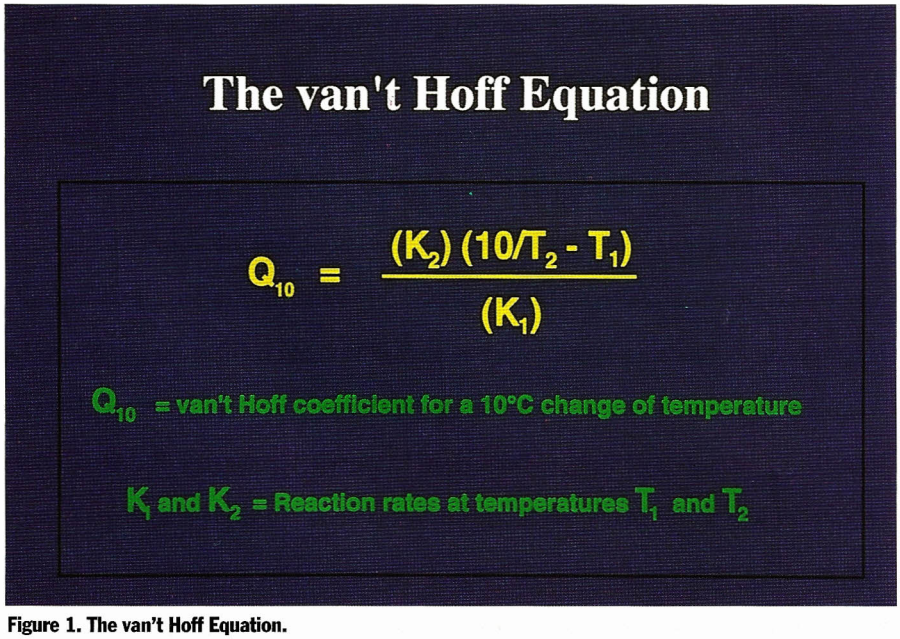

Figure 1. The van't Hoff Equation.

How can we preserve organs?

The human body maintains normal metabolic activity in organs using a complex system of homeostatic mechanisms in an integrated functioning whole. It includes defense mechanisms against infection and has a life expectancy of 70 years or more. Attempts to replicate this exemplary situation using perfusion systems at temperatures close to normal body temperature have been bedeviled by infection and rapidly developing graft damage. Carrel and Lindbergh came closest to making such a system work in the 1930s using an elaborate sterile technique and copious amounts of

fresh serum with atraumatic pump and oxygenation systems. This approach has seen no practical development, and reliance is currently placed for all organs and tissues on the benefits obtained by using hypothermia.

Hypothermia is the principal factor applied in practical organ preservation. Cooling an organ to the temperature of melting ice maximizes the benefits of reduced temperature by reducing metabolic activity and by avoiding damage to cells by inadvertent freezing which may occur if more complex cooling systems are used. Attempts at freezing and then thawing solid organs, as opposed to the reliable long-term storage, have been uniformly unsuccessful in achieving satisfactory function, which has been achieved for simple unicellular systems such as spermatozoa. The van't Hoff equation (Figure 1) tells us that a reduction of temperature from 37°C to 0°C will reduce enzymatic activity and metabolic requirements by a factor of approximately 12. A simplistic approach to the matter suggests that this sort of factor can be used to multiply the period of normothermic ischaemia that an organ will tolerate and extend the safe ischaemic period for a kidney or liver from 1 to 12 hours. This underestimates the complexity of the physico-chemical and metabolic situation that applies in an organ under hypothermic conditions, but nonetheless, illustrates the potential advantages of hypothermia.

The van't Hoff equation describes the effects of temperature on enzyme related processes, although not all are affected equally and that the effects of cooling on simple physico-chemical processes such as ionic movements across the cell membrane are much less. This has adverse effects on the essential homeostatic mechanisms involved in the maintenance of cell volume. Crucial to this mechanism under normal conditions is the activity of the sodium pump. This membrane-bound enzyme system utilizes ATP under normothermic conditions to exchange sodium ions inside the cell for potassium ions outside it. Decreased activity of this pump mechanism during hypothermia will allow sodium to accumulate in the cell, followed by the accumulation of chloride and water, resulting in cell-swelling unless some counter acting mechanism is introduced. This is done by using specially formulated preservation solutions to replace the blood in the organ. This solution will minimize ionic movements and cell-swelling by physico-chemical methods. This property is generally referred to as the "solution effect."

