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Discussion

Dr. Leslie E. Rudolf (Charlottesville): At the present time there are two basic methods of preserving kidneys. One is to perfuse the organ on some type of pulsatile apparatus and, more generally, pump it with some type of cryoprecipitated plasma. The other method is simpler, less complex, not as expensive, and does not require individual monitoring. This method, as Dr. Humphries has done, is to flush out the kidney with some type of a solution and place it under hypothermic storage.

The result of Dr. Humphries' work and that of others has enabled the latter methods to approach some of the results that we achieved with pulsatile perfusion. We realize that with pulsatile perfusion we encounter many difficulties. We are dealing in this country with five or six regional organ donor programs that are interlinked with a computerized system, and when we consider transplanting or transporting organs between and among institutions, we should provide for the simplest, easiest, and least expensive technics. Some of the work that Dr. Humphries has been doing has made a significant contribution to the area.

Preservation experiments include many variables: storage temperatures, perfusate composition, perfusate flows and rates, pressure, and the element of storage duration. Dr. Humphries' study has been well controlled, and I believe the most important aspect of this work has been to measure preserved function by the ultimate test, and the ability of the kidney to sustain the dog's life.

I would like to ask Dr. Humphries one question: Would it not have been better to reimplant the 48-hour preserved kidneys as autografts rather than allografts, in an attempt to obviate some of the subsequent impairment of function that may have resulted from graft rejection, rather than changes that occurred as a result of organ preservation?

In closing, I would like to be somewhat philosophic and say that I think all of us interested in organ perfusion and preservation should be looking more closely at the effects of our technics on the vascular endothelium in the preserved organ. After all, it is the endothelium and its surrounding smooth muscle that is responsible for vasoconstriction, vasodilation, the transcapillary movement of water, nutrients and electrolytes, and hence ultimately responsible for organ edema, metabolism and ion exchange, all of which determine an organ's basic function.

Dr. John McDonald (New Orleans): Dr. Campbell's paper nicely defines the various syndromes that rejection may produce. His manuscript outlines the many diagnostic tools that can be used in establishing the diagnosis of rejection. The multiplicity of these methods makes it obvious that it is sometimes difficult for the clinician to determine whether or not he's dealing primarily with rejection or some other intercurrent problem, and even if all of these methods were ideal, it is evident that all of the signals of rejection that are now in use occur too late; that is, they are all a reflection of injury to the grafted organ. Of more value would be a means of establishing when rejection is about to occur, before organ damage is apparent. In this regard I would like to relate some experiments currently proceeding in our laboratory.

All people have a circulating antibody to rat erythrocytes which is apparently a naturally occurring immunity. Milgrom and colleagues noted a few years ago that the titer of this antibody was substantially higher in patients bearing renal allografts that were doing poorly than in patients bearing allografts that were functioning normally. We began to study this heterophile antibody for other reasons, but have encountered an interesting set of observations.

(Slide) This slide is not current. It shows the changes in the heterophile titer which occurred in 14 patients. Our data now include 25 patients, and 31 rejection episodes. The titer rose more than four times the control in only two of twelve patients studied who never had any rejection episode. However, it rose sixteenfold in seven of eight patients who had rejection crises which were not controlled. The dotted portions of these lines show the temporal relationship with the rise in titer and the change in clinical function.

Small changes in titers occurred in four of five

patients who had reversible rejection episodes, while no changes occurred in six patients with chronic rejection.

The particularly pertinent aspect of these studies is the close temporal relationship between the rise in titer and onset of rejection. Retrospectively, these changes seem to have occurred 1 or 2 days before clinical signs appeared. A prospective study is now under way to determine if the test system can be used for the serologic diagnosis of rejection.

I should point out that we are not overly optimistic in this regard, because the changes that we have seen when the rejection was reversible—that is, was treatable—have been relatively small, as compared to the very large changes which occurred when rejection was irreversible. However, if this proves to be the case, it will be helpful to determine when we are dealing with a situation which cannot be salvaged.

