Current Status of Renal Homotransplantation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. LLOYD H. SMITH, JR.*1: I think we would all agree that there are few areas in medicine in which there have been more dramatic and rewarding advances over the past few years than in homotransplantation. We can also say that it is an area of medical activity which illustrates par excellence the importance of very close cooperation between all of the medical disciplines. This cooperation, particularly between the Departments of Surgery and Medicine, is reflected in the superb results that have been achieved in this hospital. It represents success that has been won with great difficulties. I think this point will be illustrated in the presentations that will be given today.

The program this morning is under the direction of Drs. John Najarian and Paul Gulyassy.

DR. JOHN S. NAJARIAN*2: Last year we talked about the history of tissue transplantation and discussed the present status of kidney transplants. This morning we should like once more to bring our material up to date and delineate the horizons of transplantations. We shall point out the stumbling-blocks and some of the problems that we have overcome. I think it well to preface our remarks by indicating the areas of major interest and possible improvements that can be made in the results of tissue transplantation. Specifically, we shall be talking about renal homotransplants. I should like to point out that kidney transplantation is a very definite therapeutic measure that can be used in patients with end-stage kidney disease, although the scope of its application is still limited. I think that all who have participated in our own program would agree. The important thing is that now this particular tool is available, we must

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define more clearly some of the obscure changes occurring in our patients and their transplanted kidneys. We must ask how we can improve our results.

Of major interest to those actively engaged in transplantations is histocompatibility typing. In the steadily enlarging field of transplantation, people are constantly trying to find better ways to obtain genetic matching. We can summarize what has happened in this regard across the country (Chart 1). The chart is taken from the National Kidney Registry at Boston and summarizes data through 1964. It is well to remember that the number of transplants performed up to the year 1961 was 56, most of them in identical twins. There was some interest in renal transplantation in 1961, which increased greatly in the latter part of 1962 and the method became firmly established in 1963 with the advent of immunosuppressive drugs. We are now in the phase of immunosuppressive drug therapy and there has been an almost exponential rise in the number of transplants performed in this country and abroad. Although the Registry figures are not up to date, it has been estimated that approximately a thousand renal homotransplants have been performed in patients who were not identical twins. You will notice that the over-all survival rate continues to improve; it was between 38 per cent and 48 per cent in 1964, and in 1965 it was slightly higher.

Let us focus on the problems that are now before us. The first is genetic matching methods for donor selection. Because of limited funds and facilities we have not applied these procedures, but instead have concentrated our efforts on consanguinous or blood-related donors. We have transplanted kidney grafts from unrelated donors and have performed one graft with a cadaver donor. However, we are quite interested in methods for obtaining a better genetic match between donor and recipient. I have listed four possible tests (Table 1) but there is also a fifth test. The first method is the triple skin graft. This technique, developed initially in Boston, has been more or less abandoned. It involved using a volunteer who became a third-party for a skin graft from the recipient and eventually from the prospective donor; accelerated rejection of the skin graft indicated some degree of genetic similarity—a very crude test which did not prove to be worthwhile.

The second test was based on a delayed sensitivity skin reaction; peripheral leukocytes were obtained from the recipient and then were injected beneath the skin of the donor. The amount of reaction was supposed to reflect the genetic similarity between the donor and recipient. Again, this method was unsatisfactory for many reasons.

The third test involved lymphocyte transformation. We all thought at first that this was the answer; this technique, proposed by Bains and Hirschhorn, was based on the transformation of lymphocytes in vitro, which depended upon the genetic dissimilarity between cells of the graft donor and recipient. The degree of transformation was directly related to the genetic difference between the individuals. Unfortunately, it has subsequently been found that cells from uremic patients do not respond in the same way as do those from normal people.

The fourth test involves antilymphocytic antibody and we will discuss this at length later in the presentation. Dr. Paul I. Terasaki and Dr. Roy L. Walford at UCLA have used this particular method as a matching technique. They obtain leukocyte cells from the prospective recipient and the prospective donor and test them against a large spectrum of antiserum obtained from 150 persons, against lymphocytes. The degree of matching between these lymphocytes is indicated by the number of tubes that are similar in the degree of cytology caused by a particular antilymphocytic serum. This has proven to be a fairly worthwhile test, but cumbersome.

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**TABLE 1.—Genetic Matching Procedures For Donor Selection**

| 1.  | Triple skin graft          |
| 2.  | Delayed sensitivity skin reaction (Brent) |
| 3.  | Lymphocyte transformation (Hirschhorn) |
| 4.  | Antilymphocytic antibody (Terasaki) |

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We have been engaged in a retrospective study in which our own results were correlated with leukocyte agglutination tests. This is a method of typing leukocytes developed by Dr. Herbert Perkins (U.C. Medical Center) and by Dr. Rose Payne (Stanford Medical Center). The results are still incomplete. We hope that eventually we can type leukocytes as well as red cells and that with proper leukocyte type-matches we shall find good genetic donor combinations.

