II. Differential Diagnosis and Management

Infection usually does not embarrass renal function, while rejection is characterized by abrupt renal failure. Steroid therapy will not prevent a febrile response to an infection but will produce rapid defervescence in a rejection crisis. Control of side effects is important. Granulocytopenia requires reduction or discontinuance of cytotoxic agents. Hypogammaglobulinemia is treated with immune globulin. Hyperglycemia and glycosuria are managed with insulin and diet.

THE INCIDENCE and types of infectious diseases occurring in patients treated with renal homotransplantation have been described in part I. Analysis of these cases suggested that the consequences of immunosuppression, including granulocytopenia, steroid-induced diabetes, and hypogammaglobulinemia, predisposed these patients to a variety of septic processes caused by organisms of endogenous origin. These infections as a group constituted the single most frequent cause of therapeutic failures which occurred in this series.

A homograft rejection crisis, characterized by fever and deteriorating renal function, occurs in virtually all patients at some time following renal homotransplantation.[1] The routine occurrence of attempted graft rejection and the high collateral incidence of infectious diseases at this time have, therefore, made the etiologic diagnosis of fever one of the most important problems encountered in the treatment of these patients.

In this communication, the differential diagnosis of fever will be discussed with particular reference to features which distinguish between infection and homograft rejection. In addition, the management of several types of infectious disease problems unique to this group of patients will be described.

The clinical material and the methods used are as in part I.

Differential Diagnosis of Fever

Homograft Rejections.—A recognizable rejection attempt occurred 1 to 42 days following renal transplantation in 28 of the 30 patients in this series. The efficacy of corticosteroids and actinomycin C in the reversal of this process has been described.[1] The clinical features of rejection and the characteristic response of this syndrome to therapy is illustrated in the following case report (Fig 2):

CASE 2 (LH-15).—The patient was a 22-year-old white male with chronic glomerulonephritis. Following 21 days of azathioprine therapy, he underwent bilateral nephrectomy, splenectomy, and renal homotransplantation which resulted in an immediate diuresis. On the first postoperative day, however, fever and oliguria appeared, and on the following day prednisone and actinomycin C therapy was begun. The patient's temperature promptly fell to normal and over the next five days renal function rapidly improved.

In this patient, a vigorous and early homograft rejection process appeared on the first postoperative day. This was characterized by malaise, fever, hypertension, leukocytosis, oliguria, and an increase in the serum urea and creatinine concentrations. In addition, the creatinine clearance rate and the urinary urea concentration declined. These abnormalities were promptly reversed by prednisone and actinomycin C therapy.

Infectious Diseases.—The characteristic appearance of infectious diseases after institution of antirejection treatment has been discussed in part I, and is illustrated in the subsequent course of case 2.

CASE 2 (continued).—With antirejection therapy, renal function improved; however, the white blood cell count dropped to 2,800/cu mm and mild glycosuria appeared. On the 16th day, fever recurred, and tenderness, heat, and swelling appeared over the implant site. The incision was open, yielding frankly purulent material which contained coagulase-positive staphylococci from the subcutaneous tissue. Sodium methicillin and sodium oxicillin therapy was begun, the patient defervesced, and over the ensuing three weeks the wound healed by secondary intention.

A staphylococcal infection in the transplantation site occurred 15 days after institution of antirejection therapy. Despite the daily administration of 100 mg of prednisone, the patient's temperature rose to 39.5 C (103.1 F); however, this responded to drainage of the wound and antibiotic therapy. In contrast to the severe renal failure that accompanied the rejection phenomenon, renal function was maintained and actually improved somewhat during the development and course of the staphylococcal infection.

Infection Plus Rejection.—When initial good renal function follows transplantation, the appearance of either rejection or infection occurring alone can usually be recognized as described above. However, when infection and rejection are superimposed during the postoperative period, the characteristics of either process are frequently obscured by the other. The complexities of this situation are evident in the following case (Fig 3).

