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NEPHROLOGY FORUM

Long-term complications of renal transplantation

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Case presentations

Patient 1. A 41-year-old white man with severe hypertension and end-stage renal disease secondary to chronic glomerulonephritis received a renal transplant from his 45-year-old brother 26 years ago. Two days prior to the transplant, the patient had bilateral nephrectomies and a thymectomy. Retrospective histocompatibility testing performed 11 years after the operation indicated that the brothers were HLA-identical. The recipient's course was relatively uncomplicated except for a staphylococcal wound infection and an *E. coli* urinary tract infection that responded to chloramphenicol therapy. The patient was discharged 4 weeks after receiving the transplant; the serum creatinine was 1.3 mg/dl. He required no further antihypertensive therapy. Medications at discharge included prednisone, 75 mg/day, and azathioprine, 200 mg/day. The patient returned to work within 6 months after the transplant and started his own company. By fourteen months after surgery, the prednisone had been decreased to 2.5 mg/day, and it was discontinued altogether 21 months after the operation.

Twenty-three years ago, a basal cell carcinoma was removed from his upper lip. Another basal cell carcinoma was removed from his lower eyelid 13 years ago. He continued taking azathioprine, 200 mg/day, until 10 years ago, when the drug dosage was decreased to 150 mg/day. Nine years ago, his serum creatinine was 1.2 mg/dl, the creatinine clearance was 153 ml/min, and he had no proteinuria. Squamous cell carcinomas on his temple and cheek, and a basosquamous carcinoma on his leg were removed 3 years ago.

The patient has not required hospitalization since the time of his renal transplant. He was self-employed, managing his own company full-time, until his retirement at age 65. His serum creatinine in September, 1988 was 1.6 mg/dl and the total cholesterol 231 mg/dl; urinalyses have shown 2+ proteinuria. His blood pressure is 118/80 mm Hg, and his medications are azathioprine, 150 mg/day, and nadolol, 20 mg once a day. The kidney donor remains in excellent health.

Patient 2. A 59-year-old white man, a retired forklift operator, was first seen at the Cleveland Clinic 13 years ago with hypertension of 3 years' duration, a serum creatinine of 3.5 mg/dl, and nephrotic-range proteinuria. An electrocardiogram showed a remote inferior myocardial infarction. He had a 35 pack/year history of cigarette smoking; the total cholesterol was 200 mg/dl. Percutaneous renal biopsy disclosed glomerulosclerosis with interstitial fibrosis and tubular atrophy by light microscopy. Immunofluorescence demonstrated a diffuse, 3+, coarsely granular deposition of C3 in the glomeruli. Electron microscopy revealed extensive dense deposits and collapsed peripheral capillary loops in the mesangial areas. The biopsy was difficult to classify because of the extensive degree of glomerulosclerosis.

The patient's renal function deteriorated over the next few months and peritoneal dialysis was started 12 years ago. Because of angina, the patient had a coronary angiogram 11 years ago, which showed total obstruction of the proximal third of the right coronary artery, with a good distal artery filling from the left coronary artery, a mildly irregular left main trunk, 30% obstruction in the left anterior descending artery with 75% narrowing in the diagonal branch, and diffuse irregularities in the circumflex artery. The left ventricle showed moderately impaired contractility and marked hypertrophy.

Ten years ago, the patient received a cadaveric transplant from a 23-year-old man. The recipient's HLA antigens were A1, A31, B8, and B40; the donor's antigens were A11, A31, B35, and B40. The preformed antibody level was less than 4%. The native kidneys were left in place. Immunosuppression consisted of 1 g of methylprednisolone in divided doses beginning just before transplant surgery; 2 mg/kg of prednisone on a tapering schedule; azathioprine, 1.0 to 2.0 mg/kg according to the white blood cell count; and Minnesota antilymphocyte globulin for 14 days. After 3 days of acute tubular necrosis, the transplant began to function. The patient was discharged 3 weeks after surgery; the serum creatinine was 1.8 mg/dl and the 24-hour urine protein excretion was 274 mg. Medications at discharge included prednisone, 30 mg, and azathioprine, 100 mg.

Between 4 and 11 months after the transplantation surgery, the serum creatinine remained stable; the 24-hour urinary protein excretion ranged between 217 and 645 mg. Hypertension (160/108 mm Hg) was controlled (120/70 mm Hg) with alpha-methyldopa and furosemide. Fourteen months after surgery, the serum creatinine was 1.6 mg/dl, but the 24-hour urine protein excretion had risen to 7.7 g. Subsequently it rose to 26.2 g/24 hours, with a serum creatinine of 1.9 mg/dl and total cholesterol of 580 mg/dl. Venograms performed one month later showed no thrombosis in the allograft vein, external iliac, common iliac, or inferior vena cava. From 12 to 15 months posttransplant, his hematocrit increased from 51.7% to 59.4% and the hemoglobin rose from 16.2 g/dl to 19.5 g/dl. The arterial pO_2 was 87.5 mm Hg with a saturation of 96.5% on room air. The patient underwent phlebotomies totaling 3 units of blood. Open renal transplant biopsy, performed 15 months after transplantation, disclosed extensive interstitial edema and lymphocytic infiltrates with lymphoid follicles and no vascular abnormality. Immunoperoxidase studies showed 3+ finely granular dense deposits of IgG and C3 in the epimembranous portion of the glomeruli, 2+ finely granular deposits of IgM predominantly in the mesangium,

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and 1+ granular deposits of C3 in arterioles and in some tubular basement membranes. Diffuse epimembranous deposits were found in the peripheral capillary loops, and basement-membrane-like material was present between the deposits. The findings were consistent with grade I-II membranous glomerulonephritis and acute cellular rejection.

The patient was treated for acute rejection with 3 g of intravenous methylprednisolone, and warfarin was added. Three months after the renal biopsy, the serum creatinine was 1.6 mg/dl; the total cholesterol, 324 mg/dl; and the 24-hour urinary protein excretion, 1.45 g. Within 10 months, with the serum creatinine still 1.6 mg/dl, the 24-hour urinary protein excretion decreased further to a range of 120 to 610 mg.

Twenty-one months after transplantation, the patient was hospitalized with a 2-week history of crescendo angina. A coronary angiogram showed progression of the occlusive lesions. Three months later, he had successful coronary artery bypass surgery and saphenous vein grafts to the left anterior descending and right coronary arteries. Medications at that time were 15 mg of prednisone, 150 mg of azathioprine, dipyridamole, warfarin, clofibrate, and furosemide.

Ten months after coronary bypass surgery, the 24-hour urinary protein excretion had increased to 2.0 g. The 24-hour urinary protein excretion rose to 3.3 g 5 months later, and he was treated with another 3 g of intravenous methylprednisolone. One month later, the 24-hour protein excretion had decreased to 340 mg. Intermittent phlebotomies were required because of a hemoglobin of 18 g/dl and a hematocrit of 57%. The following year the patient was treated surgically for squamous cell carcinoma of the face at the lateral aspect of the left eye and the nasolabial fold.

The patient required readmission to the hospital because of recurrent chest pain 2.5 years after the bypass surgery. Coronary arteriography revealed that both saphenous vein grafts were still patent but somewhat irregular. The patient continued to smoke, although at a reduced rate of approximately 3 cigarettes/day. He was being treated also with transdermal nitroglycerin, diltiazem, and atenolol. During this time his serum creatinine remained 1.5 mg/dl with a 24-hour urinary protein excretion of 280 mg.

Five years after renal transplantation, the iothalamate glomerular filtration rate was 59 ml/min/1.73 mm^2 with a serum creatinine of 1.3 mg/dl and a 24-hour urinary protein excretion of 1.1 g. Despite a low-cholesterol diet and clofibrate, total cholesterol remained elevated at 328 mg/dl. Four years ago, a small saccular abdominal aortic aneurysm was detected that measured 4.0 × 3.5 × 3.5 cm by ultrasonography. The need for intermittent phlebotomies continued. His 24-hour urinary protein excretion was 940 mg 3 years ago. At that time the total cholesterol had decreased to 268 mg/dl; the HDL cholesterol was 42; the LDL cholesterol, 202; and the triglycerides, 120 mg/dl.

One year ago, 8 years after his initial coronary bypass surgery, the patient developed unstable angina, had coronary angiograms at another hospital, and again had coronary artery bypass surgery, with a left internal mammary artery implant to the left circumflex, and three other saphenous vein grafts. The two previous saphenous vein grafts were 50% and 75% occluded. The patient was discharged on the eighth postoperative day with a serum creatinine of 1.3 mg/dl.

Four months ago, the patient developed transient ischemic episodes that were determined, after cerebral angiograms and electrocardiographic monitoring, to be due to transient ventricular arrhythmias rather than to carotid artery disease. A basal cell carcinoma was removed from his neck 3 months ago. His medicines included prednisone (10 mg/day), azathioprine (100 mg/day), and dipyridamole, warfarin, aspirin, verapamil, furosemide, digoxin, encainide, and lovastatin. The serum creatinine was 1.2 g. Blood lipid examination after a 13-hour fast showed a total cholesterol of 196 mg/dl; HDL cholesterol, 36 mg/dl; LDL cholesterol, 138 mg/dl; and triglycerides, 129 mg/dl.