I would like to stress that all these techniques would involve the use of unrelated donors or cadaver kidneys. We need better methods of organ preservation before these donors are really practical.

The second major area we shall discuss today is that of immunosuppressive drugs. The agents currently available are rather crude. In essence they are like large malles where a rather small hammer is needed. We are looking for more specific methods of immunosuppression.

The third problem that we shall discuss is that of early renal failure. Chart 2 is taken from Benjamin Barnes' analysis of the data from the Kidney Registry. On the top line are listed identical twins. We see that they have survived for some eight years and that about two-thirds of all the identical twins that were operated upon are still living and have functioning kidneys. From these data we can also extrapolate what happens to sibling donors. We see that there is a very pronounced rate of early attrition; deaths from early failure usually occur within the first two months, then there is a leveling off period. The rate of attrition of these patients is minimal after the first year.

The problems to which we have addressed ourselves are: (1) what is the cause of this early attrition, and (2) can we find some means of treating early renal failure or at least of making the results closely resemble those obtained with identical twins. Dr. Gulyassy will discuss this in detail in just a moment.

Today we would like to discuss how we select our donors and recipients, how we prepare our recipients for transplantation, the drugs we currently use for immunosuppression, and perhaps in a crystal-ball fashion try to envision techniques of better immunosuppression. We will then talk about rejection. We shall present several patients and will try to allow enough time for discussion. Dr. Gulyassy will now talk about the selection of the donor-recipient and the preparation of the recipient.

**DR. PAUL F. GULYASSY**

Before we consider how we evaluate both the recipient and the donor for transplantation, I would like to emphasize the following point: Although we do not make the decision to proceed with homotransplantation until the potential recipient has clearly reached the end stage of renal disease and rigid medical management can no longer safely maintain the patient, we would like to evaluate potential recipients long before this time is reached. The reason is that we must go through a very complex, time-consuming series of evaluations of both the recipient and potential donors. In addition, the ultimate deterioration of the patient who has had chronic renal disease for some time is totally unpredictable. We are in a poor position to evaluate and prepare the patient with chronic uremia if his disease has been allowed to progress to the point of convulsion and coma. We urge that any potential recipients be called to our attention when the patient has moderately advanced, but not terminal uremia.

In considering the potential recipient the major criteria which we evaluate are as follows. First, the patient as stated must have irreversible and advanced renal failure. The usual methods are used to prove that the problem is not one of acute or subacute renal disease, and only after all attempts have been made with medical management to produce reversal of symptoms and abnormalities will we consider the patient for more definitive therapy. Second, we must be sure that the patient does not have irreversible, advanced systemic disease of such a nature that even with a successful, perfectly functioning graft he is liable to die anyway. We have done transplantations in patients with minor systemic defects when the particular
disease was stable and would not be affected by surgical or drug therapy. Third, obviously a suitable donor must be available and in our experience we have so far used mainly consanguinous, living donors. We will consider any patients between approximately 10 and 50 years of age. Below or above these age limits, we will consider only very carefully selected patients. Finally because of the very extensive and trying experience which both the preoperative and postoperative course entails, we must have patients who are free of any major psychiatric disorders.

Let us consider the donor. When we are using living, consanguinous donors, we must do an exhaustive evaluation of the donor for two reasons: First, to insure that he has a normal kidney and genito-urinary tract; and second, that the major operation of nephrectomy will be safe for him. Therefore, we perform a meticulous examination of the donor's renal and genito-urinary system and a general medical evaluation. The last major requirement is that the donor have at least one kidney that has a single artery (demonstrated by arteriography) since double artery anastomosis is technically extremely difficult and the only situation in which Dr. Najarian will undertake such an operation is one in which the donor is an identical twin. We have also limited ourselves to ABO and Rh blood group compatible patients because a very high proportion of grafts are immediate failures when the blood compatibility barrier is crossed.