CASE 3 (LH-28).—The patient was a 49-year-old white male with chronic glomerulonephritis; he was admitted with severe uremia, bilateral pleural effusions, and possible aspiration pneumonia. Sputum cultures revealed coliform bacilli and nasal cultures yielded *Staphylococcus aureus*. He was treated with sodium methicillin and chloramphenicol with little change in clinical status. After nine days of pretreatment with azathioprine, the patient underwent bilat-

eral nephrectomy, splenectomy, and renal homotransplantation. The bilateral pleural effusions cleared, revealing, on the third postoperative day, a cavitary lesion in the superior segment of the right lower lobe. An intermediate strength purified protein derivative tuberculin test was negative. Sputum smears on four occasions showed no acid-fast bacilli; however, two sputum cultures obtained on the 9th and 11th postoperative days were later reported to be positive for tubercle bacilli. Colistimethate sodium was added to the therapy because of persistence of coliform organisms in the sputum. Following initial good renal function, evidence suggestive of homograft rejection appeared and on the 14th day prednisone, 200 mg daily, was begun. This resulted in improved renal function and defervescence; however, hyperglycemia and glycosuria developed. On the 23rd day, the patient became acutely febrile; a chest x-ray revealed left lower lobe pneumonia, blood cultures grew *Esch coli*, and the patient died on the following day.

In this case, right lower lobe cavitary tuberculosis was undoubtedly present during the preoperative period but was obscured by extensive bilateral pleural effusions and pulmonary congestion. The progress of this disease may well have been hastened postoperatively by the immunosuppressive drug therapy.

The temperature course followed by this patient was atypical for a pure rejection crisis. The gradual appearance of fever early postoperatively probably reflected the presence of the pulmonary tuberculosis. The decline in renal function, however, did suggest an immunologic assault on the transplanted kidney; and, accordingly, corticosteroids and actinomycin C were administered. Defervescence followed and renal function improved, but in the presence of the suppressive agents, a fatal *Esch coli* pneumonia and septicemia occurred. It is of interest that prednisone controlled the fever of the granulomatous disease, but not that of the acute bacterial sepsis.

Febrile Disease Simulating Infections.—A recurrence of the homograft rejection process has occurred four times in two patients in this series. In these instances, fever reappeared during the withdrawal of the corticosteroids that had been administered in the treatment of the initial rejection attempt. The usual features of rejection obtain during such recurrences and the diagnosis may be confirmed by the prompt response to increased dosages of prednisone and actinomycin C. It has been observed, however, that recurrent rejections may be more violent than the initial episode and require more active therapy for their suppression.

In addition to the relatively rare recurrent rejection phenomenon, which is characterized by fever and deteriorating renal function, fever alone is frequently associated with the withdrawal of steroids after control of a rejection crisis. This febrile response appears when the prednisone dosage is decreased below a critical level, usually about 40 mg daily, and subsides over a period of weeks despite continued tapering and ultimate withdrawal of the steroids.

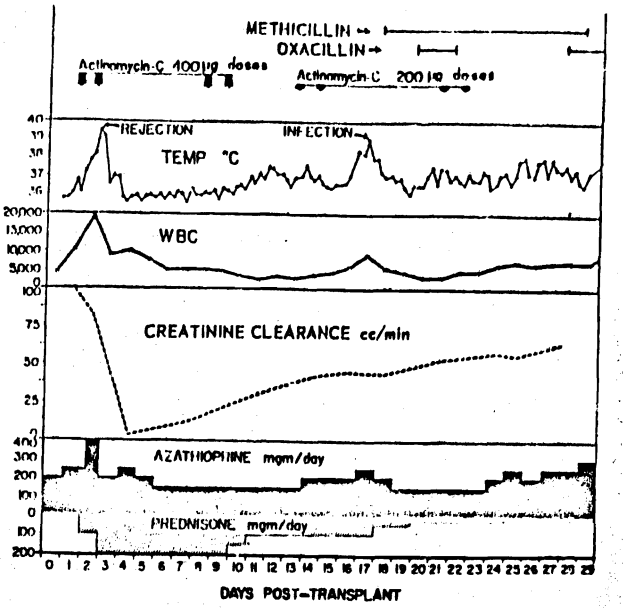

Fig 2 (case 2).—Course and treatment after renal homotransplantation.