Discussion

DR. WILLIAM E. BRAUN (*Consultant in Transplantation, and Director, Histocompatibility and Immunogenetics Laboratory, Departments of Hypertension and Nephrology and Immunopathology, The Cleveland Clinic Foundation, Cleveland, Ohio*): The two patients presented demonstrate some of the major complications of transplantation. The first patient, the recipient of an HLA-identical allograft, has had both squamous and basal cell carcinoma of the skin. In addition, proteinuria developed after 20 years, which might have been due to immunologically mediated chronic rejection, de novo glomerulonephritis, or non-immunologically mediated glomerular sclerosis. Because of his excellent HLA match and the small amount of proteinuria, I favor non-immunologically mediated glomerular sclerosis in a solitary, aged kidney as the cause of the proteinuria. The second patient had coronary artery disease, the most frequent cause of late posttransplant mortality, before he received his transplant. His coronary artery disease progressed, and he required coronary artery bypass surgery 2 and again 9 years after transplantation. Erythrocytosis, likely due to the presence of his native kidneys and a well-functioning transplant, might have had some part in his progressive coronary occlusive disease. Moreover, he developed the nephrotic syndrome and membranous glomerulonephritis 14 months after transplantation, and he was responsive then and 25 months later to treatment with methylprednisolone. Finally, he also developed skin cancer, the most frequent neoplasm seen after renal transplantation.

Transplant patients such as these are becoming a large component of the practice of nephrology. The number of renal transplants has been increasing steadily in the last decade. During the 1980s, more than 71,000 renal transplants will have been performed in the United States [1, 2]. The annual number of renal transplants has been about 9% of the number of patients being dialyzed in that same year. For the 5 years 1982 to 1986, the percentage of dialysis patients who received renal transplants increased from 8.1% to 9.9% [1, 2]. In 1987, however, that percentage fell to approximately 9.1% and has leveled off at approximately 9000 renal transplants from a total of more than 120,000 dialysis patients [1, 2]. Among this large number of transplants, rejection losses are cumulatively now sizable enough to make failure of a previous transplant one of the most frequent causes of end-stage renal disease, along with glomerulonephritis and diabetic nephropathy in native kidneys.

To manage well this growing number of renal transplant recipients, it is important for us to know the major causes of patient morbidity and mortality as well as the major causes of graft loss or dysfunction. A summary of 21 studies of adult renal transplantation from 1974 to 1988 provides important long-term patient and graft statistics: for recipients of a cadaver kidney, 10-year patient survival ranged from 27% to 67% and first cadaver graft survival from 25% to 56% [3]. Patient mortality (in the 21 studies) was primarily due to coronary artery disease in 14% to 50%, neoplasia in 9% to 28%, sepsis in 7% to 28%, and liver failure in 0% to 28% [3].

My review of our data on 150 of our transplant patients whose allograft functioned for more than 10 years provides more detailed information. Of these 150, we have followup data on 144. The mean duration of allograft function in the 144 patients was 14.7 ± 3.6 years (range, 10.0 to 25.5 years). The causes of end-stage renal failure were glomerulonephritis in 87 patients; tubulointerstitial disease in 31; polycystic disease in 7; congenital disease in 6; nephrosclerosis in 5; 2 each with systemic lupus erythematosus, diabetic nephropathy, Alport's syndrome, medullary cystic disease, multicystic disease, and unknown cause; and one each with vasculitis and nail-patella syndrome. The 150 long-term recipients comprised: 91 male and 59 female patients with a mean age of 28.6 ± 10.4 years (range,

9 to 58 years); 144 whites and 6 blacks; 138 (92%) having their first and 12 (8%) having repeat transplants; and 96 (64%) receiving transplants from living-related donors and 54 (36%) receiving cadaveric kidneys. The native kidneys were removed in 128 (85%), the spleens in 39 (26%), and the thymuses in 9 (6%) of the 150 recipients. Over the same time period, 424 allografts were performed that functioned for less than 10 years. In this group 350 (82.5%) received first and 74 (17.5%) received repeat transplants; 133 (31%) received living-related grafts, and 291 (69%) of the grafts came from cadavers. Thus, long-term successes, defined as allografts surviving at least 10 years, had about one-half the percentage of repeat grafts (8% versus 17%) and more than twice the percentage of living-related donors (64% versus 31%).

Prednisone and azathioprine were used in virtually all our recipients; none received cyclosporine. Other immunosuppression in the 150 long-term allograft recipients included thymectomy and/or splenectomy in 40 recipients during a period when local irradiation of the graft, actinomycin C, and an intramuscular preparation of locally produced horse antilymphocyte globulin also were used [4]. Eight patients who received transplants in 1978 were part of a controlled, randomized, double-blind study of Minnesota antilymphocyte globulin [5]. Rejection episodes typically were treated with larger doses of oral prednisone, 1 g of intravenous methylprednisolone daily for varying lengths of time, or both.

Of the 150 allografts that functioned for more than 10 years, 32 subsequently were lost. Sixteen patients died with a functioning allograft. Death was due to myocardial infarction in 5, malignancy in 5 (4 non-Hodgkin's lymphomas and 1 hepatoma), and infection in 3; 2 died of unknown causes and 1 of progressive encephalopathy. The 16 other patients lost their grafts because of: chronic rejection in 11; chronic rejection with prior systemic fungal infections and amphotericin B therapy in 3; chronic rejection and obstruction in 1; and recurrent renal artery stenosis in 1. Five of the 16 patients with failed grafts subsequently died: 2 of probable myocardial infarction, 1 of septicemia and gastrointestinal hemorrhage, 1 of candidal pneumonia, and 1 of unknown cause. Of the 11 living patients, 9 have had successful retransplants (7 cadaveric and 2 living-related), all of which are functioning for 1 to 9 years; 2 patients continue to be dialysed.

Causes of patient mortality

Coronary artery disease. Patients who developed ischemic heart disease after renal transplantation, when compared with those without vascular disease, were 10 years older (49 ± 12 versus 39 ± 13 years), predominantly male (76% versus 56%), and more likely to be diabetic (34% versus 22%) and to have hypertension (64% versus 51%) [6]. In addition, the patients with ischemic disease had twice as many pack-years of smoking (18 ± 23 versus 9 ± 15), higher cholesterol levels (275 ± 82 versus 244 ± 62 mg/dl), slightly lower HDL cholesterol levels (56 ± 24 versus 60 ± 19 mg/dl), and higher trigylceride levels (215 ± 165 versus 176 ± 129) [6]. All these are known risk factors of varying importance, even in non-transplant patients [6, 7]. All these differences are statistically significant ($P < 0.05$), save for the differences in HDL cholesterol and triglycerides [6]. Posttransplant patients with ischemic heart disease had 50% more rejection episodes (1.2 ± 1.2 versus 0.8 ± 1.0), and higher cumulative prednisone doses (16.8 ± 5.0 versus 15.5 ± 4.5 g) than did transplant patients without ischemic heart disease [6]. Not surprisingly, the list of risk factors for posttransplant ischemic heart disease is headed by pretransplant ischemic heart disease (Table 1) [6]. Overall, the risk of vascular disease within 4 years after renal transplantation was three- to fivefold that of age- and sex-matched controls [6].

Table 1. Risk factors for posttransplant ischemic heart disease[a]

Variable	Relative risk
Pretransplant ischemic heart disease	5.41
Diabetes	3.39
Male	2.02
Rejection episodes[b]	1.35
Smoking (*pack-years*)	1.10
Age at transplant (*years*)	1.05
Hematocrit (%)[c]	1.05

[a] Modified from Ref. 6.
[b] Indistinguishable from cumulative prednisone dose.
[c] Not an independent risk factor but was significant by the Cox Proportional Hazard Analysis.

The mortality rate from coronary artery disease was 25-fold that of age- and sex-matched controls in Sydney, Australia, tenfold increased in Stockholm, and three- to fourfold increased in Minneapolis [3]. Successful renal transplantation thus does not reduce, and in fact appears to accelerate, the rate of atherosclerosis.

The possible role of prednisone in this accelerated atherosclerosis is suggested by the cumulative higher doses in a study of 36 patients with systemic lupus treated with glucocorticoids; only 1 of 17 patients treated for 6 months developed greater than 50% coronary narrowing, compared with 8 of 19 patients treated for an average of 38 months [8]. In patients with rheumatoid arthritis who received steroids, peripheral arteriosclerosis with medial necrosis and calcification was seen three times as frequently as in controls [9].

Abnormal lipid metabolism after transplantation may be a major factor in the accelerated development of coronary artery disease [10–12]. The adverse effect of LDL cholesterol and the protective role of HDL cholesterol on the development of coronary artery disease are well documented [10]. The change from hypertriglyceridemia as the typical lipid abnormality in chronic dialysis patients to hypercholesterolemia after transplantation, as well as its multifactorial basis, has been well described [11, 12]. Ettinger and colleagues noted that after successful renal transplantation, triglyceride levels decreased approximately 20% in males and 31% in females, LDL cholesterol increased approximately 65% in females and was stable in males, and HDL cholesterol increased approximately 59% in females and 50% in males [12]. The HDL_3 subfraction, however, contributed to 86% of the rise in HDL after transplantation in females and to 94% of the rise in males [12]. It is the persistence of low HDL_2 levels that may perpetuate or aggravate the coronary risk of successful transplant recipients [12]. The fact that males still account for the majority of posttransplant coronary events, even though females share the same lipid abnormalities, indicates that other factors must also contribute to coronary artery disease [12].