Having met these criteria—that is, a donor-recipient pair having been established—we must then proceed with preparation of the recipient. Since by intention we wait as long as we possibly can for the patient to have a useful life with conservative medical management, the patient is in a state of chronic advanced uremia by the time the decision is made and corrective measures must be carried out before the operation. In the course of long-standing, chronic uremia virtually every organ system is afflicted with profound disturbances, and it sometimes takes two and a half to three weeks to reverse these complex abnormalities. The azotemia itself must be controlled, since in some fashion most of the abnormalities of chronic uremia are a consequence of some poorly characterized nitrogen metabolites. Although chemically azotemia can frequently be controlled with a single dialysis, the effects on many of the organ systems are very slow to reverse and may take as long as two or two and a half weeks of optimal hemodialysis control before we have satisfactorily reversed the abnormalities. The same holds for fluid and electrolyte abnormalities which with modern dialysis techniques can be quickly reversed; however, the more subtle changes—for example, long-standing abnormalities in intracellular pH and in intracellular ionic composition—probably are only gradually restored to normal.

Hematologic abnormalities consist not only of anemia but include a very significant bleeding tendency which exists in patients with chronic renal failure. Early in our experience, when operation was attempted after only a limited period of dialysis, the surgeons encountered excessive bleeding. Cardiovascular abnormalities consist of hypertension and our most feared complication, hemorrhagic pericarditis. This occurred in two of some 35 patients. In one of them open chest drainage was required, and in the other clotting of blood in the pericardial sac made thoracotomy necessary. Neuromuscular disorders are very prominent. Metabolic disorders consist of glucose intolerance and profound disturbances in protein metabolism which have gradually evolved over months or years.

DR. NAJARIAN: Our program of immunosuppressive therapy is more or less similar to that used in most other centers throughout the United States. At present we use one of the major antimetabolites—"Imuran,"® an imidazole derivative of 6-mercaptopurine.

I might just take a moment to talk about the action of these drugs, how and when we use them, and why we use them as we do. The antimetabolites as a general rule are basically analogues of various metabolites. Three are shown in Chart 3. Methotrexate is a folic acid inhibitor and the close chemical similarity between methotrexate and folic acid can be seen. The pyrimidine inhibitor 5-fluorouracil is similar to uracil, and 6-mercaptopurine is chemically similar to the purine, adenine. These antimetabolites act by competitive inhibition or by other routes which are poorly understood. However, the drug that we use most often is 6-mercaptopurine, actually in its imidazole form, "Imuran."® The way it acts is shown on a very simple chart of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) synthesis (Chart 4). Beginning with simple precursors, the folic acid inhibition of methotrexate would block the incorporation of these carbon compounds into purine. The purine analogues or the antimetabolites that we are using,
The alkylating agents that attack the DNA directly and in this fashion act very much like X-ray, (2) the antimetabolites, which block the synthesis of RNA and thereby block the ability of the lymphoid cells to divide, and (3) the actinomycin C and D and mitomycin apparently interfere with the transfer of information from nuclear DNA to nuclear RNA and block the formation, or

such as 6-MP, block the incorporation of the purine into polynucleotides either by substitution or by competitive inhibition, or they may affect the enzyme systems in a particular part of the chain of DNA synthesis. In like fashion the pyrimidine inhibitors act to block the pyrimidine that is being incorporated into the polynucleotides, such as DNA and RNA.

The following explains why these agents are so effective in transplantation and why the doses can be lowered to tolerable amounts in long-term patients. The clonal selection theory of antibody formation proposes that a lymphoid cell or a group of cells is committed to a specific antigen; further, that this group of cells continues to replicate with an intermitotic time of two to ten days or two to four days and that the group of cells remains fairly stationary in number. However, if an antigenic stimulus is given to this group of cells, there follows a rapid replication and exponential rise in the number of cells. Under these conditions intermitotic times can be shortened to four to six hours. By this means cells are formed in the vast numbers necessary to accomplish an immunological response against the foreign protein.

We suppress this cell replication in the following fashion: The day before transplantation we give Imuran, the antimetabolite, then higher doses during the day of transplantation and for three or four days after transplantation. By one week after operation the dose of the drug is down to tolerable levels for the patient, or about 3 mg per kilogram of body weight. We use as much as 6 to 7 mg per kilogram in the initial period when the graft is in place and the strongest antigenic stimulus is offered to the immunologically competent cells.

I have listed the three major agents in immunosuppression: (1) The alkylating agents that attack the DNA directly and in this fashion act very much like X-ray, (2) the antimetabolites, which block the synthesis of RNA and thereby block the ability of the lymphoid cells to divide, and (3) the actinomycin C and D and mitomycin apparently interfere with the transfer of information from nuclear DNA to nuclear RNA and block the formation, or

![Chart 3. The natural antimetabolites and their parent compounds.](chart3)

![Chart 4. Action of immunosuppressive drugs.](chart4)
at least the production of messenger RNA from the nucleus. We give these agents at the time of rejection because we believe that at that time the cells are beginning to make antibody to attack the graft. In theory an ideal agent would be one such as puromycin, which actually attacks the protein synthetic mechanism; the proteins we are interested in are antibodies. Chloromycetin may act in the same way. If this is true, these may be very effective immunosuppressive agents when rejection occurs. Therefore, we use actinomycin at the time of rejection but give Imuran® from the very beginning.

