GORDON WILSON LECTURES

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1954 ALLEN O. WHIPPLE, M.D. "The Splenic Circulation in Relation to Certain of the Splenopathies."

SUCCESSFUL HOMOTRANSPLANTATION OF THE KIDNEY IN AN IDENTICAL TWIN

By JOHN P. MERRILL, M.D. and (*by invitation*) J. HARTWELL HARRISON, M.D., JOSEPH MURRAY, M.D., and WARREN R. GUILD, M.D.

BOSTON

Homotransplantation of the kidney, by which we mean the grafting of the kidney from one individual to another of the same species, has not to date been successfully accomplished with the exceptions to be mentioned. In spite of a vast amount of work in the animal laboratory, kidney transplantation in dogs has been uniformly unsuccessful. When a kidney is transplanted from one dog to another, the course of the graft is similar in almost every case, regardless of the efforts made to modify it. Following transplantation, the kidney may secrete urine for periods varying from four to twelve days, and then characteristically hematuria ensues, formation of urine ceases and the homograft no longer functions. When one examines such a kidney histologically, the picture is strikingly similar. Infiltration of the tissue by round cells is characteristic. There are scattered thromboses of the smaller arterioles with multiple small infarcts and edema.

In human homotransplants the story is much the same. As you might have guessed, the first attempt at transplantation of human kidney was made in 1936 by the Russians.[1] This, however, was not successful, and the Soviet scientists then went on to attempt the invention of the steamboat, telephone and airplane. In our own country other sporadic attempts at human homotransplantation of the kidney were likewise unsuccessful. Last year Dr. David Hume, Dr. Ben Miller, Dr. George Thorn and I reported nine cases of transplantation of the human kidney.[2] Of these nine, four developed significant renal function; and of these four, the function in two was of definite clinical importance. In one of these two cases, kidney function lasted for five and one half months following transplantation and enabled the patient, who had been admitted in severe uremia, to be discharged from the hospital, to travel and to lead a reasonably comfortable existence. In all but one of these cases the kidney was transplanted into the thigh where by the previous raising of a pedicle flap a pocket was provided for the transplanted organ. The renal artery was anastomosed with the profunda femorus in an end-to-end anastomosis, and the renal vein to the common femoral vein with an end-to-side anastomosis. The ureter was brought out through a skin ureterostomy, and the urine from this skin ureterostomy

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collected by means of a colostomy cup attachment. Eventually, in all these cases the homograft ceased functioning. Presumably failure was due to the same antigen antibody response which results in the ultimate rejection of all homografts with the possible exception of cornea. However, in this series there did seem to be some difference from the animal experiments. The microscopic picture was not quite the same, and the duration of function was, of course, much longer. It seemed possible that since we had transplanted a sick kidney into a sick donor that this might in some way have modified the immune response. Since many of these kidneys came from chronic cardiacs shortly after death and were transplanted into severely uremic patients, it seemed possible that either the transplanted tissue, or the host, or both, might be incapable of the violent rejection response which characterizes the transplantation of healthy tissue into a healthy host. For this reason it seemed worth pursuing further the problem of transplantation of the kidney in the human.

From the foregoing, however, it appeared that there were certain technical difficulties to be eliminated. In the first place it was essential that the donor and the recipient have the same blood type. It was necessary also that if possible we ascertain beforehand that the donor have a kidney which was free of disease. Certain preliminary evidence made it seem important that the donor be pre-treated in such a way as to further prevent the so-called immune response. Therefore the use of elective donors rather than cadavers would be important. Secondly, it seemed desirable to place the kidney intra-abdominally rather than in the thigh. In the majority of the previously described cases, infection played a significant role in destruction of the kidney. This might be avoided if we could obviate the use of the skin ureterostomy. Thirdly, we had to know whether the normal kidney might regain normal function after a period of anoxia such as would be necessary during transplantation. Finally, since the blood supply to the first third of the ureter is derived from the kidney itself, one might be assured of good supply to the ureter and also avoid the possibility of uretero-ureteral anastomosis with the consequent danger of stricture if the first third of the ureter were implanted directly into the bladder. We were, however, somewhat concerned about this last point since this would necessitate placing the transplant in the pelvis and anastomosing it to the pelvic vessels. We knew from previous dog experiments[3] that placing a dog's own kidney in an abnormal position in the same animal might result in poor kidney function. However, Dr. Joseph Murray in a series of experiments transplanted a dog's kidney into the pelvis and ascertained after more than a year with a single kidney thus transplanted that the animals maintained normal renal function and good health.