Table 2. T-lymphocyte subsets in long-term renal transplant recipients with or without coronary artery disease

	CD2(T11)	CD3(T3)	CD8(T8)	CD8+/CD11b+	CD8+/CD11b−
	E Rosette	Pan T	Cyto/supp	T Supp	T Cyto
Coronary artery disease[b] (n = 5)	856.0 ± 309.9[a]	733.8 ± 373.3	254.0 ± 123.6	54.0 ± 34.3	199.8 ± 102.5
No coronary artery disease (n = 27–29)	1631.6 ± 788.1	1665.7 ± 726.9	577.7 ± 321.6	106.3 ± 114.8	471.2 ± 288.7
P uncorrected[c]	.039	.009	.035	NS	.05

[a] Absolute counts/mm^3.
[b] Mean age, 53.8 years (range, 37–69 years).
[c] Nonpaired t test; *P* uncorrected for number of leukocyte markers tested.

The most flagrant example of a group with end-stage renal disease that is at high risk for silent ischemic heart disease is insulin-dependent diabetics. We studied 100 patients with insulin-dependent diabetes mellitus and end-stage renal disease; 25 patients had greater than 70% coronary occlusive disease, and 29 had moderate to severe left ventricular dysfunction (including 15 with greater than 70% occlusive disease) [13]. Thirteen of the 25 with more than 70% occlusive disease (52%) had a new myocardial infarction at an average time of 21.3 months following coronary angiogram. Although the other 75 patients had less than 70% occlusive disease prior to transplantation, 8 (11%) nevertheless had a new myocardial infarction an average of 35.9 months following angiography.

Erythrocytosis, as exemplified by today's second patient, also can be a factor in vascular occlusions and must be looked for particularly in patients retaining their native kidneys [14, 15]. Whether the risk of thrombosis will be increased in the near future by the general use of erythropoietin needs further study [16].

Because of the significant mortality rate from coronary disease after transplantation both in diabetics and nondiabetics, we extended our use of thallium stress testing and coronary angiography. Among our 150 long-term allograft recipients, 42 had 61 ^{201}thallium stress tests and 28 had coronary angiograms. The 61 thallium stress tests were performed in 42 patients (35 males and 7 females) 3 to 22 years (mean 11.9 ± 4.2 years) after transplantation. Of the 61 tests, 44 were normal, 9 were inadequate because of failure to achieve at least 85% of the maximum predicted heart rate, and 8 were abnormal, including one at a submaximal heart rate. These 8 patients all were males, age 34 to 67 years, the youngest 4 of whom (ages 34, 40, 44, and 51 years) had either 20 to 50 pack-years of cigarette smoking (3), or more than 30 years of insulin-dependent diabetes mellitus (1). Three of these 8 patients had classic, 2 atypical, and 3 no angina. However, in 2 patients, coronary angiography showed only 60% and 40% occlusive disease. From our experience, the greatest value of posttransplant thallium stress testing is in males who had coronary artery disease prior to transplantation, are insulin-dependent diabetics, have classic or even atypical angina, have long smoking histories, have had their transplant and corticosteroid therapy for at least 8 years, have hypertension, or are over 65 years of age. Eighteen patients (14 males and 4 females) had 28 coronary angiograms because of anginal pain in 12, positive thallium stress test in 4, previous myocardial infarction in 2, combinations of these in 6, and for other reasons in 4. Progression from a normal to abnormal coronary angiogram (>70% occlusive disease) occurred over a 6- to 9-year period in 3 patients, 2 nondiabetics (ages 57 and 67), and one 44-year-old diabetic. Of the 18 patients studied, coronary artery bypass surgery was performed in 8 patients and percutaneous transluminal angioplasty in one.

We compared our 19 long-term patients with coronary artery disease (defined by the presence of myocardial infarction, >70% coronary occlusive disease determined by angiography, or positive thallium stress test) with 30 patients without coronary disease (rigidly defined as those with negative coronary angiogram or negative thallium stress tests). The results showed that the "coronary" group was older (47.6 ± 9.2 versus 42.4 ± 10.9 years, $P < 0.05$), had a higher frequency of hypertension (74% versus 30%, $P < 0.004$), higher LDL cholesterol levels (177.2 ± 29.2 versus 151.1 ± 36.1, n = 12 and 27, respectively, $P < 0.05$), and more frequent classic or atypical angina (84% versus 13%, $P < 0.001$). Overall, no significant differences were seen in gender, source of the kidney, prevalence of smoking or diabetes, or level of total cholesterol, HDL cholesterol, or triglycerides. However, among the 7 patients with coronary artery disease who were under 45 years of age (32–44 years), 6 were hypertensive, 5 smokers, and one a diabetic. Knowledge that more rejections and cumulative glucocorticoid dose are risk factors for posttransplant coronary artery disease does not yet provide clinically helpful information; that is, there does not appear to be a specific cut-off point [6]. Our "coronary" patients did not have a more rejection-filled course or higher cumulative glucocorticoid doses, although our data in the latter area are not finalized. The preponderance of more compatible living-related recipients in both the non-coronary (77%; 23 of 30) and coronary group (68%; 13 of 19) might have obscured such differences, however.

Before moving on to a discussion of the problems of cancer after transplantation, I want to point out an intriguing immunologic observation in our patients with coronary artery disease. We do not yet know its full significance. A small group of our long-term allograft recipients with coronary artery disease (5) showed a 50% decrease in levels of all T cells as defined by both the CD2 (T11 or Leu5) and CD3 (T3 or Leu4) pan-T cell markers, as well as in T-suppressor (CD8+/CD11b+) and T-cytotoxic cells (CD8+/CD11b−) when compared with 27 to 29 patients without coronary disease (Table 2). The differences noted cannot be explained by age or gender. Whether the decreased T-cell populations reflect active involvement of those cell types in the arterial lesions or simply represent an epiphenomenon is unclear at present [17]. Recent work has shown, however, that CD3+ T-lymphocytes exceed CD14+ macrophages in early fibrous atherosclerotic plaques and are nearly

Table 3. Malignancies in renal transplant recipients[a]

Neoplasm	Malignancies following Prednisone and azathioprine (%)	Cyclosporine (%)
Total number of patients/ malignancies	2837/3054	366/373
Skin cancer (SCC > BCC)[b]	1217 (40)	74 (20)
Carcinoma of cervix	172 (6)	6 (2)
Carcinoma of vulva	92 (3)	5 (1)
Lymphoma	352 (12)	111 (30)
Kaposi's sarcoma	104 (3)	42 (11)
Carcinoma of kidney	86 (3)	21 (6)
Carcinoma of lung	153 (5)	20 (5)
Carcinoma of colon/rectum	113 (4)	12 (3)
Carcinoma of breast	103 (3)	13 (3)
Carcinoma of head/neck	86 (3)	7 (2)

[a] Modified from Ref. 18.
[b] SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

equal to macrophage numbers in advanced complicated plaques [17]. Induced expression of class-II and/or increased expression of class-I HLA molecules on the vascular endothelium and smooth muscle cells in response to interferon gamma produced by activated T-lymphocytes also may be the basis for T-cell attachment [17].

Malignancy. Increased susceptibility to malignancies remains a serious posttransplant concern. The transplant community is indebted to Dr. Israel Penn for collecting extensive and valuable data on this subject over the last 20 years. The Cincinnati Transplant Tumor Registry reported that a total of 3054 malignancies occurred an average of 64 months following predominantly renal transplantation in 2837 patients treated primarily with standard immunosuppression (prednisone, azathioprine, and in a few cases cyclophosphamide) [18]. In contrast, the 366 patients whose treatment featured cyclosporine developed 373 malignancies at a much shorter average time after transplantation, 25 months. Skin cancer (squamous cell carcinoma and basal cell carcinoma), carcinoma of the cervix, and carcinoma of the vulva, all seen after both standard immunosuppression and cyclosporine, had a much higher frequency after standard immunosuppression [18] (Table 3). In contrast, lymphoma, Kaposi's sarcoma, and carcinoma of the kidney were more common in patients treated with cyclosporine [18]. Further, Kaposi's sarcoma and non-Hodgkin's lymphomas occurred earlier in the cyclosporine-treated patients (after 12 months) than in those treated with standard immunosuppression (after 25 and 44 months, respectively) [18]. In a recent study of 132 kidney or heart allograft recipients receiving triple therapy with cyclosporine, azathioprine, and prednisone, there was a disturbing increase in the frequency of B-cell lymphoma to 5.3% compared with a 0.3% frequency in 698 renal transplant recipients treated with only prednisone and azathioprine [19].

A different report from the same transplant tumor registry demonstrated that the relative risk following renal transplantation was 28- to 49-fold for non-Hodgkin's lymphoma, up to 400- to 500-fold for Kaposi's sarcoma in renal transplant recipients compared with controls of the same ethnic origins (Arabic, Jewish, black, or Mediterranean ancestry), 4- to 21-fold for skin cancer, 8- to 9-fold for melanoma, 14-fold for carcinoma of the cervix, 100-fold for carcinoma of the vulva/anus, and 30-fold for hepatobiliary carcinoma [20]. The non-Hodgkin's lymphomas ranged from polyclonal B-cell hyperplasias to frankly malignant monoclonal B-cell lymphomas from which Epstein-Barr virus has been isolated. Some non-Hodgkin's lymphomas, usually of the polyclonal variety, have regressed following drastic reduction of immunosuppression or the use of acyclovir [18]. Similarly, Kaposi's sarcoma has remitted in 29% of affected patients after sharp reduction in immunosuppression as the only therapy [18].