In our program we also give corticosteroids before, during and after transplantation. This is not a common practice in other transplant groups. Two years ago we began to use corticosteroids early, in an effort to blunt an immunological response rather than wait for a rejection crisis to occur. In most persons receiving a kidney transplant, rejection will occur sometime within the first ten days to two weeks, despite immunosuppressive therapy with Imuran®. Corticosteroids are very effective in reversing the rejection process. With these agents, we thought we might even be able to abolish rejection crises altogether and permit some degree of graft-host adaptation to take place. We began using corticosteroids in high doses from the time of transplantation and reducing the doses sequentially thereafter. If rejection did occur, we gave corticosteroids in a slightly higher dose and then reduced the amounts once again. We are still not quite sure how they act. Their action may be related to their lympholytic or their anti-inflammatory properties; or they may act because of their membrane-stabilizing qualities. We have studied this problem in our laboratory. We did kidney transplants in eight dogs and, using in vivo and in vitro techniques, we found that there is a significant amount of antigen in the renal vein effluent. At four hours after transplant, six of the eight dogs had free antigen in the plasma issuing from the kidney. At two days, four had antigen in this fluid. We used this observation to study the effect of corticosteroids and found that they did indeed reduce but did not eliminate the amounts of antigen excreted.

In other studies we found that when the injury to the kidney was increased, either by prolonging ischemia or by exposure to X-ray, the amount of antigen that issued from the kidney increased. We then gave corticosteroids to a group of dogs. In these preliminary studies, three animals were given prednisolone (50 mg a day) before and after transplantation. In one animal we found antigen after four hours and at one day, in the second animal at two days and none at all in the third, certainly not after the two-day period. The amount of antigen that issued from these kidneys seemed to decrease in the dogs treated with corticosteroids. These studies are going to be confirmed by in vitro analysis of the antigen, which we hope will be a more accurate technique.

As a result of these observations we believe that the corticosteroids do have an effect on stabilizing membranes, thereby decreasing the amount of antigen from the kidneys. Perhaps for this reason we are able to abrogate at least partially the immune response that has occurred with rejection as early as ten and fourteen days. With corticosteroids our average time of early rejection, when it does occur, is 37 days, and it is very mild and easy to control. We think that this is a real addition to the immunosuppressive therapy regimen.

Immunosuppressive drugs are not ideal agents. Drug toxicity and sepsis are still major causes of death. What looks best in the future, if we again look into our crystal ball, is the antilymphocytic serum now used by several investigators, including the group at the Massachusetts General Hospital, and Dr. Woodruff in Edinburgh. Although antilymphocytic serum will reduce the total lymphocyte count to the same degree as thoracic duct drainage or intravascular radiation, it is a more effective immunosuppressive agent. Some investigators, such as Sir Peter Medawar, feel that perhaps the antiserum masks the immunologically competent cells so that they do not recognize the tissue as a foreign invader and do not attack it. This may be rather fanciful but, from animal experiments, it appears that this is what is going on. Many provocative experiments tend to support this. When antilymphocytic serum will become available for clinical use is dependent upon many factors; and the use of heterologous serum in humans presents its own problem—that of immunologic reaction. It looks as if there may be a ray of hope in this type of immunosuppression, which is different from chemical immunosuppression and is a direct immunological type of immunosuppressive attack.

The other problem with immunosuppressive drugs occurs in identical twins. There should be a 100 per cent success rate with homotransplantation in identical twins, for there is no immuno-
logical barrier; but the success rate across the country is still only about 66 per cent. Because of these disappointing results we have examined the kidneys in our cases of this kind and have re-read the original reports of Murray and his associates which indicated that in one or two of the cases of transplants from identical twins, glomerulonephritis had developed in the newly transplanted kidney when the recipient identical twin had glomerulonephritis. If the recipient had pyelonephritis or polycystic kidneys, glomerulonephritis did not develop. Apparently in almost 80 per cent of these recipient identical twins with glomerulonephritis, glomerulonephritis developed later in the transplanted kidney. In homotransplants between non-identical twins in which immunosuppressive therapy was given, only two questionable cases of glomerulonephritis have been seen. Our experience now extends for some three years, so we are well within the time when we should see glomerulonephritis if it is going to develop. The only difference between these two groups is that one is given immunosuppressive therapy and the other is not. We have recently been taking fluorescent photomicrographs of the kidneys that are removed. We have found, as have other investigators, that there is an immunological component to glomerulonephritis. We can routinely show fluorescence, either with antiserum to complement, to 7-S $\gamma$ globulin or even to M $\gamma$ globulin that localizes in the basement membranes of the glomeruli of all kidneys involved with glomerulonephritis. A similar thing can be found with the patients with lupus erythematosus but not in those with pyelonephritis. An identical twin is scheduled for transplantation in our program and we will probably give this patient modest doses of immunosuppressive drugs in the postoperative period.

