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Infectious Diseases Associated With Renal Homotransplantation

I. Incidence, Types, and Predisposing Factors

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Infectious diseases occurred in 26 of 30 renal homotransplantation patients and contributed to eight of the 12 deaths in this series. There were 52 infections, 17 occurring before and 35 after transplantation. Infections were produced primarily by staphylococci, Pseudomonas species, and the enteric gram-negative bacilli. Staphylococcal infections occurred in 17 of 19 carriers of this organism and in only one of 11 noncarriers. Thirty-three of the 35 postoperative infections followed the intensification of immunosuppressive therapy for treatment of attempted homograft rejection. Granulocytopenia, steroid-induced diabetes, and hypogammaglobulinemia, from suppressive drug therapy, routinely preceded the onset of these complications. The infections, largely of endogenous origin, occurred when the host's defense mechanisms were depressed.

RECENT ADVANCES in methods available for modification of the homograft rejection process have permitted preliminary evaluation of renal transplantation on a clinical level. Studies at this center indicate that the immunosuppressive agents necessary for this procedure must be accurately titrated between insufficient dosage with rejection of the graft, and excessive dosage with toxicity and death of the host from sepsis. The purpose of this communication is twofold; first, to analyze the infectious diseases which have occurred in the first 30 patients treated by renal homotransplantation at the University of Colorado Medical Center and, second, to define certain consequences of immunosuppressive therapy.

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Patient Material and Methods

Renal homotransplantation procedures were performed on 25 male and five female patients ranging in age from 6 to 49 years. The renal diseases included 21 cases of chronic glomerulonephritis, three cases of polycystic disease, two of chronic pyelonephritis, one each of idiopathic nephrosis and gouty nephropathy, and two cases of unilateral renal aplasia. One of the last two patients had hydronephrosis with pyelonephritis. The other's functioning kidney had been inadvertently removed at another hospital. In 28 cases, homografts were provided by living volunteer donors. Cadaveric kidneys were used for the other two, resulting in sluggish or absent renal function.

The surgical procedures and general care employed for these patients have been described elsewhere.[1] Thymectomy was performed prior to renal homotransplantation in nine of the first 13 patients. Splenectomy was performed in 29 of the 30 patients. In the earlier patients in this series, thymectomy and splenectomy were usually done two to four weeks prior to bilateral nephrectomy and renal homotransplantation. In the later patients in whom thymectomy was not done, splenectomy, bilateral nephrectomy, and renal homotransplantation were most commonly performed in a single operation. Just prior to surgery, an indwelling urethral catheter was inserted and approximately 100 ml of sodium chloride solution containing 0.5 gm of neomycin sulfate and 50,000 units of bacitracin was instilled into the bladder. After renal implantation, the wounds as well as both subphrenic spaces were irrigated with the same amounts of these antibiotics in 500 ml of sodium chloride solution.

All patients were placed in strict isolation at the time immunosuppressive drug therapy was begun. Isolation precautions included caps and masks, sterile gowns, surgical gloves, cloth shoe covers for

Table 1.—Infections in Renal Homotransplantation Patients

Infection	No. of Patients	No. of Infections	Etiology	Outcome: Cured	Outcome: Suppressed	Outcome: Not Cured
Septicemia	8	8	Staphylococcus	3	....	....
			Staphylococcus, enterococcus	....	1	....
			Staphylococcus, pseudomonas	....	....	3
			Esch coli	....	....	1
Pneumonia	5	7	Staphylococcus	2	1	....
			Esch coli	1	....	....
			Staphylococcus, pseudomonas	....	....	1
			Staphylococcus, Esch coli C albicans	....	....	1
			Staphylococcus, Esch coli Myco tuberculosis	....	....	1
Wound abscesses	11	13	Staphylococcus	8	2	1
			Staphylococcus, pseudomonas	....	....	1
			Staphylococcus, pseudomonas, proteus	....	....	1
Mediastinitis	4	4	Staphylococcus	....	....	1
			Staphylococcus, pseuromonas	....	....	1
			Staphylococcus, enterococcus	....	1	....
			Staphylococcus, streptococcus, pseudomonas	....	1	....
Bacteruria	15	15	Gram-negative bacilli*	9	2	1
			Staphylococcus, gram-negative bacilli*	2	....	1
Agranulocytic angina	2	2	Unknown	2	....	....
Subphrenic abscess	1	1	Unknown	....	....	1
Pancreatic abscess	1	1	Unknown	....	....	1
Brain abscess	1	1	C albicans	....	....	1

*Gram-negative bacilli: coliform, proteus, pseudomonas, paracolon.

hospital personnel, and mats soaked with detergent at the door of the patient's room.