When considering a patient with a prior treated malignancy for transplantation, a suitable waiting period (that varies for different neoplasms) should be observed [21]. For example, a 2-year waiting period with no recurrence probably would avoid 81% of posttransplant recurrences of renal cell carcinoma [21]. We know that end-stage kidneys in patients remaining on dialysis can develop atypical cysts, solid or cystic renal cell adenomas, and carcinomas [22]. A similiar risk is present in renal transplant recipients as well [18].

Given the staggering increase in relative risk for a variety of cancers, what tests should be done routinely? Pelvic and Pap tests are necessary in female transplant recipients annually, or more frequently if a suspicious lesion is detected. Allograft recipients should be instructed that because sun exposure promotes skin cancer, protective sunscreens are essential for minimizing the risks of malignant tumor development. Careful skin examinations, particularly of exposed areas, and prompt treatment of suspicious lesions also are required. Regular surveillance for colon and rectal cancer and for breast cancer is recommended by the American Cancer Society.

Thirty-two of our 150 long-term patients developed a malignancy (Table 4). Only 63% of the patients were male, but males predominated (90%) among those with skin cancer and lymphoma. One female died with a metastatic hepatoma nearly 23 years after receiving a living-related transplant.

Can immunologic methods be used to identify patients at special risk for malignancies? We tested 8 patients with and 19 without a malignancy for certain lymphocyte subsets by flow cytometry. Of particular interest were subsets of the natural killer (NK) cells, large granular lymphocytes with surface receptors for the Fc portion of IgG that are believed to defend against viruses and malignancies [23–27]. Using two-color immunofluorescence flow cytometry (with Leu7 as a marker for large granular lymphocytes and Leu11 for the Fc gammaR), we evaluated three NK subsets: Leu7+/Leu11+ with variable NK activity, Leu7−/Leu11+ with strong NK activity, and Leu7+/Leu11− with weak NK activity [23, 26–28]. Eight cancer patients without a splenectomy exhibited a decrease in the cell number of the Leu7−/Leu11+ subset (strong NK) and an increase in Leu7+/Leu11− (weak NK) compared with 19 long-term allograft recipients without cancer or splenectomy (Table 5). Previous studies in transplant recipients have described a decrease in the absolute number of NK cells (Leu11+), particularly the most cytotoxic, strong NK group (Leu7−/Leu11+), and a smaller decrease in the variable strength NK group (Leu7+/Leu11+) [26, 28]. The present study suggests that the long-term trend toward a decrease in Leu7−/Leu11+ strong NK cells becomes even more pronounced in patients with certain cancers. Also detected in the

Table 4. Malignancies in 32 long-term renal transplant recipients

Neoplasm	Number of patients (*deaths*)	Gender M:F	Mean age (*range*)	Mean years to onset posttransplant (*range*)
Skin	18 (1)	16:2	45.6 (31–64)	11.1 (3–23)
Basal cell[a] (1 with melanoma)	8	7:1	44.9 (31–64)	14.5 (6–23)
Squamous cell	4 (1 with lymphoma)	4:0	50.8 (45–60)	11.8 (4–17)
Both	6	5:1	43.0 (32–56)	6.2 (3–11)
Lymphoma	4 (4)	4:0	42.8 (38–49)	12.9 (8–17)
Female genital	9 (0)	0:9	33.2 (20–46)	8.8 (4–13)
Cervix	4	0:4	36.3 (28–46)	11.3 (10–13)
Cervix and vulva	5	0:5	30.8 (20–43)	6.8 (4–11)
Other[b]	4 (2)	2:2	(39, 47, 60, 61)	(7, 13, 17, 22)

[a] Another patient had basal cell cancer after returning to dialysis.
[b] Other solitary cancers were adenocarcinoma of the lung and hepatoma in 2 patients; double cancers (prostate and skin, vulva/vagina and colon) occurred in 2 other patients.

Table 5. T-lymphocyte subsets in long-term renal transplant recipients with or without cancer

		Leu 7+/ Leu 11+	Leu 7−/ Leu 11+	Leu 7+/ Leu 11−
		Variable NK	Strong NK	Weak NK
Cancer[a]				
Yes 8	Relative %	4.3 ± 6.1	1.5 ± 1.2	19.9 ± 20.2
No 19		4.2 ± 6.2	2.9 ± 2.2	18.9 ± 13.5
Yes 8	Absolute	54.4 ± 67.7	22.1 ± 13.0	327.1 ± 438.6
No 19	counts/mm^3	53.6 ± 54.7	40.9 ± 24.6	299.4 ± 225.1
			P uncorrected = .053	

[a] Seven with basal or squamous cancer of the skin (1 with melanoma also) and 1 with vulva/cervix cancer; no splenectomy. Nonpaired t test; *P* uncorrected for number of leukocyte markers tested.

cancer group without splenectomy was an increase in the relative frequency of the T-cell suppressor-inducer subset (CD4+/2H4+) from 18.5 ± 8.5% to 32.1 ± 16.1% with a decrease in the relative frequency of the helper-inducer subset (CD4+/4B4+) from 23.3 ± 10.5% to 18.6 ± 8.2%, similar to changes reported in clinically healthy and stable renal transplant recipients [29]. These subsets were not affected by the duration of the transplant, by age greater than or equal to 45 years, or by donor source.

Our most surprising finding was an increase in Leu7−/Leu11+ cell counts/mm^3 in 4 splenectomized patients compared with 19 without splenectomy (74.8 ± 37.1 versus 40.9 ± 24.6, respectively; *P* uncorrected = 0.032). Both the Leu7+ and Leu11+ populations increased. The impressive distortions in the Leu7−/Leu11+ subset in long-term transplant recipients with splenectomy imply that changes in this subset cannot simply be ascribed to the duration of the allograft and to immunosuppression. Although these findings are preliminary, they might offer help in identifying long-term renal transplant patients at greater risk for certain cancers.

Late infections. Patients who have a continuing high risk for "late" posttransplant infections (defined as greater than 10 years) are those with poor renal function, higher levels of immunosuppression, leukopenia, and those who have had their spleen removed [3, 30–32]. The most common infections that occur long after transplantation still are the community acquired pneumonias (including influenza) and urinary tract infections, at times with bacteremia [30]. The syndrome of overwhelming sepsis in splenectomized patients makes it mandatory that these patients receive polyvalent pneumococcal vaccine [31, 32]. The daily use of prophylactic penicillin (or erythromycin in those who are penicillin sensitive) also has been recommended for splenectomized patients [31].

A number of infections seen in chronically rejecting, often heavily immunosuppressed patients, are classic opportunistic ones. These included fungal infections (such as cryptococcosis and pneumocystis), nocardia, viral infections (such as herpes zoster), and bacterial infections (such as Listeria) [30]. In addition to searching for opportunistic infections in febrile transplant patients, one also should consider unusual sites of infection such as the intervertebral disc space, central nervous system, and gastrointestinal tract, particularly the large bowel. Patients receiving long-term immunosuppression should be given prophylaxis against bacterial endocarditis when they undergo dental procedures, surgery of the upper respiratory tract, and surgery or instrumentation of the gastrointestinal and genitourinary tract, according to the recommendations of the American Heart Association [33]. We have followed these same recommendations before orthopedic and peripheral vascular surgery as well. Prevention of late infection follows the same principle as that for prevention of malignancy: avoidance of unnecessarily high doses of immunosuppressive agents.

Our long-term transplant patients developed only three fatal infections. Moreover, all these infections were associated with another life-threatening event—a serious motor vehicle accident, a perforated colon, and pneumonia following aortic valve replacement. The problem of chronic hepatitis B infection deserves separate consideration.

Liver failure and chronic hepatitis B antigenemia. Liver failure in HBsAg$^+$ patients may be related to reactivation of hepatitis B virus replication (as can be provoked by corticosteroids); superinfection possibly with the delta agent, non-A, non-B superinfection; drug hepatotoxicity (particularly azathioprine, but also cyclosporine and others); and alcohol abuse [34]. Liver failure in patients who are HBsAg$^-$ might be related to a number of other viruses (cytomegalovirus, Epstein-Barr, varicella zoster, herpes simplex, adenovirus, and hepatitis A),

drug hepatotoxicity, veno-occlusive disease, alcohol abuse, and peliosis hepatis [34]. The most common concern following renal transplantation centers on the patient with chronic hepatitis B antigenemia. Early studies in 1974 suggested that chronic antigenemia did not correlate with hepatic failure or poor short-term allograft survival and might even be associated with slightly better 1- to 2-year graft survival [35–37]. After longer followup, however, the survival of the $HBsAg^+$ patients began to deteriorate beyond 2 years [38–40]. Liver dysfunction contributed heavily to the mortality in this group, either directly or in association with bacterial sepsis [38–40]. Using persistently elevated SGOT levels as indicators of chronic liver disease, two groups of investigators reported a high frequency of death from liver disease in patients with chronic hepatitis B antigenemia [39, 40]. In one study, however, when patients had chronic elevations of hepatocellular enzymes, virtually the same mortality rate occurred in $HBsAg^+$ (45%) as in $HBsAg^-$ (47%) patients with chronic liver disease because of chronic alcoholism, cytomegalovirus infection, and other unknown causes [40]. The most unfavorable results estimated the risk of death from liver disease in $HBsAg^+$ renal transplant patients to be 4.1% per patient-year [39].