**Dr. Paul Gulyassy:** Dr. Najarian is so atypical a surgeon that he has not even bothered to tell you the details of how the operation is performed, but we will assume that everything has gone very smoothly and successfully and that the patient is now in the postoperative state. About 14 months ago when we last reviewed our results at Medical Rounds, we had reached a total of 14 patients in our series. In looking at our results as well as the world results, there was one fact that was very striking. That is that early failures—grafts that either failed to function at all or that functioned initially but failed within the first 48 hours—still make up a very important proportion of graft failures. As we studied this problem over and over we could find no reasonable explanation for these early failures. One usual explanation for early failures, renal ischemia, hardly seemed applicable to our experience. The average ischemia time of 21 minutes achieved for this group of patients by Dr. Najarian was well under what is considered the safe limit. In addition, we have not used blood incompatible donor-recipient pairs and the usual type of explanation that perhaps these early failures represented pre-sensitization of the recipient did not seem to have any valid basis in either experimental fact or in any actual measurements in patients.

As we further considered the possible causes of these early failures and how we might prevent such failures, one fact emerged which was very striking. That is that although there are several hundred living patients who have had renal transplants, there is not a single report of what happens to the donor kidney during the course of nephrectomy. We thought that it would be wise to take a look at the function of the donor kidney as the surgeon is isolating it and preparing it for removal. We therefore undertook to observe patients during nephrectomy and it soon became very apparent that we must pay very close attention to what is going on with the donor kidney during nephrectomy. For example, we observed in the first patient we studied that shortly after anesthesia, as is well known, striking oliguria occurred as a consequence of the fall in blood pressure which occurs with induction. In addition to this functional effect we found evidence of renal injury occurring despite very careful attempts by the surgeon to be as atraumatic as possible when handling the kidney and its arteries. We found up to 2 plus proteinuria occurring as soon as the surgeon handled the renal pedicle; in addition, there was striking hematuria and cylindruria. In this patient a more alarming fact was that for approximately 30 minutes preceding actual nephrectomy no urine appeared in the bladder.

After these observations we have introduced two major changes in our program. First, urine output is continuously followed throughout the nephrectomy and the surgeon is notified if it falls below 1.0 ml a minute. Second, we instituted a program which was somewhat of a shotgun approach, of necessity, in which we incorporated all possible measures that we felt might protect the donor kidney from intraoperative injury, which
then is followed by a period of unavoidable injury during approximately 20 to 25 minutes of total deprivation of blood as perfusion, cooling and anastomosis of the kidney is performed. What we did was to hydrate the patient, or I should say that we corrected the normal surgical dehydration associated with enemas and thirsting over night, by infusing the patient with 15 ml of half-normal saline solution per kilogram of body weight during one hour before anesthesia. Second, the anesthetist carefully maintained normal blood pressure by continuous fluid replacement and plasma replacement where necessary. Third, when despite these measures urine output fell early in the course of operation, we injected modest amounts of mannitol (12.5 gm) to induce a mild osmotic diuresis. Then, just before clamping of the kidneys, we injected a second dose of mannitol to reduce the concentration of coagulable materials as well as potential toxins to a minimum and perhaps also to prevent the very rapid collapse of the tubular lumen which is known to occur after cessation of filtration. The results of these measures have been truly striking. In our early experience, we as others had a failure rate of about 40 per cent within the first 48 hours. Among the last 20 patients (with the exception of one who had a problem with a tortuous vein), we had no initial failures. We have no observations on the patients operated on before the institution of these measures, but some observations that Dr. Duffy collected from the two kidneys simultaneously and separately in a recent group show the magnitude of the depression of renal function which still persists despite these measures. Table 2 compares the urine output in five donors from the ureter of the kidney which is about to be removed and from the contralateral side as measured by the bladder output. With one exception there is a striking difference just before nephrectomy in the urine output from the two sides; for example, 15 ml per minute against 4 ml per minute, 3 against 0.5, 6 against 1.3, and 2.5 against 0.3.