In the fall of 1954 we were afforded an unusual opportunity to answer

the other questions posed above. Richard H. a 24 year old man with chronic glomerulonephritis was transferred to the Peter Bent Brigham Hospital following unsuccessful attempts in an outside institution to maintain him with conservative therapy. In the week prior to admission he had had several convulsions and because of constant nausea and vomiting had been maintained entirely on parenteral therapy. Shortly before admission he had become combative and overtly psychotic. Dialysis with the artificial kidney resulted in good clinical improvement, and he was able to leave the hospital three weeks after admission. It had previously been suggested by Dr. David Miller of the transferring hospital that because the patient had a twin brother renal transplantation might be possible. We knew that if this twin was a monozygotic (identical) twin that there was real reason for considering this possibility. We knew, for instance, that skin grafts had been made between identical twins and had taken permanently.[4] Furthermore, in 1950 the successful grafting of skin between identical twins was used by an English Court of Law to establish the identity of a twin who had been separated from his brother at birth.[5] Therefore, it seemed probable that skin grafts would take successfully between these twins if they were identical. There was, however, no precedent for kidney homografts. We knew, though, that skin and kidney transplants in animals showed the same type of histologic rejection response when the grafts failed. We knew also that there appeared to be a common antigen in these tissues, since skin transplanted from one animal to another would accelerate the rejection of a kidney transplanted at a later date. It, therefore, seemed likely if the twins were indeed identical that a transplanted kidney might survive much as transplanted skin. The next step was to establish beyond reasonable doubt that the twins were identical. Although their parents were dead, and the physician who had delivered them had died some years before, it was possible to determine that there was a common placenta at birth. With the help of the Blood Grouping Laboratory at Children's Hospital we were able to ascertain that the twins had identical antigens for 21 blood sub-groups. A geneticist who was good enough to help performed various taste tests, studied the irises and the configuration of the ears among other factors and opined that "the chances were 98.5% that the twins were identical." It was felt, however, that the best test of identity was the practical one; i.e., the success of skin grafts transplanted between the two brothers. This was done, and the patient discharged from the hospital. During this interval, his blood pressure rose precipitously, and he developed all the stigmata of the malignant hypertensive syndrome. He was readmitted in severe distress; with retinal hemorrhages and exudates, marked cardiomegaly, and both peripheral and pulmonary edema. On December 17, 31 days after the skin grafts had been made, the transplant margins were biopsied and found to

show no evidence of the "rejection response". Six days later on December 23rd a kidney was removed from Ronald, the healthy twin, and transplanted into the right pelvis of Richard. The renal artery was anastomosed to the hypogastric artery and the renal vein to the common iliac vein. The ureter was placed in the bladder, and a polyvinyl catheter placed therein, leading externally through a cystotomy. The total period of anoxia of the homograft was one hour and twenty minutes. The postoperative course of the donor was uneventful.

Immediately after the clamps were released on the transplanted kidney, it became pink and shortly thereafter urine was seen issuing from the plastic catheter. The urine volume increased, and renal function improved daily. Figures I and II show the striking improvement during the postoperative course. Of particular importance is the fact that following operation the blood pressure decreased to normal values, and the cardiomegaly and edema disappeared. The eye grounds became normal except for a few old