Flagg and colleagues reported a more optimistic outlook for patients with hepatitis B antigenemia [41]. Results at 5 years demonstrated that patients positive for HBsAg (acquired before or after transplantation), when compared with $HBsAg^-$ patients, had no significant difference in patient survival (60% versus 66%, respectively) or allograft survival (31% versus 29%, respectively) [41]. In contrast, Debure and coworkers in France studied 532 renal transplant patients, performing liver biopsies in 230 of them, 131 within the first 2 months after transplantation [34]. Although no difference was found in patient or graft survival at 10 years in $HBsAg^+$ patients (81% and 58%) compared with $HBsAg^-$ patients (85% and 55% respectively), a difference was noted in total number of deaths and in deaths from hepatic failure in $HBsAg^+$ patients (18% and 8%, respectively) when compared with $HBsAg^-$ patients (8% and 0%) [34]. The French investigators thought that standard liver function tests did not reflect the true frequency of serious liver disease, an involvement detectable in many patients only by liver biopsy [34]. Only 40% of the biopsied patients (this included 69% of all the $HBsAg^+$ patients) had an elevated SGPT for more than 6 months, yet 60% had chronic liver disease by liver biopsy. The authors classified chronic liver disease on the biopsy specimen as chronic persistent hepatitis, chronic active hepatitis, and cirrhosis based on the degree and location of fibrosis, hepatocyte necrosis, and mononuclear infiltration, as well as nodular regeneration [34]. Among those patients who had at least two liver biopsies, the pathologic findings worsened in 77% of those who had antibody to HBe, in 60% of those who were $HBsAg^+$ and $HBeAg^+$, but only in 22% of the $HBsAg^+$ patients without HBe markers [34]. An important prospective study of a subset of these patients demonstrated that immunosuppressive therapy increased viral replication (measured by in-situ hybridization of hepatitis B virus DNA in serum and liver biopsy specimens) not only in $HBsAg^+$ (92%), but also in $HBsAg^-$ (20%) patients [42]. Finally, the contribution of chronic liver disease to patient mortality differs from region to region, with Paris, Montreal, and Boston reporting the most serious consequences [34, 39, 40].

Two major questions regarding chronic HBsAg positivity are whether such a person should undergo renal transplantation and, if so, should azathioprine be used, reduced, or discontinued? In certain cases, the best information for patient selection might be gained only from a liver biopsy prior to transplantation [34]. After transplantation, it seems reasonable to avoid or minimize the use of azathioprine early in a patient with liver dysfunction. Prolonged reduction of azathioprine, however, does not appear to slow the progression of liver disease once established, and obviously may adversely affect transplant function [43, 44]. If the liver dysfunction is primarily cholestatic, then azathioprine itself or cyclosporine may be responsible, and dose reduction or cessation of the drug may be essential. In fact, in 8 patients (5 of whom were $HBsAg^+$), Debure and colleagues reported that cholestasis disappeared within a mean interval of 7 months after withdrawal of azathioprine in 6 and oral contraceptives in 2 patients [34]. As I noted, in many centers chronic alcoholism is a significant contributor to chronic liver disease, and every patient should be warned of its added potential danger after transplantation.

In our long-term transplant recipients, 8 had chronic hepatitis B antigenemia; 6 of them acquired the infection one to 11 years posttransplant. All (except one who had hepatitis pretransplant) are receiving azathioprine in doses from 37.5 to 100 mg daily. The SGOT levels in these patients range from 30 to 61 units, and no patient has died from liver disease in this small group. As I mentioned earlier, the single death from liver disease resulted from a metastatic hepatoma nearly 23 years after transplantation in an $HBsAg^-$ patient.

Causes of patient morbidity

In a 1982 study of 217 renal allografts functioning for more than 5 years, Kirkman et al catalogued the major morbidity factors: hypertension (46%), cataracts (24%), avascular necrosis (18%), malignancy (14%), urinary tract infection (17%), pneumonia (9%), steroid-induced diabetes (6%), chronic hepatitis (6%), peptic ulcer disease (4%), diverticulitis (3%), myocardial infarction (4%), and cerebrovascular accident (2%) [45].

Hypertension. Hypertension occurred in 72 of our 150 long-term patients. As a percentage of the specific donor source, hypertension was slightly more common after a cadaver graft (53.7%) than following a living-related transplant (44.8%). The frequency of hypertension in our long-term recipients may have been favorably influenced by the fact that 85% of the recipients had native-kidney nephrectomies and 64% had living-related donors.

One approach to the evaluation of posttransplant hypertension (Fig. 1) uses a stable serum creatinine of less than or equal to 1.4 mg/dl to define one arm of the differential diagnosis, and a rising or impaired serum creatinine of greater than 1.4 mg/dl to define the other. Hypertension after renal transplantation can be due to problems with the allograft itself, such as rejection [46–52], cyclosporine nephrotoxicity [52–55], recurrent and de-novo glomerulonephritis [56–62], and renal artery stenosis [46–48, 52, 63–67]. Hypertension also can result from other factors, including the diseased native kidneys [46–48, 51, 52, 59, 63, 67–70], increased body weight [72, 73], hypercalcemia [71], corticosteroids [51, 52, 71–74], as well as any of the other causes of hypertension in a nontransplanted patient. Frequently, more than one reason for hypertension is present (for

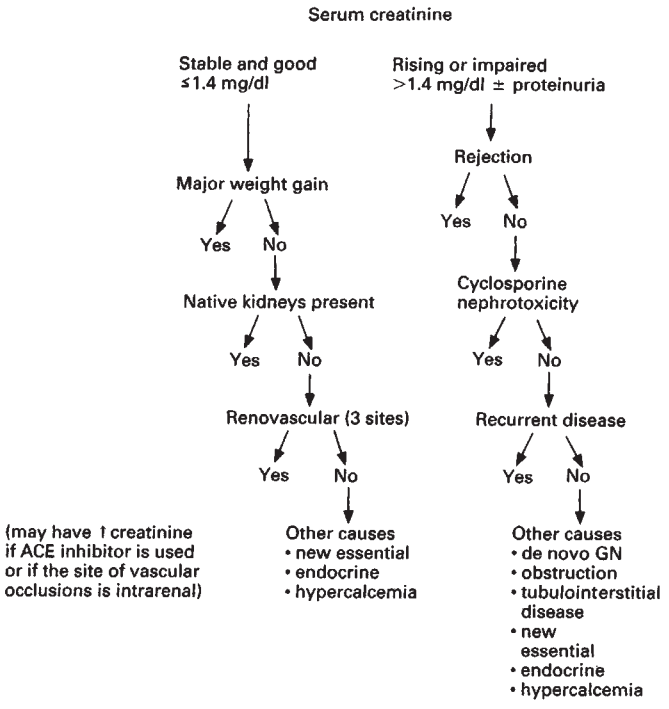

Fig. 1. *Approach to posttransplant hypertension.*

example, rejection and cyclosporine nephrotoxicity, rejection and excess weight, or native kidneys and rejection or renal artery stenosis). Luke recently reviewed the issue of posttransplant hypertension in detail at this Forum [52]. Despite the high incidence of hypertension after transplantation, it is encouraging to know that a successful renal transplant, typically with removal of the native kidneys, can reverse essential hypertension [75]. It is important to know that calcium antagonists, currently the most effective way to treat cyclosporine-associated hypertension, can raise cyclosporine levels and act as immunosuppressives themselves [54, 55, 76, 77].

Because most transplant recipients at present have their own kidneys in place, the contribution of these native kidneys to posttransplant hypertension is of special interest. The use of renal-vein-renin levels to localize the kidney responsible for the hypertension has not been consistently helpful [47, 49, 59, 63, 68, 69]. In an incisive study of 10 hypertensive patients with serum creatinine levels less than or equal to 2.0 mg/dl one year posttransplant, all had bilateral, native kidney nephrectomies regardless of renin localization or arteriographic findings [59]. Nine of the 10 had substantial improvement in their hypertension, even though in 3 renin activity was localized to the allograft and in 4 (in just 2 of whom renin was localized to the allograft) there was substantial stenosis of the renal allograft artery [59]. In stable renal transplant recipients with severe hypertension (who are not receiving cyclosporine), captopril can be used as a predictor of the role of the native kidneys in the hypertension. Captopril decreases blood pressure, increases effective renal plasma flow, and produces no change in plasma creatinine levels in these patients, and typically they have an excellent response to removal of the native kidneys [67]. In contrast, in hypertensive patients with hemodynamically significant renal artery stenosis, captopril decreases effective renal plasma flow and produces a reversible rise in the serum creatinine level [67]. Unfortunately, because cyclosporine-induced renal vasoconstriction does not respond to converting enzyme inhibitors, the captopril test is not useful in most current transplant recipients who are receiving cyclosporine [52, 54, 55].