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<th>TABLE 2.—Urinary Output Immediately Before Nephrectomy</th>
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*R = Remaining kidney; D = Donor kidney (to be transplanted).

The effects of this change in attention to the donor during nephrectomy in terms of renal function early and subsequently is shown in Table 3 in which the mean creatinine clearances for our initial group, who received routine preoperative and intraoperative management, were compared with clearances in a subsequent group who were managed with measures to protect the kidney from injury. The mean clearance at 12 hours rose from approximately 20 ml in the initial group to 60 ml in the donor-treated group. There still was a striking difference at three days and seven days. Beyond seven days, where we included only the survivors from the initial group—the surviving 60 per cent—the difference began to disappear. Therefore the survivors did go through a course of tubular necrosis of a reversible nature but ultimately had reasonable function.

The effects of this virtual elimination of initial failures is shown in an increase in over-all survival in the second group over the first. Where at the end of seven days in our first series we were dealing with a survival rate of approximately 70 per cent, and of about 55 per cent at 40 days, we are at 100 per cent in the second group. There persists an attrition beyond 40 days which is now clearly an immunological rather than a renal and hemodynamic problem, and it remains the major problem for solution in clinical transplantation.

Dr. NAJARIAN: The classic signs of rejection include fever, leukocytosis, pain or tenderness over
the kidney and perhaps myalgia and arthralgia. If we blunt these signs with corticosteroids, we must look for much more subtle signs of rejection. The earlier that rejection is diagnosed, the more effectively can it be treated. Therefore, we have examined two indications of kidney damage which may occur earlier than gross alteration of renal function; these are a rise in serum creatinine and a fall in creatinine clearance. We have recently reported on work that has been done with Dr. Noble. We have found, both experimentally and clinically, that lysozymes in the urine are a very good indication of tubular damage. We have been measuring urinary lysozymes in all of our patients. For a while we measured serum lysozymes but found them to be quite erratic. The urinary lysozymes may represent the tubular lysozyme content that goes down into the urine, so that this is a potentially direct measurement of tubular damage. In addition, it has long been known that proteinuria, protein in the ultrafiltrate from the kidney, is a sign of glomerular damage. The Masugi nephritis experiments showed this very nicely in the case of a purely glomerular lesion. The first signs of this are evident from the protein in the urine of the rats so treated. So we have two measurements we can use to detect some degree of destruction in the kidney: Lysozymuria and proteinuria.

Chart 5 gives pertinent data on a girl who is now approximately 20 months post-transplantation of a kidney from her mother. We have plotted on the ordinate the urinary lysozymes in mg per ml, urine proteins in grams per 24 hours, creatinine clearance, serum creatinine, urine outputs and prednisone dosage. On the day of transplantation and shortly thereafter, in all of our patients, there is a very high lysozyme content in the urine, which is indicative of the degree of tubular damage that occurs from the relative ischemia in the donor and the absolute ischemia imposed during transplantation.

In this particular patient, who is in the first group that Dr. Gulyassy discussed, there was severe tubular damage. The lysozyme did not return to normal for some ten days. In addition, there was a very slow rising creatinine clearance indicative of a damaged kidney that was slowly recovering. When the first rejection crisis occurred, there

![Chart 5 - Clinical course following renal homotransplantation in a girl 14 years of age. Donor was her mother, 49 years of age.](chart)

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was a very subtle change in the serum creatinine and a definite drop in the creatinine clearance. This was preceded by a significant rise in urinary protein, to 6 or 7 grams in 24 hours.

In this patient the pattern of rejection was mainly that of proteinuria and, we would judge, primarily a glomerular type of lesion. Eventually the rejection process became manifested by a rise in the creatinine and fall in the clearance. This was treated by increasing steroids, actinomycin C and local radiation to the kidney. The patient survived this particular rejection crisis and is doing perfectly well, with satisfactory clearance and a good serum creatinine. She is now taking 7.5 mg of prednisone a day.

Let us take another example, a case in which there was a prompt fall in serum creatinine, and lysozymes fell to normal levels by about the eighth day. A slowly rising creatinine clearance indicated some degree of damage to the kidney. Everything went along fairly well; the serum clearance was 1.5 to 2 mg per 100 ml, and the creatinine clearance was fairly good. By the seventieth or eightieth day, there was a definite rejection reaction. There was a decrease in the urinary output followed by a rise in the serum creatinine and a fall in the creatinine clearance. This occurred several days after the lysozyme level rose. This is predominantly a tubular type of rejection pattern, marked by a very high urinary lysozyme level and modest degree of proteinuria, predominantly glomerular in origin. The other was manifested by lysozymuria, or a tubular lesion. When we measure lysozymes and protein in the urine, we find these reflect rejection approximately a day before we see the changes in creatinine clearance. At the earliest signs of this damage treatment is begun.