Acute hemorrhagic pancreatitis with temperature to 39 C (102.2 F), adbominal distention, adynamic ileus, and a serum amylase level of 820% (normal, 65%-135%), proved fatal in one patient 73 days following transplantation. This complication was probably related to prolonged prednisone therapy. The renal function remained adequate in this patient, even terminally.

Spondylitis with erosion of the L1-L2 articular surfaces (Fig 4) radiographically suggestive of a pyogenic lesion occurred in one patient.

Case 4 (LH-10).—This 46-year-old man had a temperature of 38.2 C (100.8 F) and back pain while prednisone therapy was being withdrawn approximately three months after renal homotransplantation. Aspiration of the involved L1-L2 interspace under radiographic control yielded about 1 ml of serous fluid which was sterile on culture. Surgical exploration was subsequently performed under methicillin coverage and granulomatous material was curetted from the intervertebral space. This was again sterile and microscopically demonstrated evidence of "acute and chronic inflammation." Following this orthopedic procedure and discontinuance of prednisone, the patient improved.

The pathological process which this patient presented may have been similar to those cases of aseptic bone necrosis secondary to steroid administration reported by Sutton and associates.[6] No evidence for an infectious origin was obtained. The low-grade fever was related either to the spondylitis or to steroid withdrawal as described above.

Management of Infectious Diseases

While a variety of infectious diseases were encountered in these patients, the management of only those which presented either features or problems peculiar to this group of patients will be illustrated.

Septicemia.—Preoperative staphylococcal infections at the site of hemodialysis catheters occurred

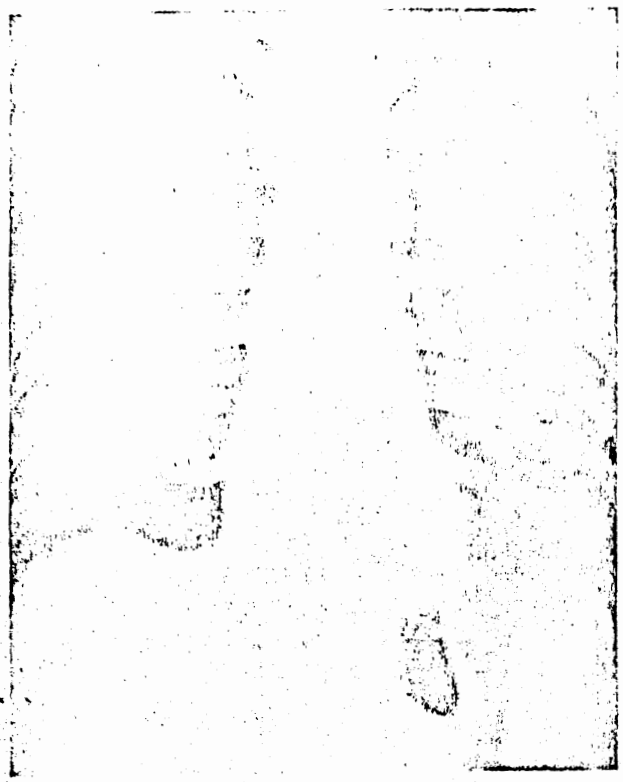

Fig 3 (case 3).—Chest roentgenogram taken on day prior to death. Tuberculous cavity in the right lower lobe and *Esch coli* pneumonia in left lower lobe.

in five patients in this series, resuling in septicemia in two. All five patients were staphylococcal carriers.