For all patients, azathioprine was used as the primary drug for immunosuppression and was supplemented by total body irradiation only in the first patient. Following homotransplantation, corticosteroid therapy was initiated at the first sign of graft rejection. In 27 of the cases, actinomycin C was given intermittently at this time.

Bacteriological studies were done by the usual clinical laboratory methods and antibiotic sensitivity testing was by the disk method. In general, preoperative cultures were taken of the anterior nares, pharynx, skin, urine, and stool. Postoperatively, cultures of the urine and pharynx were obtained at least twice weekly. In addition, other cultures were taken both pre- and postoperatively as the clinical situation indicated.

Results

Incidence of Infections.—Infectious diseases occurred in 26 of the 30 patients in this series (Table 1). In five patients, infections appeared and were eradicated in the immediate preoperative period. In 21 patients, infections appeared following transplantation; however, in six of these patients, one or more of their septic complications originated prior to the surgical procedure.

A total of 52 individual infections occurred. Seventeen of these arose preoperatively of which 11 were cured, while six were carried over into the post-transplantation period. Following surgery, 35 additional infections appeared for the first time.

Mortality.—Infectious diseases caused or contributed to eight of the 12 deaths which occurred in this series (Table 2). In two of these eight cases, one or more of the infections present terminally appeared to have originated prior to transplantation.

The eventual outcome of each of the 52 infections is summarized in Table 1. It is apparent that the best therapeutic results were obtained with pure culture staphylococcal infections. In contrast, mixed infections with gram-negative bacilli, usually pseudomonas, were extremely refractory.

Infecting Organisms.—Infections due to coagulase- and mannitol-positive staphylococci developed in 18 patients and these bacteria were present in 33 of the 52 infections observed—in 13 of the 17 infections appearing in the immediate pretransplantation period and in 20 of the 35 post-transplantation infections. Staphylococci were involved in each of the eight cases in which infection contributed to the death of the patient.

Pseudomonas infections appeared 16 times in these patients and were present in six of the eight patients in whom death was related to infectious diseases. They appeared in 5 of the 17 pretransplant and 11 of the 35 post-transplant infections.

The enteric gram-negative bacilli were involved in 19 infections, primarily of the genitourinary tract. Representatives of most of the common species within this group were isolated; however, they will not be discussed individually as none of them established a unique disease pattern nor

Table 2.—Terminal Infectious Diseases in Eight Renal Homotransplantation Patients

Patient Number	Patient Age, Yr	Survival, Days	Infectious Diseases	Etiology
LH-4	35	113	Pneumonia	Staphylococcus, pseudomonas
			Septicemia	Staphylococcus, pseudomonas
			Mediastinistis*	Staphylococcus, pseudomonas
			Subphrenic absess	Unknown
CH-1	21	25	Septicemia	Staphylococcus, pseudomonas
			Implant abscess	Staphylococcus, pseudomonas
LH-5	49	11	Septicemia	Staphylococcus, pseudomonas
			Pyelonephritis	Staphylococcus, pseudomonas
			Mediastinitis†	Staphylococcus, pseudomonas
CH-2	29	40	Mediastinitis	Staphylococcus, pseudomonas, streptococcus‡
			Septicemia	Staphylococcus
			Pneumonia	Staphylococcus
			Implant abscess	Staphylococcus
LH-7	25	78	Septicemia	Staphylococcus, pseudomonas
			Implant abscess	Staphylococcus, pseudomonas
LH-11	35	24	Nephrectomy abscess	Staphylococcus, pseudomonas, proteus
			Mediastinitis	Staphylococcus, streptococcus*
LH-21	41	76	Pneumonia	Staphylococcus, coliform, candida
			Brain abscess	Candida
LH-30	49	25	Pneumonia	Staphylococcus, coliform, tubercle bacillus
			Septicemia	Coliform

*Patient had thymectomy before and pulmonary embolectomy after transplantation.
†Patient had thymectomy before and open cardiac massage at time of transplantation.
‡Not group A.

were their numbers sufficient to warrant analysis.