Many of the "rejection crises" that we have seen or treated were in fact not rejection crises. We were misled by infection on several occasions. We have been fooled by other things. We are fooled less frequently now. One finding that we reported recently is fat embolization that occurs following use of corticosteroids. There is also a possibility of fat embolization to the kidney with decreased function, which simulates a rejection crisis. We have had several such cases. Two patients actually had embolization to the kidney. One was reported in the New England Journal of Medicine. This patient's kidney was functioning well for approximately four months, then there was a rapid fall in the creatinine clearance and a rise in serum creatinine. When arteriograms were obtained, a very peculiar pattern was seen. The arterioles going out into the kidney formed little puffs and in areas throughout the kidney there was no contrast medium. The only thing that can cause this is embolization. A biopsy of the kidney showed that it was perfectly normal in these areas, but in the intermediate areas there was massive necrosis. In true rejection, we must find the earliest signs of rejection and treat them as promptly as possible with steroids, actinomycin and local radiation. Crises that occur late are easy to reverse, for the most part.

We would now like to present three cases. In the first the patient is a boy who is approximately two years post-transplantation and is now going to school. The second case was presented to you last year; the patient is now approximately 20 months post-operative. The third patient is a young woman who received a transplant just 14 days ago. Dr. Gilbert Ashor, who is on the Transplant Service, will present the patients.

**Resident in Surgery.

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**Dr. Gilbert L. Ashor**: The first patient we would like to present today [introducing him] is a young high school student who was 16 years old at the time of renal transplantation, and is now 17. At age 12 he was discovered to have proteinuria. He did well, however, and was asymptomatic until age 15, four months before his admission to University of California Hospital. At that time he had blood nitrogen of 230 mg per 100 ml and a serum creatinine of 15.6 mg per 100 ml. Peritoneal dialysis was performed several times before bilateral nephrectomy-splenectomy was performed 7 April 1964. Two weeks later his mother’s left kidney was transplanted in him. The total “ischemic time” during the operation was 25 minutes and the patient’s postoperative course was complicated by a mild rejection crisis in August and again in December 1964. He received actinomycin, radiation therapy to the transplanted kidney and large doses of prednisone. Currently, the patient is receiving 100 mg of 6-mercaptopurine (Imuran®) and 7.5 mg of prednisone daily.

**Dr. Najarian**: The patient is now a senior in high school and is fairly active in school and extracurricular activities. Bobby, what do you participate in at school?
PATIENT: I participate in the sports we have in physical education and extra activities after school.

DR. NAJARIAN: He also wrestles and weight-lifts. We place no real physical restrictions on these patients. While the patient is here, are there any questions that anybody in the audience would like to direct to him?

DR. WILLIAM A. ATCHLEY*: Do you instruct him about severe dehydration?

DR. NAJARIAN: No, we have not.

DR. ATCHLEY: Do you think you should?

DR. NAJARIAN: We believe that these kidneys can concentrate and dilute as well as any other kidney. We see no reason why special precautions should be taken.

DR. SMITH: Has he had any problem with infections over the last two months?

DR. NAJARIAN: Have you had any infections?

PATIENT: I don’t think so.

DR. NAJARIAN: He has had none. These patients have been exposed to measles, chicken pox, all the viral and bacterial infections, and they have resisted these very well.

DR. ASHOR: The next patient to be presented is a housewife, 49 years of age, who was well until her first symptom developed in June of 1963. At that time she had weakness, nausea, vomiting and fatigue, and she entered the hospital. A diagnosis of severe anemia was made and multiple blood transfusions were given. In February of the following year, 1964, the same symptoms developed again and a diagnosis of uremia was made. The serum creatinine level was 17.2 mg per 100 ml. She was subsequently admitted to the University of California Medical Center, where a renal biopsy showed medullary cystic disease. She had multiple hemodialyses, and on 7 July 1964 she underwent a combined procedure including bilateral nephrectomy-splenectomy, and received a transplanted kidney from a donor brother. The total time of ischemia was 24 minutes. On the first day postoperatively the serum creatinine was 2.4 mg per 100 ml and the second day postoperatively it was 0.9. The patient is currently receiving 75 mg of Imuran® and 7.5 mg of prednisone daily.

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*Associate Professor of Medicine.