CASE 5 (LH-27).—The patient was a 20-year-old white woman with chronic glomerulonephritis who had staphylococcal furunculosis prior to operation. In preparation for surgery, an arteriovenous dialysis shunt was inserted and azathioprine immunosuppression was begun. Eight days later, her temperature suddenly rose to 39.5 C (103.1 F) and she became disoriented. Examination revealed purulent material at the site of the shunt. Cultures of this material and three blood cultures yielded *Staph aureus*. The azathioprine was discontinued, the arteriovenous shunt was removed, and the patient was started on methicillin and penicillin G intravenously. As the staphylococcus was found to be penicillin sensitive, methicillin was discontinued. The patient required two dialyses during the period of sepsis. She responded promptly to antibiotic therapy and after nine days the azathioprine was restarted. Two days later, bilateral nephrectomy, splenectomy, and renal homotransplantation were performed. The postoperative course was uneventful, and the penicillin was discontinued on the 31st day.

Preoperative staphylococcal septicemia was readily controlled by antibiotic therapy following removal of the contaminated dialysis catheters. Azathioprine, which had been started in preparation for transplantation, was discontinued during the initial nine days of antibacterial therapy. Penicillin was continued postoperatively until the transplantation wounds had healed. We have encountered no complications attributable to early transplantation after this type of systemic infection.

Pyelonephritis.—The presence of bacteruria presents a problem of first importance in renal transplantation patients. Apparent eradication of these infections with antibiotic therapy has been achieved in 12 of 15 patients. In one case, however, acute pyelonephritis superimposed upon polycystic disease could not be controlled preoperatively by antibiotic therapy alone. The management of this case is illustrated below:

CASE 6 (LH-22).—The patient was a 15-year-old white girl with polycystic kidney disease who was transferred from another hospital where she had been receiving chloramphenicol therapy for acute pyelonephritis. Urine cultures showed small numbers of *Esch coli* and *Candida parakrusei*. Chloramphenicol was continued and penicillin G added; however, the patient continued to run a febrile course which was not altered by the subsequent addition of kanamycin sulfate and ampicillin. Because the patient's temperature was above 40 C (104 F), a bilateral nephrectomy and splenectomy were performed, following which the temperature promptly fell to normal and the antibiotics were discontinued. Cultures of the cystic fluid from the kidneys yielded *C parakrusei* in pure culture. Microscopic examination, however, failed to reveal any evidence of invasion of renal tissue by this fungus. The patient was maintained by hemodialysis for 21 days and renal homotransplantation was then performed. The postoperative course was complicated by an *Esch coli* and Proteus bacteruria which responded to antibiotic therapy.

In this case, acute pyelonephritis superimposed upon polycystic renal disease was refractory to antibacterial therapy. There was, however, a prompt and dramatic cure following bilateral nephrectomy and successful renal homotransplantation was accomplished three weeks later.

Bacteruria resulting from chronic pyelonephritis may be carried over into the post-transplantation period despite removal of the infected kidneys if there is an associated lower urinary tract infection. The therapeutic difficulties are evident in the following case:

CASE 7 (LH-12).—The patient was a 48-year-old white male with chronic glomerulonephritis in whom preoperative Proteus and Pseudomonas bacteruria became apparent following cystoscopy and retrograde pyelography. The bladder was irrigated intermittently with neomycin sulfate, bacitracin, and polymyxin B sulfate for six days prior to bilateral nephrectomy, splenectomy, and renal homotransplantation. The Proteus and Pseudomonas bacteuria persisted postoperatively and was suppressed only after 84 days of continual antibiotic therapy which included courses of tetracycline chloramphenicol, streptomycin, kanamycin, colistimethate, methenamine mandelate, and nalidixic acid. During treatment with this latter drug, urine cultures became negative and the patient currently is being maintained on sulfisoxazole, 2 gm daily.

The long-term effects of bacteruria following renal homotransplantation have yet to be assessed. It would seem reasonable to assume, however, that lower urinary tract infection in these patients with a single homograft kidney who are receiving cytotoxic drugs and corticosteroids could lead to ascending pyelonephritis and impaired renal function.