DR. GARLAND D. PERDUE (Atlanta): At Emory University we have approximately 50 patients with transplants with accumulative survival approaching 70%—about 76% in patients with living related donors and 56% in patients with cadaver donors of kidneys.

Particularly distressing to us have been those patients who appeared to have an acceptance of the kidney with normal renal function for a period of months, and then slipped into the phase of chronic rejection described by Dr. Campbell. In many instances this has appeared to us to be related to the development of an infectious complication, often having its origin at the time of operation, and which necessitates modification of the immunosuppressive regime. The incidence of bacteriuria and the incidence of urinary leakage from the reconstruction is sufficiently great so that such chronic smoldering infections may be expected in a number of instances to make themselves known in a much later period.

In an effort to try to combat this, we have established a program in which we do remove pyelonephritic kidneys prior to transplant. We certainly attempt to control any residual urinary tract infection. We irrigate the bladder mechanically clean, and intraoperatively we give a very short course of cephalothin. We keep it short so as not to allow the development of resistant strains of organisms.

Our hope is that we can limit intraoperative contamination, and thus limit the delayed infections which seem so often to correlate with the onset of chronic rejection.

DR. JAMES D. HARDY (Jackson): Much has been learned about the allograft rejection reaction, and it is not unrealistic to assume that in due course the problems involved will be solved. Within the last decade considerable clinical progress with kidney allotransplants has been realized. Furthermore, this increasing success has been achieved through a more perceptive use of two drugs which were available a decade ago, namely, prednisone and azathioprine (Imuran). In fact, the success of kidney transplants in experienced centers exceeds those of operations for carcinoma of the pancreas, esophagus and perhaps even the lung. Thus there is much room for optimism in the whole transplantation movement.

Meanwhile, developments in the field of artificial organ support and replacement have continued to unfold. In certain aspects the quality of artificial organ support and replacement has achieved a level of sophistication which approaches that of transplants. Therefore, the time has now come to fuse transplant research and artificial organ development into a single "organ support and replacement objective." The two fields both complement and supplement each other, and more rapid progress toward dependable organ replacement will be made by combining the two disciplines.

DR. GILBERT S. CAMPBELL (Closing): We, too, have used Collins' solution for flushing the donor kidney. The point that most are aware of should be stressed again. At times we find people perfusing a kidney in preparation for implantation with a syringe which is a dreadful mistake. Pressure should be monitored either with hydrostatic elevation of the bottle above the kidney or with a pressure transducer in the perfusion line.

The other problem that has been brought up so beautifully in the discussion is: What is, and what is not, rejection? There is bound to be a period of ischemia coincident with any renal transplantation. This ischemic insult causes temporary loss in renal function. The kidney may be recovering from the ischemic insult at the same time that there is a worsening of function because of immunological injury to the kidney. It is the resultant vector of these things that we are observing. Something that resembles a plateau in renal function may be seen, but actually that kidney is already undergoing rejection, and I believe we may fail to recognize this.

I read in Dr. Francis Moore's book on *Give and Take* (pages 46–48) that Dr. Carl S. Williamson (of the Mann-Williamson operation) demonstrated the difference between an autografted kidney and an allografted kidney. After leaving the Mayo Clinic where he did this work, Williamson came to the University of Arkansas in 1928 as Chairman of Surgery, and after 2 years left Little Rock and entered private practice in Green Bay, Wisconsin. He died in 1952. So Arkansas indirectly had a look-in on kidney transplantation because of Dr. Williamson's interest in the late 1920's.

DR. A. L. HUMPHRIES, JR. (Closing): In answer to the question about whether we should have used an autografted model, instead of allografted, I would certainly have to agree, and our pathologist would particularly agree, since the pathologist's role in looking at these kidneys after a week or two is very difficult because of the rejection present.