Renal artery stenosis in transplant patients has a prevalence ranging from 1% to 25%, with best estimates of the overall frequency at 10% [65]. In experienced hands [66], percutaneous transluminal angioplasty can be "a reasonably safe and efficacious first-line therapy" of renal transplant artery stenosis [65]. The occlusive area can also be proximal to the transplant artery, for example, in the iliac vessels. On the other hand, distal, intrarenal vascular occlusions (seen as infarctions by a technetium glucoheptonate scan that can be used if the serum creatinine is less than or equal to 3.0 mg/dl, or by angiography if the serum creatinine is higher) represent a third site of renovascular occlusive lesions associated with hypertension [49]. Because hypertensive patients with intrarenal vascular lesions already have focal infarctions, these patients often have an elevation of the serum creatinine and thus are usually distinguishable from patients with renal artery or iliac artery stenosis.

Avascular necrosis. The prevalence of avascular necrosis (AVN) varies considerably among transplant centers (3% to 41%) but generally is less than 10% [78, 79]. Avascular necrosis initially was thought to be caused by fat microemboli, but a variable correlation with cumulative prednisone dosage was recognized [78, 80]. If standard radiographs do not reveal AVN in patients with symptoms of AVN of the hips, the diagnosis should be pursued with a bone scan or preferably magnetic resonance imaging to detect this lesion early. When the lesion is detected early, the patient should avoid bearing weight on the symptomatic side by using crutches and be reevaluated periodically, initially at about 6 weeks [81]. Surgical decompression procedures, developed because the pathophysiology includes increased intraosseous pressure, may be useful in some cases, but many patients will require hip arthroplasty [78–81]. Thirteen of our long-term transplant recipients have developed overt AVN posttransplant—10 in the hips, 2 in the knees, and one at both sites. An interesting bimodal appearance was evident; 4 cases occurred 7 to 15 years after transplantation and 8 appeared at approximately one year. Nine patients have had one or more surgical procedures. Two other patients requiring surgery had acquired AVN before receiving the allograft. As an aside, this is a convenient and appropriate place to mention the preparation of patients with functioning renal transplants for surgery. It is important that these patients be hydrated appropriately (preferably starting the night before the procedure), have a "steroid prep" begun the evening before as well, and receive brief courses of prophylactic antibiotics according to the site of the procedure and the sensitivities of the recipient. Pre- and postoperative monitoring of renal function and blood pressure must be meticulous. Immunosuppressive agents should be administered as usual, unless the clinical condition demands otherwise. Most important, when possible, one should avoid using all nephrotoxic drugs and nonsteroidal antiinflammatory agents.

Diabetes. Posttransplant diabetes typically has been attrib-

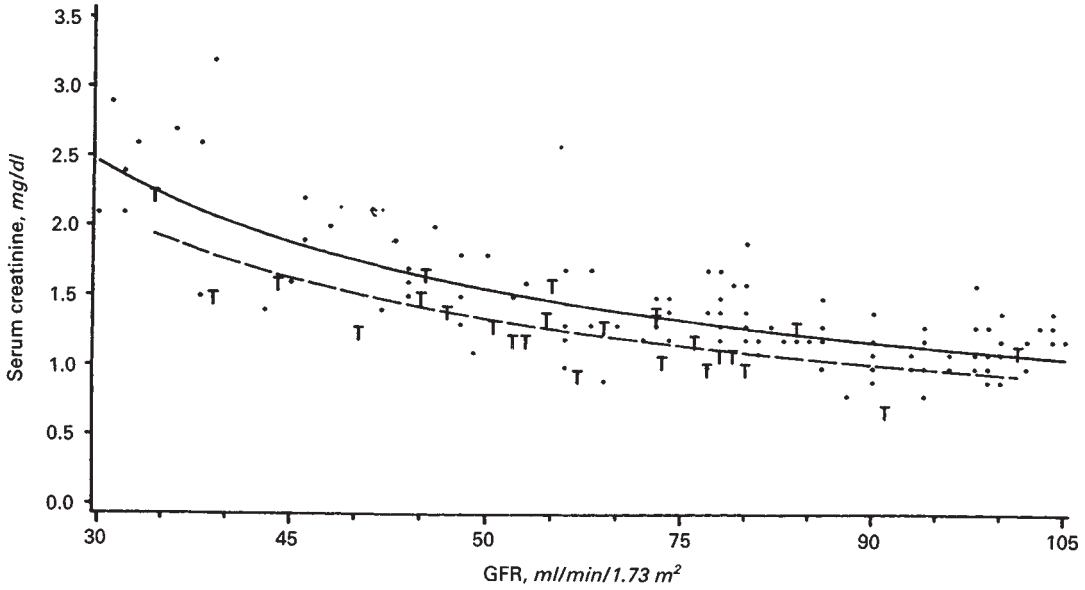

Fig. 2. *The relationship of serum creatinine in the range of 0.7 to 2.4 mg/dl and ^{123}iothalamate glomerular filtration rate in the range of 30–105 ml/min/1.73 m^2 for males age 31–40 years is shown in the upper curve for 112 non-transplant patients and in the lower curve for 25 transplant recipients.* The model used fit a linear regression between ln serum creatinine (mg/dl) and ln glomerular filtration rate (ml/min/1.73 m^2). For transplant patients the equation is: ln creatinine mg/dl = 3.19 − 0.67× ln glomerular filtration rate (ml/min/1.73 m^2), and for non-transplant patients: ln creatinine mg/dl = 3.04 − 0.67× ln glomerular filtration rate (ml/min/1.73 m^2) [90]. Analysis of covariance has shown a significant difference for transplant versus non-transplant patients ($P < 0.001$, student t = 3.81). T = transplant data with fitted line (*dashed*); ● = non-transplant data with fitted line (*solid*).

uted to the use of corticosteroids, although cyclosporine now may be involved as well [82, 83]. This recent observation regarding the role of cyclosporine is of interest in view of the fact that cyclosporine has been used to treat early cases of insulin-dependent diabetes mellitus [84]. The production of diabetes in renal transplant patients likely depends on immunosuppression promoting a viral infection within the pancreas. The prevalence of posttransplant steroid-associated diabetes has ranged from 3.4% to 46.0%, depending on the criteria for diagnosis and the duration of followup [82]. Among our long-term nondiabetic recipients, 14 subsequently developed post-transplant diabetes. The diabetes appeared an average of 10.2 years after transplantation (range, 3 to 19 years) for the 11 non-insulin-dependent patients and 1 to 14 years for the 3 insulin-dependent diabetics. However, the early onset of post-transplant diabetes has been reported in 16% of 758 nondiabetic recipients, 54% of whom became hyperglycemic within just 3 weeks of transplantation [82].

Monitoring

Monitoring of renal function following renal transplantation is essential. Although acute rejection can occur long after transplantation, generally the rejection process years after transplantation is an asymptomatic, insidious event [85, 86]. The multiple nonimmunologic and immunologic factors involved in chronic rejection (and its treatment) are beyond the scope of this discussion and have recently been reviewed elsewhere [86, 87]. There is usually little or no early decrease in urine output, fever, or discomfort near the allograft. Instead, the blood pressure gradually rises, proteinuria increases, anemia gradually worsens, and the serum creatinine steadily rises; all these changes could elude the patient. Because the diagnosis of chronic rejection thus is based on laboratory findings, it is mandatory for all recipients, even those with the best functioning long-term allografts, to have at least a serum creatinine, BUN, urinalysis, complete blood count, and blood pressure measurement no less frequently than every 6 months. Annual physical examinations (with particular emphasis on the skin, cardiovascular, musculoskeletal, and genitourinary systems) and other studies as indicated have an important role in the long-term welfare of the transplant recipient.

In quantitating more precisely the allograft function of our long-term transplant recipients, we obtained 125 ^{123}iothalamate glomerular filtration rate measurements in 65 of these patients and related these data to serum creatinine measurements made at the same time. Because of the dominant effect of sex- and age-derived muscle mass on serum creatinine levels, the iothalamate GFRs (range, 30 to 105 ml/min/1.73 m^2) were plotted against serum creatinine levels (range, 0.7 to 2.4 mg/dl) according to the patient's gender and age by decade [88, 89]. All iothalamate GFRs were corrected to 1.73 m^2 body surface area. When the curves relating iothalamate GFRs from 30 to 105 ml/min/1.73 m^2 and serum creatinine levels from 0.7 to 2.4 mg/dl were plotted for both transplanted and nontransplanted males 31 to 40 years of age (derived from a study of more than 3000 such determinations [89]) the curve plotted from the transplant patients' results was significantly lower than that of nontransplant patients (Fig. 2) [90]. I recognize the difficulty in constructing a separate "transplant curve" based on a limited number of observations and confined to only a portion of the GFR curve. Nevertheless, this observation suggests that a serum creatinine value in the 0.7 to 2.4 mg/dl range in a transplant patient reflects a lower GFR than in a nontransplant patient. Possible explanations for this finding include increased

renal tubular secretion of creatinine because the transplanted kidney usually operates *from the beginning* in the 40–80 ml/min/1.73 m^2 GFR range, precisely the range where the tubular secretion of creatinine is greatest (34% ± 4%) and can most effectively delay the predicted rise of the serum creatinine [91]. Combining decreased creatinine generation from chronic glucocorticoid therapy (thereby keeping serum creatinine low) [92] and the frequent use of older kidneys (thereby imposing lower GFRs) could also produce the same effect [88, 93, 94]. When the data were replotted using kidney age based on the donor's rather than on the recipient's age (but still using the gender of the recipient), the number of data points decreased, and virtually all of them still fell below the standard curve for values of that decade of age.