For this reason, it is believed that the risk attendant upon the cautious administration of potentially nephrotoxic antibiotics in an attempt to eradicate these infections is warranted.

Pneumonia.—The following case illustrates the treatment of pneumonia with antibiotics and the control of several consequences of immunosuppression which probably contributed to the development of this infection.

CASE 8 (LH-25).—The patient was a 33-year-old white male who was readmitted 56 days after renal homotransplantation complaining of fever and a "wheezing" sensation in his chest. His therapy at that time included azathioprine and 100 mg prednisone daily. His temperature was 101 F (38.3 C), and the blood pressure of 130/90 mm Hg was unchanged from previous examination. X-ray examination of the chest showed a right middle lobe pneumonia and sputum cultures revealed coliform organisms. The white blood cell count was 10,700/cu mm with 87% mature polymorphonuclear neutrophiles, 5% band forms, and 8% lymphocytes. Serum electrophoresis done one week previously showed a gamma globulin concentration of 320 mg%. A fasting blood sugar was 356 mg% and 3 plus glycosuria was present. The patient was treated with antibiotics, gamma globulin, insulin, and dietary control. His clinical response was satisfactory. The infiltrate cleared slowly over the next two weeks, and the patient remains well at this time.

Again illustrated in this case are the development of an infection in a patient demonstrating steroid-induced diabetes and hypogammaglobulinemia, and the appearance of fever with infection despite high-dosage prednisone therapy. This case suggests that serious infections in these patients receiving immunosuppressive drug therapy can be successfully managed by antibiotic therapy in conjunction with control of the side effects of the suppressive agents.

Comment

The presentation of both homograft rejection and infectious diseases as acute febrile processes has made the etiologic diagnosis of fever one of the most frequent and difficult problems in the management of renal homotransplantation patients. This differential is of particular importance in that the therapeutic approaches to the two conditions are diametrically opposite and even mutually antagonistic. The rejection phenomenon, as indicated previously, is treated by increasing the dose of azathioprine and by the addition of large doses of corticosteroids and actinomycin C. It is apparent that if the fever be due to sepsis, these drugs will act only to impair further the already depressed resistance of the host. In contrast, if only antibiotic therapy is instituted in a rejection crisis, then progressive damage to the transplant will ensue which may, at least in part, be irreversible.

The features which characterize the rejection crisis have been described from several centers.[1,10,11] The symptoms are those of malaise and vague uneasiness. The clinical signs are fever, oliguria, hypertension, and tenderness over the homograft site. Laboratory studies reveal leukocytosis and occasionally eosinophilia, azotemia, proteinuria, and a decreased creatinine clearance rate and urinary urea concentration.