Practical development of organ preservation

Initial attempts at transplantation made use of simple surface cooling with ice slush, but this is a relatively inefficient method of cooling down a bulky solid organ. The first major refinement was the introduction of flush cooling where the aorta is cannulated and the organ perfused with an ice cold flush solution, which rapidly lowers the core temperature to 15°C to 20°C and efficiently removes blood from the organ.[1]

The next step forward came by Dr. Folkert Belzer in 1967 [2] with the introduction of the concept of hypothermic machine perfusion with a cryoprecipitated plasma based solution for kidney storage. In his system, organs were flush cooled as already described and then attached to a pump circuit incorporating a membrane oxygenator. This method made use of the advantages of hypothermia, but with the theoretical advantage of maintaining aerobic metabolism, albeit at a low rate. The system was complex, but effective, in

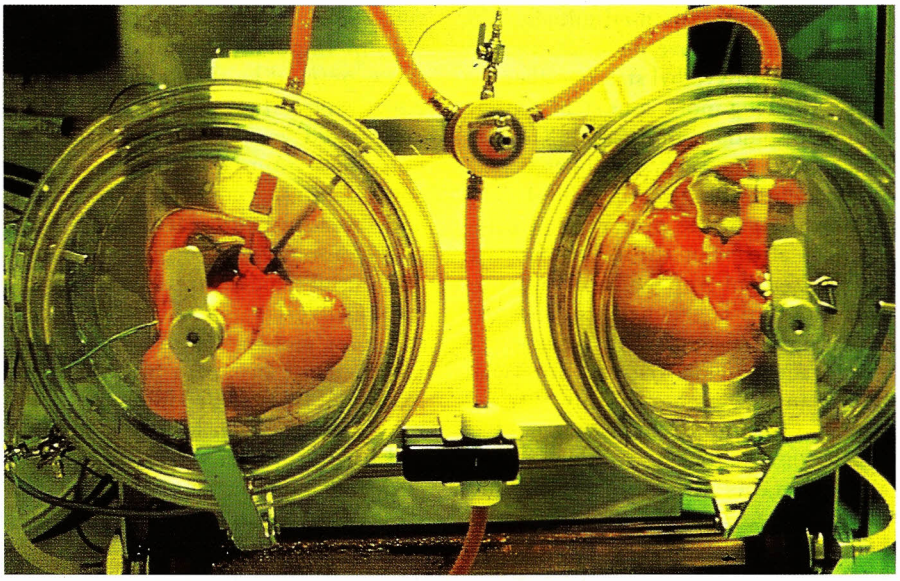

Figure 2. A pair of kidneys undergoing machine perfusion preservation. By kind permission of Drs Belzer and Southard of the University of Wisconsin Hospital and Clinics.