DR. NAJARIAN: This is one of our more remarkable patients. We once thought that we should not perform transplantation on people over the age of 45, but as a result of this patient’s success, we are reconsidering this notion. The remarkable thing was her determination to get well. On the first postoperative day after a procedure that lasted six or seven hours, Dr. Gulyassy and I walked into her room and she was reading the newspaper and eating breakfast. We thought that she might have some trouble later, but she continued to do well. She has never had a rejection crisis and it is now almost two years since the operation. She now travels around the Central Valley area to give talks on transplantation to various groups, and she borrows our slides from time to time. We try to keep her up to date on current developments in transplantation. (Addresses patient): How do you feel?

PATIENT: Wonderful.

DR. NAJARIAN: This is a complete summary. Would anyone like to ask her questions? She works about 14 hours a day, running a bicycle shop in Madera. Have you had any problems from your kidney transplant?

PATIENT: None.

DR. NAJARIAN: In answer to Dr. Smith’s question about infection, several suture abscesses with staphylococcal infections did develop. The abscesses were easily controlled, incised and the sutures were removed without any difficulty.

DR. ASHOR: Our last patient is the most recent to have a transplant. She is a 21-year-old coed from UCLA. The patient was well until, in the summer of 1961 contact dermatitis developed and was followed by leg edema which progressed to anasarca. In August of 1961 she was discovered to have albuminuria, hematuria and casts in the urine. A diagnosis of nephrosis was made. She was treated with prednisone and chlorothiazide and remained well for the subsequent four years except for periodic ankle edema and easy fatigability. In November 1965 she was again seen for severe epistaxis and at that time was discovered to have a packed cell volume of 23 per cent, blood urea nitrogen of 125 mg per 100 ml and serum creatinine of 11.3 mg per 100 ml. In December of 1965 she entered the hospital with similar findings: Anemia, blood urea nitrogen of 216 mg per 100 ml and serum creatinine of 16.4 mg per 100 ml. An intra-
venous pyelogram showed bilateral contraction of the kidneys, and a diagnosis of chronic glomerulonephritis was made. Multiple hemodialysis was carried out. On 23 February 1966 bilateral nephrectomy and splenectomy were done and on 2 March 1967 a kidney from her mother was transplanted in her. Her postoperative course has been one of very steady and gradual improvement, uncomplicated by any reaction. Serum creatinine on the morning of operation, after hemodialysis, was 12.4 mg per 100 ml. On the afternoon of operation it was 5.6 mg and on the day following it was 2.6 mg. Subsequently the serum creatinine ranged between 1 and 1.4. Creatinine clearance has steadily risen from a low of 26 to 60 ml per minute. The patient is receiving Imuran®, 150 mg, prednisone, 50 mg, and Aldomet®, 2 gm daily.

DR. NAJARIAN: The patient is now two weeks postoperative. (Addresses patient): How have you been since the operation?

PATIENT: Really good. I feel wonderful.

DR. NAJARIAN: The girl is a bacteriology student in her senior year at UCLA, so perhaps some day we can get some help from her from the bacteriological point of view. Are there any questions anybody would ask the patient?

DR. SMITH: What are the major changes that she has noticed since the operation?

PATIENT: The first week I was kind of sore, but I have had a lot more energy than I have had in a long, long time. I think it started about the first day after operation; I could feel it—a gradual increase in energy.

DR. NAJARIAN: Thank you for coming to see us. We wanted to show these three patients in three different lights: One, the young boy who about 255 days after transplantation had a rejection crisis which was mild and easy to reverse. He has had no subsequent difficulties. The second patient had a sibling donor and there was no rejection crisis at all. And finally, a patient just recently operated upon.

DR. SMITH: I think we would all agree that these are splendid results and that this was a superb presentation. I would like to say personally that if Dr. John Najarian ever undergoes any rejection crisis in Surgery we would be very delighted to welcome him into Medicine. Perhaps we have time for one or two comments or questions.

UNKNOWN PHYSICIAN IN AUDIENCE: What is the present status of second transplants?

DR. NAJARIAN: Second transplants are about the same as first transplants. For awhile they looked like they were even better. Of course you would suspect that they may go a little quicker because of pre-sensitization, etc. It turns out that some degree of tolerance is obtained with the first transplant. We thought it would be better, but now, with more of them being done, they appear to be about the same.

DR. MAURICE SOKOLOW**: Does the behavior of the blood pressure help you predict the likelihood of rejection?

DR. NAJARIAN: This is a very interesting question. We don’t know if the blood pressure rises because of our treatment with steroids or because of the disease. We think it is because of the disease. Almost uniformly, when rejection occurs, there is an increased need for anti-hypertensive medications.

**Generic and Trade Names of Drugs
6-mercaptopurine—Imuran®
Methyldopa—Aldomet®

**Professor of Medicine.