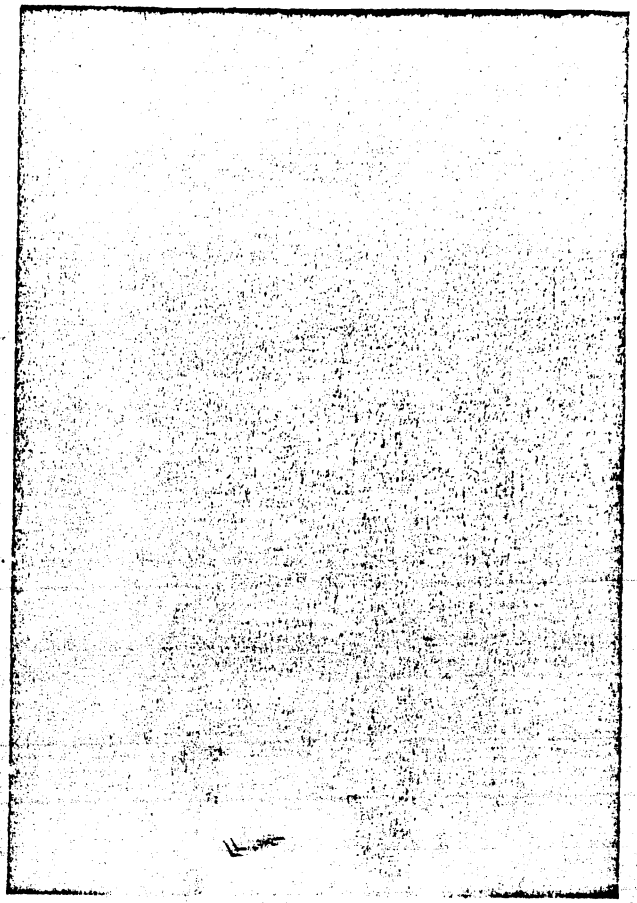

Fig 4 (case 41.—Lateral lumbar spine view. Note erosion of the LI-L2 articular surfaces.

Infectious diseases, in contrast, do not produce early and severe impairment in the renal function, although some diminution in renal function may appear late in the course of an overwhelming infection.

The white blood cell count has been found to be of little differential value for several reasons: (1) this parameter is usually being controlled by daily adjustments in azathioprine dosage; (2) infections frequently develop following neutropenia resulting from antirejection therapy; and (3) the appearance of leukocytosis with either infection or rejection is probably more a reflection of bone marrow reserve after cytotoxic drug therapy than a response characteristic of either process.[12]

Of note is that fever occurred with pneumonia in two cases despite the daily administration of 100 to 200 mg of prednisone. In general, the appearance of a temperature elevation in a patient whose rejection fever has been controlled on a stable dose of corticosteroids suggests the superimposition of an infectious disease. The reappearance of fever,

however, during steroid withdrawal may indicate the recurrence of rejection, in which case the previous larger doses of prednisone may be required for maintenance of renal function. In addition, fever without impairment in renal function may appear transiently during the process of steroid withdrawal.

Because of the high risk and serious consequences of staphylococcal infections in these patients, all staphylococcal carriers in the current series of renal transplant recipients are being treated with systemic antibiotics for several days prior to transplantation and until wound healing has occurred. Usually penicillinase-resistant penicillins are employed; however, when the staphylococcus is shown to be penicillin sensitive, as in case 5, penicillin G is used. Because of the relatively narrow spectrum of these antibiotics, superinfection has not been a problem to date. Further, we have not encountered sodium methicillin-resistant strains of staphylococci although these have been reported from other centers.[13] Sufficient data are not yet available to assess whether this therapy will reduce the incidence of infectious complications or whether it will only result in the substitution of other organisms as etiologic agents.

Bacteruria should be treated before operation and, following transplantation, antibiotic therapy is continued for one to two weeks or longer if bacteruria persists. When pyelonephritis is a part of the patient's end-stage renal disease, both ureters should be completely excised at the time of bilateral nephrectomy to avoid leaving a possibly infected bladder diverticulum.

Some of the consequences of antirejection therapy have been described. Granulocytopenia at present is treated only by reduction of dosage or discontinuance of the cytotoxic drugs. Other possible forms of therapy for this condition, such as white cell transfusions and androgen therapy, have not been investigated. Because of the apparent relationship between steroid-induced diabetes and increased susceptibility to infections, dietary control and insulin are employed whenever this metabolic disorder appears. It has been noted in the majority of patients that after prednisone dosages are decreased to 40 mg daily or less, these control measures can usually be discontinued. Hypogammaglobulinemia has been observed in six patients in association with intensive antirejection therapy. In such patients it seems justified to administer human gamma globulin when the serum concentration drops to the 0.3 gm% level in the presence of either an infection or granulocytopenia. The serum gamma globulin concentration will usually rise spontaneously towards normal when the immunosuppressive therapy is relaxed.