Non-group A streptococci occurred in mediastinal infections in two cases and in septicemia in one. *Candida albicans* and *Mycobacterium tuberculosis* were each found in one pulmonary infection.

Endogenous Source of Infections.—The source of infecting bacterial strains could most readily be adduced in the case of staphylococcal disease. The results of preoperative survey cultures indicated that 19 of the 30 patients were carriers of this organsim either in the nasopharynx or on the skin. Of the 19 carriers, 17 developed significant staphylococcal infections either pre- or post-transplant. In contrast, only one of the 11 noncarriers developed such a complication. Thus, only two of the 19 staphylococcal carriers escaped a clinical infection with this organism during hospitalization. In two patients, staphylococcal strains recovered from blood cultures were compared by means of bacteriophage typing with those previously isolated from the nasopharynx. The pair of isolates from the first patient was found to be of the same phage type while the pair from the second patient was nonphage typeable. These data suggest that in both cases the septicemia was caused by the staphylococcal strains carried by the patient in his nasopharynx.

In contrast to the epidemiology of infections caused by staphylococci, it was difficult to establish the origin of those caused by the gram-negative bacilli. The following case, however, bears upon this question:

Case 1 (LH 17).—The patient was a 15-year-old girl with chronic pyelonephritis who received a renal homograft from her mother. The recipient was placed on streptomycin and erythromycin preoperatively because of low-grade fever, although no cause for the fever was established.

While the donor's renal function was normal, an *Escherichia coli* bacteruria was demonstrated one month prior to nephrectomy. This was treated before operation with a two-week course of nitrofurantoin and repeat urine cultures after therapy were negative. At operation, the donor kidney was of normal size but showed cortical scarring compatible with chronic pyelonephritis.

Because of the possible pyelonephritis in the donor kidney, the recipient was given colistimethate sodium for the first day and then chloramphenicol for four days postoperatively. On this treatment, however, diarrhea developed and stool cultures revealed approximately 30% pseudomonas and 70% coagulase-negative staphylococci. The diarrhea subsided following discontinuance of chloramphenicol. A urine culture taken two days later showed pseudomonas in pure culture and in significant numbers. The patient was given a six-day course of colistimethate sodium with eradication of the bacteruria.

This patient received a pyelonephritic kidney from her mother who had been treated for *Esch coli* bacteruria one month before operation. Following transplantation, the patient developed an episode of diarrhea during which stool cultures revealed only pseudomonas species and staphylococci. Two days later, pseudomonas bacteruria appeared. It is believed that this bacteruria was caused by organisms carried in the gastrointestinal tract of the recipient rather than in the pyelonephritic donor kidney.

Types of Infections and Clinical Course.—Septicemia occurred in eight patients in this series (Table 2). This occurred preoperatively in two patients due to staphylococci seeded from dialysis catheters. In these two cases, the infections were cured by antibiotic therapy and prompt removal of the intravascular tubing.

In the remaining six patients, septicemia occurred in the postoperative period and was due to *Esch coli* (one case) and to staphylococci either in pure culture (one case) or in combination with pseudomonas species (three cases), and enterococci (one case). In only one of these six patients was

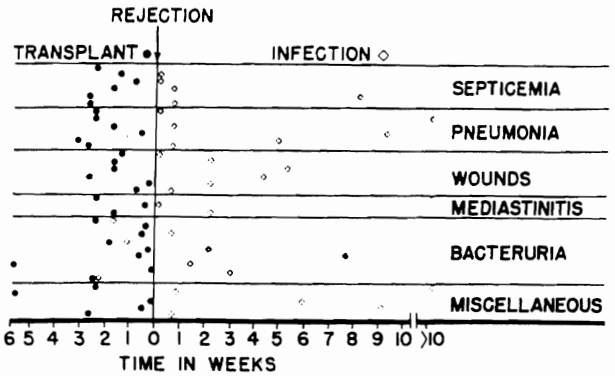

Fig 1.—Time of appearance of infections following renal transplantation. Majority occurred after homograft rejection crisis when actinomycin C and prednisone 100-200 mg daily are added to basic azathioprine immunosuppressive regimen.

the infection suppressed; ultimately, the other five patients died of this complication.

Pneumonia occurred seven times in five patients and resulted in the death of four. Staphylococci were involved in six instances and were present in pure culture in three. In one, pulmonary infection was produced by *Esch coli* alone. The tubercle bacillus and *C albicans* each accompanied pyogenic pulmonary infections in one fatal case.