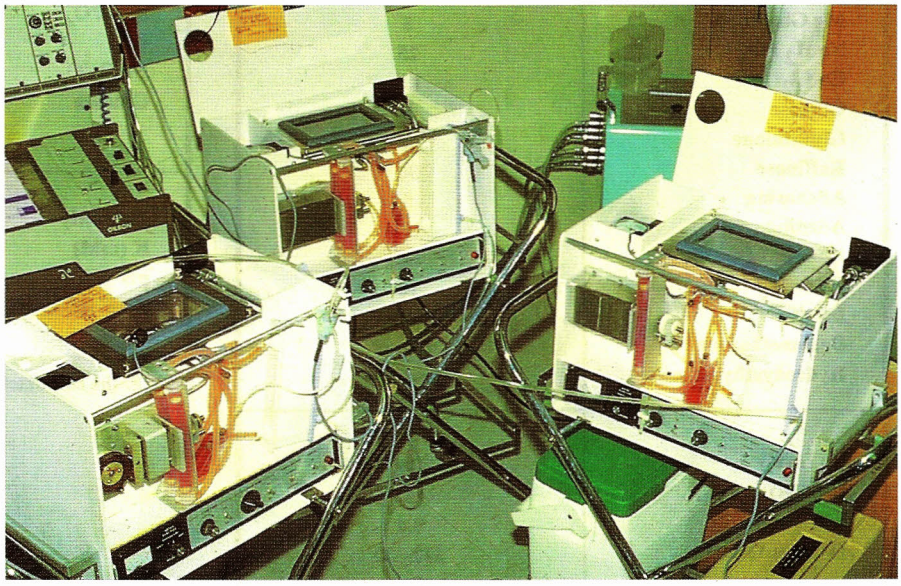

Figure 3. Three "Belzer" portable machine perfusion devices being used to perfuse human kidneys. By kind permission of Drs Belzer and Southard of the University of Wisconsin Hospital and clinics.

allowing kidneys to be stored experimentally for as long as 72 hours. A pair of kidneys undergoing perfusion preservation in this fashion in Dr. Belzer's laboratory is illustrated in Figure 2 (by kind permission of Drs. Belzer and Southard). Refinements were introduced to allow portable systems to be used, and Figure 3 illustrates 3 such "Belzer" preservation units used to preserve kidneys in a cold room at 4°C (by kind permission of Drs. Belzer and Southard). Many units, particularly in the United States still use this technique today with extremely good results. The presence of a colloid is essential in machine perfusion preservation systems to provide oncotic support and prevent tissue oedema by the Starling mechanism. Albumen was used initially, but newer solutions have been introduced based on hydroxyethyl starch as the colloid—allowing more consistent, purely synthetic solutions to be used. The formulation of one such starch-based perfusion solution[3] is given in Table 1. The composition of the preservation solution has also been altered to increase the content of impermeant moieties and metabolic precursors, and Dr. Belzer's unit are currently reporting a post-transplant dialysis rate for renal transplant recipients of only 8 to 10 percent using this technique.

The disadvantage of machine perfusion remains its complexity and expense, and in 1969, Geoffrey Collins published a simpler technique based on simple cold storage, in which the organ was flushed with chilled preservation solution and then surrounded by the same solution and packed in melting ice.[4] This approach was the first specific application making use of the "solution effect" to counter the physico-chemical effects of hypothermia and was effective out to 30 hours of storage, as was promptly demonstrated by the successful transfer of stored kidneys from Los Angeles to London, Tel Aviv and Sydney. The Collins solution was designed to minimize ionic movements across the cell membrane by mimicking the composition of intracellular fluid, although in retrospect, it was probably the inclusion of impermeant substances that were primarily responsible for its effectiveness. Eurocollins[5] (Table 2), a simplified variant of the solution, became a popular and widely used solution first for renal preservation and later for pancreatic and hepatic preservation.

Considerable research was devoted to the investigation of preservation solutions and the examination of the mechanisms involved but, with the exception of the introduction of a citrate based solution by Ross, Marshall and Escott,[6] which was adopted in the United Kingdom, Australia and New Zealand, little clinical progress was made. This solution (Table 3) has been widely used for renal transplantation, and some units have also applied it to liver preservation. Its mechanism of action is derived partly from the impermemant properties of mannitol but also, in part, from the poorly understood properties of the citrate moieties.[7] A human kidney that has been flushed in Ross and Marshall's solution and packed in the cold preservation fluid is illustrated in Figure 4(a) and packed in ice in a UK Transplant Service insulated box prior to transportation in Figure 4(b).