The selection and dosages of antibiotics used in individual cases have not been detailed here. In general, these are adjusted according to the principles outlined by Kunin and Finland.[14] The nature and severity of the infection, the mode of excretion and toxicity of the antibiotic, and the renal function of the patient are all taken into consideration. Because of these variables, doses of the more nephrotoxic antibiotics such as kanamycin and colistimethate were adjusted at frequent intervals and continuing orders for these agents are not written. A detailed description of the application of some newer bactericidal antibiotics in renal homotransplantation patients will be the subject of another communication.

The question of antituberculous prophylaxis in these patients who receive massive doses of corticosteroids and cytotoxic drugs is raised by the death of one patient in this series with cavitary pulmonary tuberculosis. In this case, the disease, although active prior to transplantation, was undoubtedly enhanced by the immunosuppressive therapy. Chest roentgenograms should be taken prior to and at intervals during immunosuppressive drug therapy. Isoniazid should be given if a lesion suggestive of inactive tuberculosis is present. Active tuberculosis would, of course, require a period of therapy before transplantation could be considered. Whether isoniazid should be given to all transplant patients without a positive tuberculin skin test remains a matter of individual judgment. It is clear that a negative skin test does not rule out this disease (see case 3).

The depression in host resistance which results from immunosuppressive therapy is presumed to be a nonspecific phenomenon. Infection may result from any of a number of microorganisms depending upon their relative pathogenicity and upon their chance occurrences at a time of sufficient host susceptibility. In four cases in this series, however, staphylococcal infections in the renal implant wound became apparent following treatment of a rejection crisis at a time when rapidly improving renal function suggested that significant host adaptation to the graft was occurring. This sequence of events could suggest that coincident with adaptation to the homograft, adaption may simultaneously occur to certain microorganisms present in the host throughout the rejection-adaptation sequence. These particular strains would no longer be recognized as foreign, and in the absence of an appropriate defense response, would produce an uncontrolled and overwhelming septic process. The appearances of mediastinal infections during antirejection therapy some weeks after thymectomy, as previously described, could possibly be explained on this basis.

In a more general sense, it might be speculated that a similar mechanism is involved in other clinical sittings. A form of host adaptation to infectious agents could be involved in reactivation of tuberculosis during steroid therapy, or in the frequent appearance of this infection in patients with sar-

coidosis and Hodgkin's disease. The loss of reactivity to microorganisms might also play a role in the pathogenesis of diseases which tend to relapse when the host's resistance is weakened, such as classical typhus, malaria, or salmonellosis.

Besides host adaptation to microorganisms, other interrelationships between infectious disease and transplantation immunity could exist. For example, bacterial endotoxins have been shown to act as adjuvants [15] and to increase the activity of the reticuloendothelial system.[16] Bacterial infections following transplantation might by such mechanisms serve to increase the antigenicity of the homograft and either hasten or increase the severity of the rejection crisis. Conversely, the finding by Jones and Shapiro [17] that pressor amines render rats susceptible to hematogenous pyelonephritis suggests that the rejection phenomenon with its accompanying hypertension could predispose to the development of renal infections.

Addendum

Since submission of this report, four additional deaths have occurred. The duration of survival of these patients ranged from 95 to 295 days. Infections contributed to death in two of the patients—Candida brain abscesses in one and Pneumocystis pneumonia with disseminated cytomegalic inclusion disease in the second.

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The bacteriophage typing of staphylococcal strains was done by the Colorado State Department of Public Health.

Azathioprine is supplied as Imuran by Burroughs-Wellcome & Co, Tuckahoe, NY; actinomycin C as Sanamycin by F.B.A. Pharmaceuticals, Haywards-Heath, Sussex, England; ampicillin as Polycillin by Bristol Laboratories, Syracuse, NY; and nalidixic acid as NegGram by Winthrop Laboratories, New York, NY.