Wound infections occurred 13 times in 11 patients, at the site of either renal implantation, nephrectomy, or insertion of polyethylene intravenous catheters for hemodialysis. In 11 instances, the infections were caused by staphylococci in pure culture; ten were either cured or suppressed and in one the infection proved fatal. In two cases, staphylococci plus gram-negative bacilli were involved and, in both instances, contributed to death.

Mediastinal sepsis occurred in four of the nine patients in whom thymectomy was done prior to renal homotransplantation. In two of these cases, however, other thoracic surgical procedures intervened between thymectomy and the appearance of mediastinitis—an open cardiac massage through unprepared skin in one case and a pulmonary embolectomy in the other. In all four cases, death occurred secondary to infection which was both local in the mediastinum and general. Staphylococci were involved in the four cases, once in pure culture and with combinations of peseudomonas species and streptococci in the others.

Bacteruria occurred in 15 patients. Gram-negative bacilli were present in all cases and, in addition, staphylococci in three. In six patients bacteruria was present preoperatively and two of these patients were cured with antibiotic therapy. In the remaining four, the infection was suppressed preoperatively but reappeared following transplantation. The bacteruria was eradicated in three of these patients and in the fourth the infection remains suppressed under antibiotic therapy.

In nine patients, bacteruria appeared following transplantation, probably as a result of indwelling urethral catheters used during the first 24 to 72 hours postoperatively. In seven of these cases, the infection was successfully treated with antibiotics. In the remaining two, the bacteruria persisted in one and was suppressed in the other. Both of the patients, however, died of other causes.

In one case each, a paravertebral gutter abscess and a pancreatic abscess occurred, and in both cases the infections proved fatal. Cultures of these lesions were not obtained. Multiple brain abscesses secondary to pneumonia caused by *C albicans* proved fatal in one instance.

Agranulocytic angina occurred in two patients. Recovery followed antibiotic therapy and temporary withdrawal of the immunosuppressive therapy.

Time of Occurrence.—The appearance of postoperative infections followed a rather unusual pattern in this group of patients. It may be seen in Fig 1 that the majority of these complications arose following the appearance of the rejection phenomenon. In contrast, only three infections developed during the interim between renal homotransplantation and the onset of the rejection crisis even though this interim averaged almost 12 days.

Following control of rejection by the therapy indicated above, the dose of cytotoxic drugs is decreased and prednisone is eventually discontinued. Infections arising during this period of maintenance azathioprine therapy have not been frequent. When such complications have occurred, however, they have usually followed the reinstitution of active antirejection therapy necessitated by a recurrent rejection attempt, or by overly zealous maintenance use of the drugs.

Predisposing Factors.—The chronology of the postoperative infectious diseases discribed above suggests a major role of antirejection therapy in predisposing to these complications. Several consequences of this therapy, including agranulocytosis, steroid-induced diabetes, and hypogammaglobulinemia, have frequently been noted to precede the onset of serious infections.

Agranulocytosis is one of the most ominous consequences of vigorous antirejection therapy. Total leukocyte counts below 3,000/cu mm with granulocytopenia of various degrees appeared in 12 patients, and this complication developed in seven of the eight in whom infection contriubted to death.

Steroid-induced diabetes was noted in ten of a total of 26 patients tested. In addition, this metabolic alteration was detected in all four patients tested who subsequently died with infectious diseases. Measurements of blood sugar concentrations in several cases indicated that glycosuria occurring in these circumstances reflected significant hyperglycemia rather than an abnormally low renal threshold for gloucose in the homograft.

Hypogammaglobulinemia, at about the 0.3 gm/100 cc level (normal, 0.7 to 1.6 gm/100 cc), was found in six of the 22 patients on whom serum electrophoresis studies were made. This deficiency was noted in association with pneumonia in two patients. Low serum gamma globulin levels have been observed only in patients receiving both azathioprine and prednisone. The serum gamma globulin level usually rises near normal as the corticosteroid dosage is decreased.

Comment

Infectious diseases have constituted both a frequent and serious complication of renal homotransplantation in the series reported here. These diseases have developed under circumstances of strict reverse isolation precautions which would render person-to-person transmission of pathogens unlikely. It has not been possible in many cases to establish the origin of these infections. However, in the case of the staphylococci, some information was obtained which suggested that infections caused by these organisms were of endogenous origin. Staphylococcal infections were confined almost exclusively to the known carriers in the group. Further, limited bacteriophage typing data in two instances tended to confirm this interpretation.