Although the significance of these trends is not entirely certain, we should be especially cautious in accepting "normal" serum creatinine levels as the equivalent of "excellent" renal function in the transplant patient.

Causes of renal allograft dysfunction and failure

Kirkman and colleagues reported that the causes of chronic dysfunction or failure in 217 renal allografts functioning more than 5 years were: chronic rejection in 74%, recurrent glomerulonephritis in 9%, ureteral obstruction in 6%, renal artery stenosis in 5%, renal infection including pyelonephritis and abscess in 3%, and acute rejection in 2% [45]. A decade ago, noncompliance with immunosuppressive medications was unusual [95]. In contrast, a recent study has exposed the fact that beyond 3 months after transplantation, noncompliance has been involved in as many as 15% of allograft rejections or failures [96].

Recurrent disease. Several types of glomerulonephritis (especially type-II membranoproliferative glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis, and hemolytic-uremic syndrome) and metabolic diseases (notably type-I diabetes, oxalosis, cystinosis, and amyloidosis) have significant, though varying, recurrence rates in the transplanted kidney and may thereby contribute to late graft dysfunction [56, 57, 61, 62]. Moreover, the hemolytic-uremic syndrome, IgA nephropathy, focal segmental glomerulosclerosis, nephritis associated with anti-glomerular basement membrane antibody, membranous glomerulonephritis, oxalosis, and cystinosis also can severely affect graft function early after transplantation [56, 57, 60–62, 97]. Whether the second patient presented today had recurrent or de-novo membranous glomerulonephritis is difficult to say because of the advanced glomerular sclerosis present when his native kidney was biopsied. If he had recurrent disease, and his HLA antigens Al and B8 via linkage disequilibrium with DR3 suggest that possibility [98], then he joins 19 other reported cases of recurrent membranous glomerulonephritis [57, 61, 62].

Cyclosporine. The effects of cyclosporine on renal structure and function are now well documented. The afferent arteriolar vasoconstrictive effect, the early arteriolopathy, the chronic arteriolar lesions that mimic nephrosclerosis, as well as the interstitial and tubular changes, continue to raise serious concerns about cyclosporine's effect on long-term renal function [53–55, 99–101]. The capacity for cyclosporine to cause, even in *low* doses (4.6 ± 0.4 mg/kg/24 hr), an obliterative arteriolopathy with downstream glomerular sclerosis [102], to produce a *macro*angiopathy involving major branches of the main renal artery (that cleared with cessation of cyclosporine) [103], and to create serious risks of de-novo and recurrent hemolytic-uremic syndrome [104] clearly makes some of cyclosporine's toxicities difficult to distinguish clinically from vascular forms of rejection often attibuted to recipient presensitization.

Urinary tract infections. Recurrent urinary tract infections (UTIs) in transplant recipients should be treated promptly because of the possibility of septicemia. Late formation of renal or ureteral calculi also can occur. Because obstruction, even without infection or calculus, is not uncommon years following transplantation, it should be ruled out in all patients with worsening function as well as in those with recurrent UTIs. Such obstructions have been seen at both the ureteropelvic and ureterovesical junctions. A renal transplant ultrasound or orthoiodohippurate renal scan with furosemide stimulation usually identifies the obstruction. An intraveneous pyelogram with laminograms may localize the point of obstruction. If that is unsuccessful, or if the serum creatinine is greater than 3 mg/dl, then a percutaneous antegrade pyelogram may be necessary, at which time a percutaneous nephrostomy tube can be placed [105].

Very late onset proteinuria. A bit of uncertainty recently has surfaced in 3 of our recipients with allografts functioning 20 to 25 years. Within the last few years, significant proteinuria (1 patient with 840 mg and 2 patients with 1.3 g/24 hours) has appeared in all 3 patients, with slight increases in the serum creatinine no greater than 0.2 mg/dl. The possibility exists that the increases in proteinuria and serum creatinine represent the combined effects of an aged, solitary kidney with focal segmental glomerulosclerosis caused by glomerular hypertension [106].

HLA histocompatibility. Because of the substantial risks that immunosuppression carries, a practical means of reducing the need for immunosuppression is highly desirable. Six studies, representing more than 400 cadaver allograft recipients, have shown one-year allograft survival between 84% and 94% in recipients of better-matched kidneys and a variable number of blood tranfusions but without the use of cyclosporine [107–112] (Table 6). Perhaps the only disadvantage of histocompatibility matching arises in living-related allografts transplanted into recipients with IgA nephropathy, hemolytic-uremic syndrome, and possibly diabetes in whom there remains the possibility of later development of the same disease in both the donor and recipient [113–117].

Questions and answers

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): I am intrigued by your comments on coronary artery disease. It sounds as if you were trying to make coronary artery disease into an immunologic disease! At least your comments about alterations in T-cells subsets in a small group of patients with coronary artery disease suggest this. Could you tell us how you came to that conclusion, your rationale, and what your hypothesis is?

DR. BRAUN: First of all, we did not start out looking for an association with coronary artery disease. We looked at 34 of our long-term transplant recipients who were willing to come in for immunologic monitoring using phenotyping of lymphocyte subsets. When we divided the patients into clinical subgroups, we looked not only at those who had cancer but also at those

Table 6. One-year cadaver renal allograft results without cyclosporine

Center	Year	One-year allograft survival (%)	n	HLA match	Transfusions
Oxford [107][a]	1984	87	46	DR 0 mismatch	Yes
U. Iowa [108]	1984	91	22	>2 A, B match; 1 DR mismatch	Yes
		87	38	>2 A, B match; 1 DR match	
U. Kentucky [109]	1985	84	43	DR 0 mismatch	Yes
Belfast [110]	1985	94	17	A, B, DR 0 mismatches	Yes
		89	46	DR 0-1 mismatch	Yes
UCLA [111]	1985	89	73	A, B, DR 0 mismatches	>4
		84	183	B, DR 0 mismatches	>4
London [112]	1986	84	128	B, DR 0-1 mismatches	*

[a] Reference number in brackets.
* Data not provided.

who had well-documented coronary artery disease without any other major interfering factor. The 5 individuals with severe coronary artery disease—and this was not seen in any of the other clinical association analyses—had across-the-board reductions of 50% to 60% of all their major T-cell subsets (CD2+, CD3+, and CD8+), with the exception of the T-helper cell population (CD4+). Considerable interest and debate, especially in the past several years, has focused on whether macrophages or lymphocytes are the primary cell involved in atherosclerotic plaques. Hansson's group has shown that, even in the early fibrous lesions, the predominant cell is the CD3+ T-lymphocyte [17]. Those cells would be able to recognize certain molecules on the cell surface of either the vascular endothelium or the smooth muscle cells. Those molecules existing there either constitutively or in inducible forms are class-II and class-I HLA molecules. The major stimulus to their being expressed is the interferons. Interferon gamma will increase the expression of both class-I and class-II HLA antigens, and alpha and beta interferon will cause primarily class-I molecules to become more expressed [118]. Either or both of those would account for a focusing of these lymphocyte populations on the vascular endothelium and smooth muscle cells. Hansson demonstrated that 25% of the smooth muscle cells in human atherosclerotic lesions were aberrantly expressing class-II HLA-DR molecules, and 93% of DR-positive cells were smooth muscle cells [17].

DR. JEROME P. KASSIRER (*Associate Physician-in-Chief, New England Medical Center, Boston, Massachusetts*): Just because something is statistically correlated doesn't necessarily mean that it is causally related. Alvin Feinstein in a landmark article in *Science* made the point that when one looks at a large data base of information, one is bound to find statistical correlations [119]. Is it possible that some of your conclusions are based on correlations that may or may not be significant?

DR. BRAUN: I pointed out that these are all *uncorrected P* values for the lymphocyte subset analyses. The point that Dr. Kassirer is making is a valid one. We became acutely aware of this potential statistical problem in the early 1970s, when we started looking for disease associations with HLA antigens [98]. When one has a highly polymorphic system like HLA antigens and is searching through many different antigens for a possible disease association, it is obvious that after evaluating 20 antigens, the chance finding of one association is a 0.05 possibility that could be miscontrued as "statistically significant" unless identified as "uncorrected." That is why I presented these data with *uncorrected P* values. These are, therefore, somewhat tenuous data at present. However, in a second analysis, when one looks at a specific antigen or lymphocyte subset, there is no longer any need to apply that correction factor. What I am offering is a lead rather than a complete answer.

DR. HARRINGTON: You showed that patients receiving azathioprine had an increased incidence of certain types of cancers, whereas patients receiving cyclosporine had an increased incidence of different, and perhaps worse, tumors. If you simply look at the effect of azathioprine versus cyclosporine on the production of cancer, which group fares better?

DR. BRAUN: The outlook for immunosuppressants is inherently one of increased risks. By their very nature they disrupt our usual defense mechanisms for handling viruses and for responding to the chronic antigenic challenge of the allograft. If you look at the time of onset of malignancy, it is shorter in cyclosporine-treated patients [18]. If you overlap certain immunosuppressants like antilymphocyte globulin with cyclosporine in reasonably high doses, there can be a remarkable occurrence of lymphomas. For example, in cardiac transplant recipients at Stanford, as I recall, there was a 7% frequency of lymphoma in patients surviving longer than 3 months, and a 13% frequency in those whose treatment included antilymphocyte globulin for rejection when they were already receiving high-dose cyclosporine, often about 18 mg/kg/day [120]. Moreover, in Roy Calne's study published in 1979, 3 lymphomas developed within one year of renal transplantation among 32 recipients receiving 17–25 mg/kg/day of cyclosporine [121].