Generic and Trade Names of Drugs

Neomycin sulfate—*Mycifradin Sulfate, Myciguent, Neomycin Sulfate.*

Bacitracin—*Baciguent, Bacitracin.*

Streptomycin sulfate—*Streptomycin Sulfate.*

Erythromycin—*Ilotycin, Erythromycin.*

Nitrofurantoin—*Furadantin.*

Colistimethate sodium—*Coly-Mycin Injectable.*

Chloramphenicol—*Chloromycetin.*

Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*

Sodium methicillin—*Dimocillin, Staphcillin.*

Kanamycin sulfate—*Kantrex.*

Polymyxin B sulfate—*Aerosporin Sulfate, Polymyxin B Sulfate.*

Methanamine mandelate—*Mandelamine.*

Sulfisoxazole—*Gantrisin.*

Isoniozid—*INH, Isoniazid, Niconyl, Nicozide, Nydrazin, Rinifon, Tisin, Tyvid.*

Sodium oxacillin—*Prostaphlin, Resistopen.*

Corticotropin—*Acth, Acthar, Corticotropin.*

Cortisone acetate—*Cortisone Acetate, Cortogen Acetate, Cortone Acetate.*

References

1. Starzl, T.E.; Marchioro, T.L.; and Waddell, W.R.: Reversal of Rejection in Human Renal Homografts With Subsequent Development of Homograft Tolerance, *Surg Gynec Obstet* 117:385, 1963.

2. Schreiner, G.E., and Maher, J.F.: *Uremia: Biochemistry, Pathogenesis and Treatment*, Springfield, Ill: Charles C Thomas, 1961.

3. Finland, M.: Serious Infections in Splenectomized Children, *Pediatrics* 27:689, 1961.

4. Laski, B., and MacMillan, A.: Incidence of Infection in Children After Splenectomy, *Pediatrics* 24:523, 1959.

5. Hume, D.M., et al: Experience With Renal Homotransplantation in Human: Report of Nine Cases, *J Clin Invest* 34:327, 1955.

6. Hume, D.M., et al: Renal Homotransplantation in Man in Modified Recipients, *Ann Surg* 158:608, 1963.

7. Murray, J.E., et al: Prolonged Survival of Human-Kidney Homografts by Immunosuppressive Drug Therapy, *New Eng J Med* 268:1315, 1963.

8. Thomas, E.D., et al: Irradiation and Marrow Infusion in Leukemia, *Arch Intern Med (Chicago)* 107:829, 1961.

9. Sutton, R.D.; Benedek, T.G.; and Edwards, G.A.: Aseptic Bone Necrosis and Corticosteroid Therapy, *Arch Intern Med (Chicago)* 112:594, 1963.

10. Murray, J.E., et al: Prolonged Survival of Human-Kidney Homografts by Immunosuppressive Drug Therapy, *New Eng J Med* 268:1315, 1963.

11. Hume D.M., et al: Renal Homotransplantation in Man in Modified Recipients, *Ann Surg* 158:608, 1963.

12. Mechanic, R.C. et al: Quantitative Studies of Human Leukocytic and Febrile Response to Single and Repeated Doses of Purified Bacterial Endotoxin, *J Clin Invest* 41:162, 1962.

13. Jevons, M.P.: "Celbenin"—Resistant Staphylococci, *Brit Med J* 1:124, 1961.

14. Kunin, C.M., and Finland, M.: Restrictions Imposed on Antibiotic Therapy by Renal Failure, *Arch Intern Med (Chicago)* 104:1030, 1959.

15. Johnson, A.G.; Gaines, S.; and Landy, M.: Studies on O Antigen of Salmonella Typhosa: V. Enhancement of Antibody Response to Protein Antigens by Purified Lipopolysaccharide, *J Exp Med* 103:225, 1956.

16. Rowley, D.: Role of Opsonins in Non-Specific Immunity, *J Exp Med* 111:137, 1960.

17. Jones, R.K., and Shapiro, A.P.: Increased Susceptibility to Pyelonephritis During Acute Hypertension by Angiotensin II and Norepinephrine, *J Clin Invest* 42:179, 1963.