While there is no direct evidence that this pattern obtains with other infectious agents, the reverse isolation techniques utilized and the appearance in one patient (case 1) of bacteruria probably derived from her intestinal flora, would suggest an endogenous origin also for certain nonstaphylococcal infections. It appears, therefore, that infections were frequently caused by microorganisms carried by the patient and developed when the host's defense mechanisms were depressed.

Those infections arising in the immediate preoperative period were probably potentiated by the impaired renal function of the patient. The increased incidence of infections in uremia has thoroughly been reviewed by Schreiner.[2]

Other factors resulting both from surgical procedures and chemotherapy may have contributed to the relatively high incidence of post-transplantation infections in these patients. In other series, splenectomy has been associated with an increased incidence of infection, but this seems to be of importance primarily in the first few months of life.[3] Recent studies suggest that the underlying disease processes which prompt the splenectomy are of greater importance in this regard rather than the loss of the spleen itself.[4] It is unlikely, therefore, that splenectomy plays a major role in the susceptibility to infection.

Thymectomy as an immunosuppressive operative procedure has been discontinued for the present due to the relatively high risk of infection attendant upon this procedure. Also, present evidence does not suggest that the procedure is essential for homograft adaptation. Probably these infections are frequent and refractory to therapy because of inherent difficulties in obtaining complete hemostasis and because sternal osteomyelitis and mediastinitis tend to complicate an otherwise simple wound infection. The possibility that a more unique immunologic defect has been created by this procedure, resulting in a decreased resistance to infection, has not been excluded. The present data, however, do not contribute to this question.

Granulocytopenia, steroid-induced diabetes, and hypogammaglobulinemia resulting from suppressive drug therapy have singly or in combination preceded most of the infectious complications in these patients. The apparent pre-eminence of these three factors may merely reflect the fact that they are readily recognized and quantitated by routine laboratory methods. Other alterations produced by the cytotoxic agents and corticosteroids may well be of equal, or even greater, potency in depressing the host's resistance to infections. Certainly the steroids predispose to such complications by means of the variety of "anti-inflammatory" effects as well as by the production of a diabetic state.

Sepsis has been a significant complicating feature in renal homotransplantation patients reported from other centers. This has occurred in seven of nine patients reported by Hume and associates.[5] In these early cases, immunosuppressive therapy with corticotropin and cortisone was employed in six of the nine patients. It is of interest that the two patients who remained free of infection did not receive these drugs. Perinephric abscesses, implant wound infections, empyema, pyelonephritis, and septicemia were noted in this group. In a more recent series of six renal transplantation patients reported by these workers,[6] one patient died postoperatively from disseminated moniliases after receiving total body irradiation and corticosteroids. Postoperative infections occurred in three of five renal transplantation patients reported by Murray and co-workers.[7] These infections, which included pneumonia, wound abscess, and bacteruria, were all controlled by antibiotics or incision and drainage.

Infectious disease may prove an important problem in the transplantation of other organs as well as the kidney. For example, among a series of five leukemia patients treated by bone marrow infusions following total body irradiation, two deaths due to *Esch coli* septicemia occurred.[8]

The factors leading to infections in the renal homotransplantation cases reported here are multiple and interrelated, and thus an analysis of the relative importance of any single deficiency becomes difficult, if not artificial. Attempts to explore some of the mechanisms involved could, however, yield information which might be applicable to various disorders of metabolic, hematologic, and neoplastic origin which are characteristictly complicated by frequent and severe infectious diseases.

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.

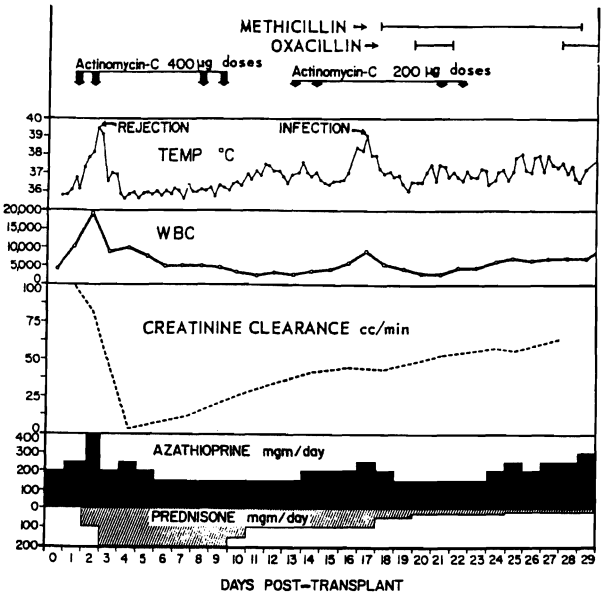

Fig 2 (case 2).—Course and treatment after renal homotransplantation.