Transplantation practice was adapted to cope with the time restrictions of storage, which gave a reasonably comfortable time of 24 to 30 hours using simple cold storage for renal transplantation (thus allowing time for tissue typing and patient preparation, although at a price of a dialysis requirement of 30 percent to 50 percent while the kidney recovered following prolonged storage). The slow, progressive decrease in viability during storage, with transitions from immediate function to delayed function to no function, is illustrated in Figure 5. However, for the heart and liver where immediate function is crucial, this safe storage limit was 4 to 6 hours for the heart and 6 to 8 for the liver. Thus such transplants required complex

Constituent	Concentration (mM)
K Gluconate	100
Mg Gluconate	5
Na H_2 PO_4	25
Ca Cl_2	1.5
Glucose	5
Glutathione	3
Raffinose	30
Adenosine	5
Adenine	1
Ribose	1
HEPES	10
Insulin	100U
Dexamethasone	16mg
Hydroxyethyl starch	5gm%
Na (mM)	30
K (mM)	125
pH	7.4
Osm. (mOsm/L)	320-330

Table 1. A Hydroxyethyl starch based machine perfusion solution.

Constituent	Concentration (mM)
KH_2PO_4	15
K_2HPO_4	42.5
KCl	15
Na HCO_3	10
Glucose	194
Na (mM)	10
K (mM)	115
pH	7.0
Osm. (mOsm/L)	355

Table 2. The constituents of the Eurocollins solution.

coordination of donor and recipient procedures to minimize the ischaemic time as well as rapid transport of organs from donor to recipient hospital, often using aircraft or helicopters. The introduction of the procedure of heart-lung transplantation was initially accompanied by concerns over the safety of any preservation technique for the lungs, which resulted in the transfer of heart-beating, ventilated, brain-dead donors to the recipient hospital so that the donor and recipient procedures could be performed simultaneously in adjacent operating rooms. Similar concerns in our own unit in the early days of liver grafting had resulted in the opposite scenario: the recipient was transferred to the donor hospital and the transplant performed there. Techniques using controlled core cooling on bypass and the development of dilute blood-based "pneumoplegic" solutions soon overcame this concern, but the safe preservation time remained short.

Thus ingenuity and careful coordination overcame the barriers to practical transplantation even where donor and recipient hospitals were considerable distances apart. This practical solution was achieved at a cost measured not only in financial terms (due to the widespread use of aircraft), but also measured in the safety of the recipient, if unexpected delays occurred, and in the risk to the donor teams, some of whom have been injured or even killed hurrying to return organs to the recipient hospital in dangerous weather conditions.

Despite continued research efforts, little progress was made, and gradually, interest and activity in the field declined leaving only a few laboratories, such as that of Drs. Belzer and Southard in Wisconsin and Dr. David Pegg in Cambridge, England actively working in this field. And it was in the laboratory of Belzer and Southard that the next major advance occurred.

The coming of UW solution

The main thrust of work on this front continued to be directed at the development of machine perfusion techniques with the continuing refinement of perfusates, including metabolic substrates, and the achievement of small incremental improvements in renal preservation. As part of this work, attention was directed at impermeant moieties, which could be used in preservation solutions to minimize cell-swelling.

Jan Wahlberg, a Swedish surgeon, came to Wisconsin to work on pancreas preservation in 1985. The pancreas was thought to be susceptible to damage during perfusion preservation, and efforts to produce a better preservation medium for this organ were thus directed at simple, cold storage. He reported a successful 72-hour preservation of the canine pancreas[8] using a new cold storage solution based on an impermeant trisaccharide raffinose and an impermeant anion lactobionate used to replace chloride; hydroxyethyl starch as a colloid from machine perfusion practice; and a number of other substances. The aim was to reduce free radical damage (allopurinol),

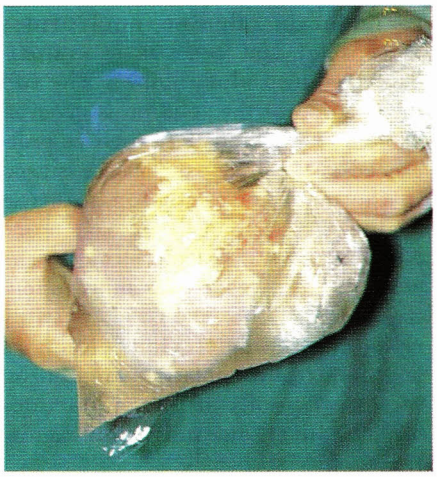

Figure 4a. (above): A human kidney which has been flushed with Ross and Marshall's solution and is packed in the same solution prior to (b) (below): storage in melting ice in an insulated UK Transplant service kidney storage box for transportation.