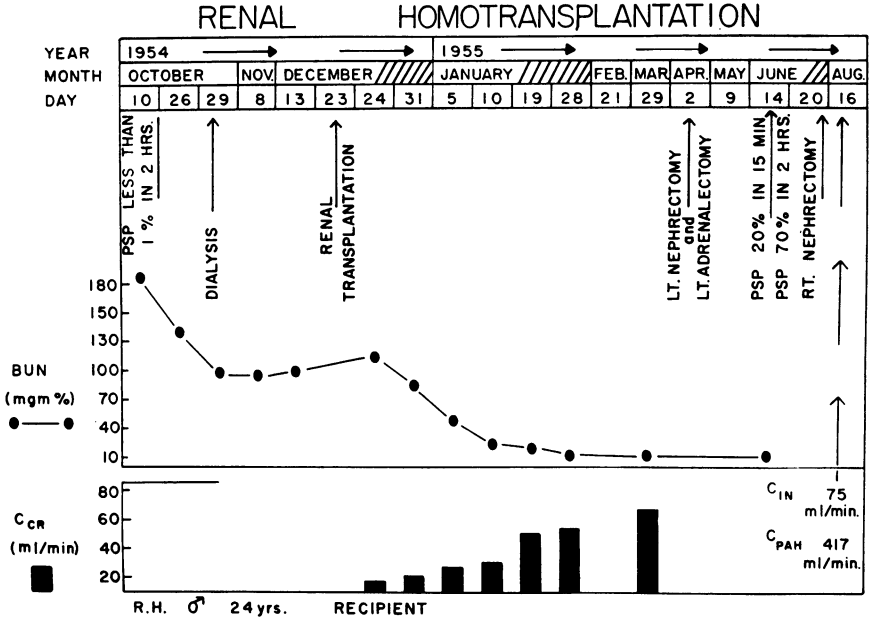

FIG. I. This figure demonstrates graphically the fall in blood urea nitrogen from 120 mg per cent at the time of transplantation to normal values where it has been maintained since operation. Eight months after operation, PSP excretion is within normal limits. Following the removal of both kidneys the filtration rate of the transplanted kidney as measured by the clearance of inulin has shown some compensatory increase, and the renal plasma flow even more of the compensatory increase of the calculated value for one kidney. The clearance of creatinine plotted in solid bars at the bottom of the graph shows a progressive increase to values consistent with the inulin clearance.

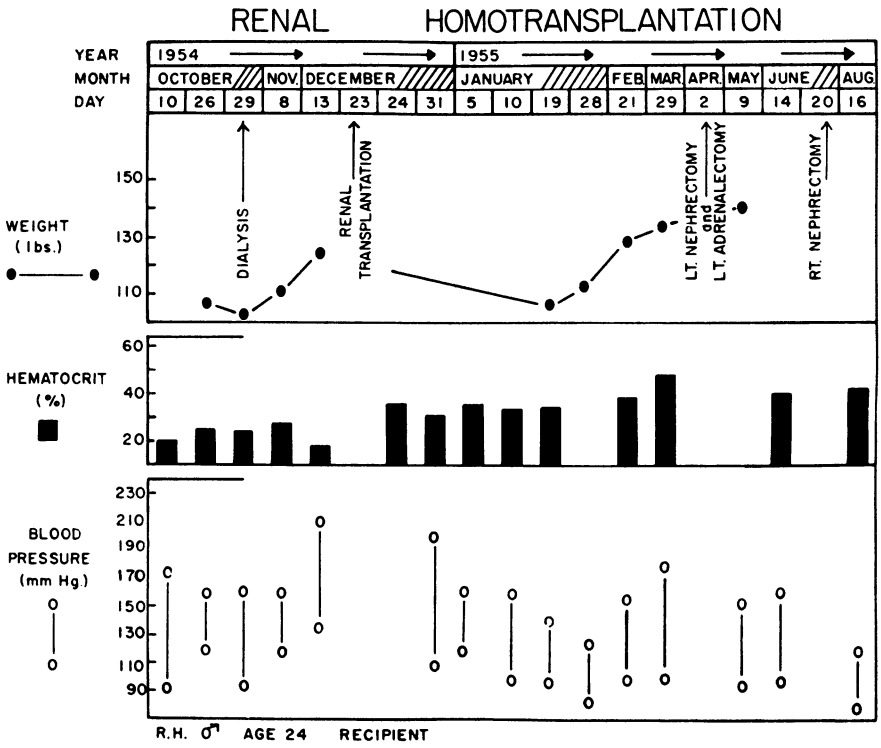

FIG. II. The increase in weight between the time of dialysis is due to the accumulation of edema fluid. The subsequent increase in weight after transplantation represents healthy body tissue. Note the striking drop in blood pressure following the grafting of a third kidney while both diseased kidneys were still in place. Two months after operation blood pressure tends to rise again, to drop following left nephrectomy, rise slightly again, and then drop to normal values following the removal of the second diseased kidney. The rise in hematocrit to normal values is consistent with the general chemical and clinical improvement shown in both Figure I and Figure II.

scars. Following discharge from the hospital, however, the blood pressure rose gradually, and the patient's urine continued to show two to four granular casts and six to ten white blood cells per high power field. Because of the possibility of infecting the transplant from the two diseased organs and because of suggestive evidence that the presence of the two abnormal kidneys might result in reappearance of hypertension, the left and then the right kidney were removed in separate operations without event. Following this, the urine became free of cells and casts and the blood pressure returned to normal. At the present time the patient is well, active, and free of all demonstrable disease except that he continues to excrete three to four grams of protein per 24 hours in his urine.