DR. MICHAEL MADAIO (*Division of Nephrology, New England Medical Center*): Could you comment on the role of both in-situ hybridization for hepatitis-B virus and/or liver biopsy prior to transplantation in patients with elevations in liver enzymes?

DR. BRAUN: I think Debure's studies pointed out very clearly that a significant level of chronic liver disease determinable by liver biopsy still existed in a certain proportion of hepatitis-surface-antigen-negative patients with or without elevated liver enzymes [34, 42]. Either persistent HBe antigen or HBe antibody marks those patients most likely to have viral replication, detectable by *in-situ* hybridization tests, a condition probably increased by immunosuppressants, notably corticosteroids.

DR. KASSIRER: Are there reliable data comparing patients matched for age, gender, race, and extent of disease between those who undergo transplantation and those who continue on dialysis with outcomes measured in terms of life expectancy or

quality-adjusted life expectancy? I am struck by the large number of possible complications in both groups. If you had to make a personal choice between maintenance dialysis and transplantation, and if you considered all factors, including quality of life and survival with each modality, what would you choose and what data would you use to make that choice?

DR. BRAUN: Roger Evans at the Battelle Institute performed some very nice studies looking at these points. Clearly, renal transplantation generally offers more in the way of a normal lifestyle and full rehabilitation [122]. In that study, 79% of transplant patients functioned at nearly normal levels compared with 48% to 59% of those treated with various forms of dialysis. Almost 75% of transplant patients were able to work, compared with 25% to 59% of the dialysis patients [122]. A second study using the Cox proportional hazards model evaluated survival of 1038 patients treated with dialysis or transplantation [123]. In that study, only transplantation from a living-related donor had a significantly longer patient survival, and cadaveric transplantation and dialysis had similar inferior outcomes [123]. That study and the Krakauer study [124] were done on patients before cyclosporine or erythropoietin were available. The current data you are asking for are being collected by federal agencies or under government contract and should provide a source of ongoing camparisons.

DR. ANDREW LEVEY (*Division of Nephrology, New England Medical Center*): Although there are not yet adequate data to compare recent outcomes of dialysis and transplantation, there are data on patients treated in the 1970s and early 1980s. Three large retrospective studies comparing the outcomes of dialysis and transplantation using proportional hazards analysis show longer survival in patients undergoing living-related transplantation compared with either cadaver transplantation or dialysis [123, 125, 126]. Survivals with cadaver transplantation and dialysis were equivalent. All three studies included transplants performed with prednisone or azathioprine immunosuppression. One study shows that the major factor influencing the probability of survival is whether the graft functions. One might speculate whether the much-improved graft survival in recipients of cadaver kidneys who are treated with cyclosporine might provide a superior survival over dialysis.

DR. DAVID CAHAN (*Nephrologist, Faulkner Hospital, Boston*): Given that both azathioprine and cyclosporine are mutagenic, but with different modes of action, does it make any sense to treat the renal transplant patient with azathioprine one year and cyclosporine the next? I have a second, unrelated question. Could you compare the incidence of coronary artery disease in long-term dialysis patients with the incidence in long-term transplant patients?

DR. BRAUN: To answer the second question first, I don't know that the incidence of coronary artery disease has been compared in those 2 groups of long-term patients (5–10 years). The other question: alternating therapies are unlikely to be useful because cyclosporine works best with an induction period. Stopping and starting it may eliminate its desired effect. Also, if you look at corticosteroids with their immunosuppressant effects in terms of inhibiting IL-1 production, reducing class-II expression on the cell surface, decreasing IL-2 receptors if given in high doses, and causing lymphocytes and monocytes to redistribute to the reticuloendothelial system, then look at cyclosporine inhibiting IL-2 production, and look at azathioprine as a purine antagonist inhibiting DNA synthesis, it is clear that they all are operating at different levels of the immune response sequence. I think one would get more of an effect with low doses of agents covering several areas rather than shifting high doses of a single agent focused on just one area. But most important is realizing that *all* these immunosuppressants increase the frequency of malignancy, and it is just an additional exaggeration of some malignancies that suggests a distinction between prednisone/azathioprine therapy and cyclosporine [18].

DR. LEVEY: The data you showed suggest that the incidence of coronary artery disease in patients after kidney transplantation is greater than that in patients without renal failure and also greater than that in patients with renal failure treated by dialysis. Sutherland et al have suggested that the incidence of peripheral vascular disease leading to amputation is much higher in diabetics who received kidney transplants than in diabetics without renal failure and in diabetics treated with dialysis [127].

DR. BRAUN: An essential piece of information necessary for identifying new or higher frequency of coronary artery disease is documenting that none existed beforehand. Even in the Kasiske study [6], neither thallium stress testing nor coronary arteriography was used in evaluating the initial absence of significant coronary disease. In fact, the whole determination of disease was based on myocardial infarction, angina, and electrocardiographic changes rather than on either thallium studies or angiography.

DR. PAUL KURTIN (*Chief, Division of Pediatric Nephrology, New England Medical Center*): You remarked that the rate of progression of coronary artery disease in insulin-dependent diabetics with less than 70% occlusion seems to be accelerated. What would be the natural history of a control population of diabetics who have less than 70% occlusion over the same time course?

You also showed a high rate of development of Kaposi's sarcoma. Because of the relationship of Kaposi's sarcoma to HIV positivity and the risk for HIV positivity in dialysis patients, was HIV tested for? Finally, in those patients with recurrent hemolytic-uremic syndrome (HUS), was the disease the familial form or the sporadic type?

DR. BRAUN: Let's start with the HUS question. There is a report of HUS in adult sisters with possible asynchronous presentation of the disease [115]. The transplanted kidney was lost with recurrent HUS, and within 2 weeks of transplantation, the donor developed HUS and required dialysis [115]. Both sisters had been using oral contraceptives at the onset of their disease [115]. The most recent review of recurrent disease in transplants did not distinguish familial from sporadic HUS [62]. That review did emphasize that cyclosporine may increase the risk of recurrent HUS, as shown by the Minnesota experience, and because cyclosporine can produce HUS by itself [62, 104].

With regard to the question of Kaposi's sarcoma and HIV testing, the patients in the present study all received transplants long before HIV testing was available. Now, of course, all recipients are being tested.

In answer to your other question, we do have information on diabetics without coronary artery disease who did not receive transplants and who remained on dialysis, as well as some who did receive renal transplants [13]. Diabetic patients without

cardiac disease who received renal transplants had an 81% 2-year survival compared with 15% for those not receiving transplants [13].

DR. HARRINGTON: Data from several groups demonstrated excellent results—85% to 95%—with cadaveric transplants without the use of cyclosporine. Should histocompatibility testing be used in place of cyclosporine? Second, how can we achieve a just and equitable country-wide sharing of organs?

DR. BRAUN: With regard to the use of HLA matching and cyclosporine, I would not necessarily use HLA matching to the exclusion of cyclosporine. I am striving to get the maximum effect from achievable levels in both: decent matching that achieves better short- and long-term allograft survival and minimizes sensitization should that graft fail, and at the same time matching that permits the use of lower doses of cyclosporine so that its complications are reduced. I would look at HLA matching and cyclosporine as a team effort rather than as an either/or proposition.

In regard to the issue of equitable organ distribution on a nationwide basis, one should recognize that when cyclosporine came into general use, there was a precipitous drop in kidney sharing across the United States. Although that made individual transplant programs quite happy, it did not serve well the community's or individual patients' best interests. Sensitized patients require access to different-sized donor pools: a small donor pool if they have low sensitization or very common HLA antigens, and increasingly larger donor pools if they are more highly sensitized or have rarer HLA antigens [128]. You can look at this model as concentric circles requiring different intensities of either matching or exposure to increasingly larger donor populations. I think that the point system of Terasaki that was just approved by the United Network for Organ Sharing after public commentary suggests that people are in fact recognizing the long-term strength of matching that becomes very apparent after 4 to 10 or more years after transplantation. Then the survival curves diverge quite clearly depending on whether there was a decent level of matching or no matching at all.

DR. HARRINGTON: What are your thoughts on using living-unrelated individuals, with appropriate HLA typing?

DR. BRAUN: That is extremely difficult to answer. I haven't formulated a fixed idea on that because the data are relatively few. However, with a donor-specific protocol, the results from the University of Wisconsin have been remarkably good: 3-year actuarial patient and graft survivals were 94% and 89%, respectively [129]. I can see certain situations in which the use of living-unrelated, HLA-matched donors might be worthwhile, but I must say from personal experience that some of the proposed living-unrelated transplant pairs I have seen have been quite unusual!

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): You said that the serum creatinine level fails to reflect the degree of renal insufficiency. Of course, that could reflect either increased renal excretion or decreased production of creatinine. Have you or Dr. Hall looked at creatinine clearances in these subjects?

DR. BRAUN: Unfortunately, in the vast majority of these cases, we stopped looking at creatinine clearances when we started evaluating the iothalamate glomerular filtration rates.

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