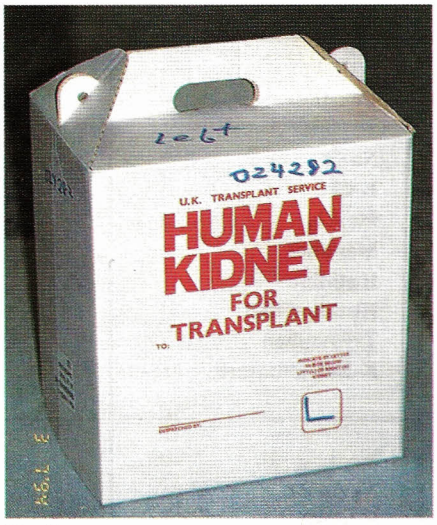

Fig. 4b.

Constituent	Concentration (mM)
Na Citrate	27.5
K Citrate	27.5
Mg SO_4	35
Mannitol	187
Na (mM)	80
K (mM)	80
pH	7.1
Osm. (mOsm/L)	400

Table 3. The constituents of Ross and Marshall's solution.

Constituent	Concentration (mM)
K Lactobionate	100
Na Lactobionate	-
Na KH2 PO4	25
Mg SO4	5
Glutathione	3
Raffinose	30
Allopurinol	1
Adenosine	5
Penicillin	200,000U
Insulin	40U
Dexamethasone	16mg
Hydroxyethyl starch	5gm%
Na (mM)	30
K (mM)	120
pH	7.4
Osm. (mOsm/L)	320-330

Table 4. The constituents of the commercially available UW solution.

to maintain adenine nucleotides (adenosine), and to act as an anti-oxidant (reduced glutathione). The full formulation of the solution is given in Table 4. Lactobionate is used in preference to the gluconate, which is used in the machine perfusion solution (Table 1), because it proved more effective for simple cold storage. The gluconate, however, was more effective for machine perfusion, possibly reflecting the deleterious effects of lactobionate in chelating calcium on the integrity of cell-to-cell junctions under continuous perfusion conditions.

When Wahlberg described his results at the American Society of Transplant Surgeons meeting in the Summer of 1986, I was excited by the possibilities raised by this new solution and approached Dr. Belzer and began work in his laboratory with the new solution in a liver transplant model during autumn of 1986. Initial results in an isolated perfusion system were encouraging,[9] and the solution was next tested in a dog orthotopic liver transplant system. Good quality preservation was achieved at 24 hours,[10] and eventually, livers were successfully preserved for as long as 48 hours,[11] although with some damage and delay in the establishment of full function. The effectiveness of the solution in suppressing cell-swelling and tissue oedema is illustrated in Figure 6, which shows the percentage changes in water content of liver tissue stored in both UW and the older Eurocollins solutions (the UW solution being clearly superior). Rutger Ploeg, a Dutch surgeon working in the laboratory at the same time, was able to show excellent canine kidney preservation at 72 hours,[12] indicating that this solution could be used for all intra-abdominal organs.

The laboratory findings were rapidly transferred to clinical practice with

Constituent	Concentration (mM)
Na Cl	15
K Cl	9
$Mg Cl_2$	4
Mannitol	30
Histidine	180
Histidine HCl	18
Tryptophan	2
K-Ketoglutarate	1
Na (mM)	15
K (mM)	9
pH	7.1
Osm. (mOsm/L)	300

Table 5. The constituents of Bretschneider's HTK4 solution.

Constituent	Concentration (mM)
Na Cl	115
K Cl	5
$Ca Cl_2$	1.3
$KH_2 PO_4$	1
$Mg SO_4$	1.2
Hydroxyethyl starch (gm/litre)	50
Allopurinol	1
Desferrioxamine	1
Glutathione	3
Nicardepine	2
Adenosine	1
Fructose	10
Glucose	10
Insulin (IU/Litre)	100
MOPS	20
pH	6.5

Table 6. The constituents of the Carolina Rinse solution.