What conclusions may we draw from this interesting sequence of events?

First and not least in importance, that it was an effective therapeutic approach to Richard's particular difficulty. Secondly, that homotransplantation of the kidney in man is at least a technically feasible procedure. Such a kidney can survive one and one half hours of anoxia and attain near normal renal function. Important also is the fact that its abnormal position does not prevent attainment of this good function. The observations on the remission of the hypertensive syndrome are perhaps of equal importance as they pertain to the etiology of renal hypertension in man. Recent evidence suggests that the role of the normal kidney may be to metabolize or to excrete some pressor substance causing hypertension. In this view, renal hypertension may be due entirely or in part to something the kidney fails to excrete or metabolize rather than something it elaborates. The fact that hypertension and hypertensive vascular disease disappeared in this patient when a normal kidney was transplanted even though the two abnormal kidneys remained in situ lends credence to this view. The demonstration that a normal kidney can be successfully transplanted from one identical twin to another perhaps brings us no nearer to answering the fundamental problem of the immune response causing rejection than do previous efforts. It does, however, allow us to proceed with the further investigation of this problem in animals with full confidence that its application to man has been reasonably established.

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DISCUSSION

Dr. Francis C. Wood (Philadelphia): This, of course, interests me greatly. I wonder if you have been in touch with Doctor Kallman of Columbia who has made a very extensive study of identical twins.

I was wondering if he might know whether nephritis was apt to occur in both of two identical twins.

Would you once more say something I did not see on your slide, as to exactly what happened to the amount of urine excretion, and how the blood pressure behaved.

It dropped somewhat before you took out the patient's diseased kidneys, but did not come down to normal; is that right?

DR. JAMES J. WARING (Denver): I would like to ask Dr. Merrill what work Alexis Carrel did on the transplanting of kidneys. It seems to me that, when I was at Hopkins in 1905, Carrel showed some dogs at that time in which he had done kidney transplantations, as well as other vascular surgery.

DR. THORNTON SCOTT (Lexington): I wonder if Dr. Merrill has his patient on continuous penicillin prophylaxis against streptococcal infection because, as Dr. Wood points out, identical twins are susceptible to identical diseases. In view of the role of the streptococcus in inducing glomerular nephritis, one suspects that this patient would still be inordinately susceptible to it.

DR. JOHN P. MERRILL (Closing): In answer to Dr. Wood's question, the fact that one identical twin has hypertension makes the other much more susceptible.

But, interestingly enough, the only good series on nephritis has been run by Dr. Addis. He had four pairs of identical twins, one of whom had glomerular nephritis and the other did not. So we feel a little happy about that, though, of course, the possibility disturbed us immensely.

The blood pressure dropped very dramatically within three or four days after operation, when the third kidney and both the other kidneys were in place.

For four or five months, we followed this boy quite carefully in the outpatient department; and what we saw was what one would see in following a patient who was susceptible to hypertension. He would come in, and his first-visit blood pressure would be perhaps 135/85, then would drop to 120/70 if we rested him.

A month later, however, his initial pressure was 150/95 and would drop to 140/50.

Finally, when we got an initial pressure of 160/100, we decided that this perhaps was something more than lability of his vasomotor system; and we took out both his own kidneys.

But the important fact is that all his vascular disease did disappear while all three kidneys were in place; and, of course, the blood pressure dropped remarkably.

Dr. Carrel did do a number of renal homografts. He took the aorta, with both renal arteries and kidneys, and transplanted them. He did publish some work which, indicated that the grafts had survived for long periods of time. However, the records were not available to us or others, and nobody since that time has been able to duplicate Dr. Carrel's work.

With regard to prophylaxis, we obviously were very concerned about this. This boy is on penicillin prophylaxis (that is, oral penicillin), and we are extremely cautious about this.

At the present time, however, while he does have some proteinuria, he has no casts and no cells in his urine. The proteinuria, I think, might well be explained by the abnormal position of the kidney because, in dogs, when the kidney is transplanted (in autografts, that is), if there is discrepancy between the renal vein and the vein with which it is anastomosed, the transplant does show some proteinuria; but, a year and a half, after operation in these kidneys our biopsies have not shown any renal lesion. So we hope, or have some reason to believe, that this proteinuria is not due to glomerular involvement, but simply to the vascular problem involved in surgical procedure.