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.[9] 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

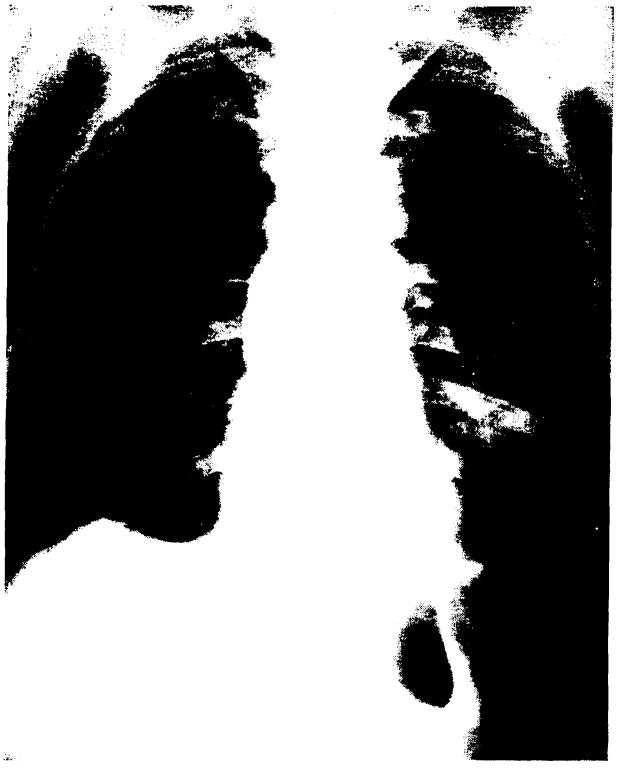

Fig 3 (case 3).—Chest roentgenogram taken on day prior to death. Tuberculous cavity in the right lower lobe and *Esch coli* pneumonia in left lower lobe.

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,

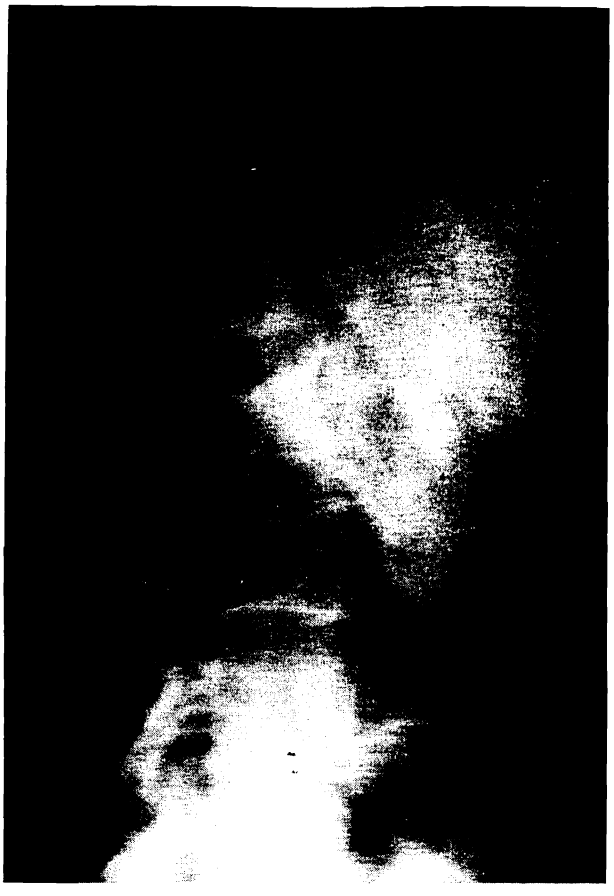

Fig 4 (case 4).—Lateral lumbar spine view. Note erosion of the L1-L2 articular surfaces.

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.

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-Health, 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—*Grantrisin.*

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.*

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