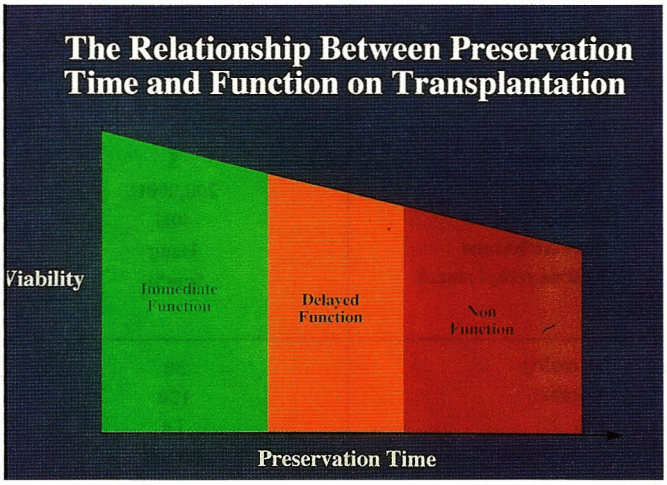

Figure 5. A schematic representation of the relationship between preservation time and function on transplantation.

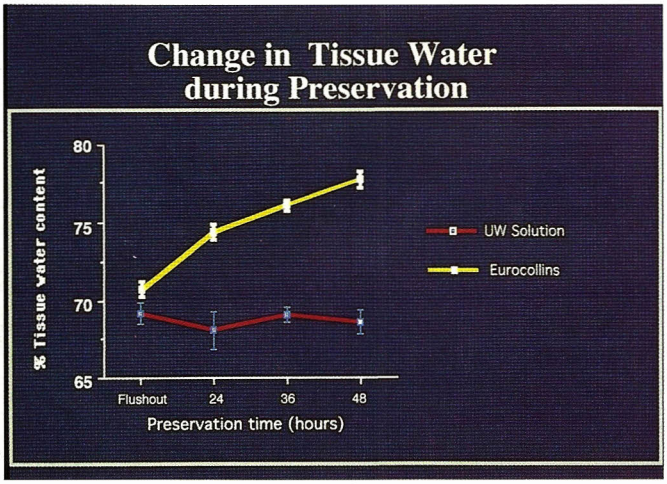

Figure 6. The change in tissue water during preservation of rat livers flushed and then stored in either UW or Eurocollins solutions for 24, 36 and 48 hours.

the greatest impact on the practice of liver transplantation. A practical, simple method allowing safe storage time of 12 to 16 hours permitted semi-elective planning of the surgical procedure. Figure 7a illustrates a human liver that has been flush cooled and perfused prior to removal from the donor. It is in a bowl surrounded by UW solution within a double wrapper of plastic bags and placed in an insulated picnic basket, which is packed with melting ice (Figure 7b). It is accompanied by separately packed donor blood samples for virology screening and donor iliac vessels in case vascular reconstruction is needed to reach appropriate arterial and venous inflow vessels in the recipient. This longer safe-storage period removes the danger of preservation-related organ damage if the recipient procedure proves unusually difficult, delaying revascularization. This method allows the surgeon to work slowly, steadily and safely—confident that an additional 2 or 3 hours storage time for the liver will not result in the graft failing to function.

This solution has become the standard preservation medium for multi-organ procurement of intra-abdominal organs. Simplified variants and even solutions with reversed ratios of sodium and potassium have been shown to be effective in the human liver but have not proved to offer any significant advantage in any studies to date. Other solutions based on somewhat different principles have also been described, such as the Bretschneider HTK 4 solution[13] (Table 5), which was initially designed as a cardioplegic solution. This solution is a remarkably effective buffer, reasonably protective against cell-swelling that has been shown experimentally and in clinical practice to be effective in liver and kidney preservation. It is, however, probably not as effective as UW solution. A different approach is represented by the Carolina Rinse solution,[14] which is used to wash out the organ at the end of the preservation period immediately prior to reperfusion with blood. This has a number of components in common with the UW solution and also contains anti-oxidants, iron chelators, free radical scavengers and calcium channel blockers to minimize the effects of reperfusion injury. It also has fructose, glucose and insulin, which have been suggested to improve post-ischaemic energy status. The formulation of this solution is given in Table 6.

The initial enthusiasm for longer preservation of the liver led many groups to extend preservation times close to or beyond the 24 hours of reliable safe storage obtained experimentally. It must be remembered that the experimental situation represents a perfect donor and perfect recipient, a situation seldom encountered in real-life clinical practice. There is a growing appreciation in human clinical practice that longer storage periods are associated with an increased likelihood of impaired early function or even of non-function. The difficulty of flushing out the biliary tree in a liver graft, and the increased susceptibility of the biliary epithelium to injury during hypothermia in the presence of bile, has resulted in a number of groups reporting increased biliary complication rates in the grafts stored for more than 13 hours. In our own practice, we remain happy with preservation times out to 14 to 16 hours,[15] but our median storage time is 11.5 hours, which allows all of the advantages of semi-elective operating without risking increased graft injury.

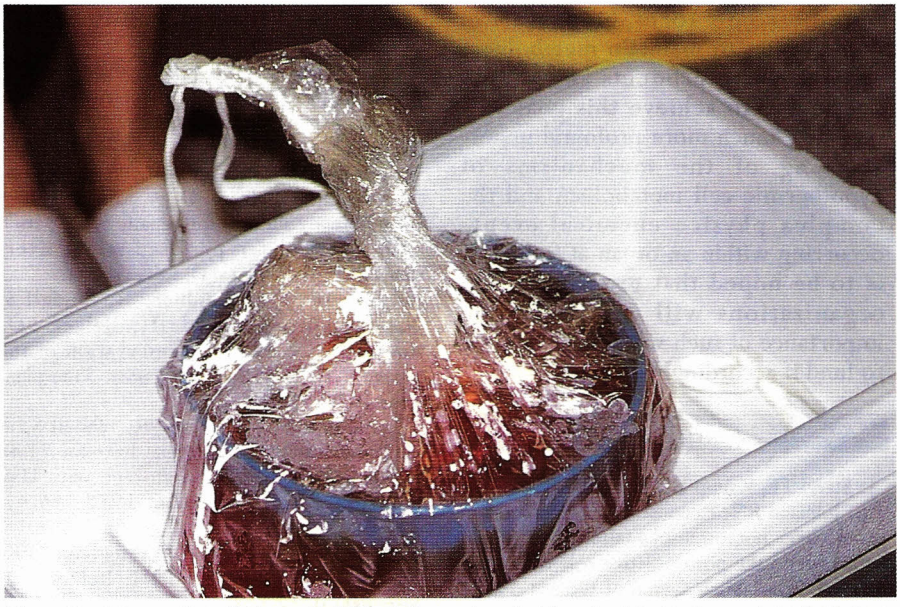

Figure 7a. A human liver flushed with UW solution and packed in a bowl inside two sealed plastic bags surrounded by UW solution ready for b) storage surrounded by melted ice. The additional containers in the organ storage box contain spare iliac vessels from the donor and donor blood samples.

Figure 7b.

What comes next?

The introduction of UW solution has proved to be a great stimulus to work in the field of organ preservation. As yet, no alternative has appeared that rivals the UW solution. Many simple modifications of the original formulation that omit components or substitute others[16,17,18,19,20] have been described, but none offer major advantages for all organs.[21] Simple cold storage continues to be appealing because of its simplicity and because it is the easiest practical solution for storage and transportation of organs for the relatively short time periods currently used. Longer term preservation, if it is ever to be achieved, will require some form of perfusion preservation to maintain metabolism, remove waste products and supply nutrients. To achieve this goal will require a much more profound understanding of the mechanisms of hypothermic cell metabolism and the complex physico-chemical events occurring within an organ at 0-4°C. It is to be hoped that grant-awarding organizations will appreciate the importance of such work and continue to fund it accordingly. STI

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