MEDICAL GRAND ROUNDS

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KIDNEY TRANSPLANTATION

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KIDNEY TRANSPLANTATION

1. THE SURVIVAL DATA

The experience of all groups performing kidney transplants has been compiled by the Registry in Human Kidney Transplantation directed by Murray and associates sponsored by the National Academy of Sciences and National Research Council (1,2,3,4).

The compiled data reflects the accelerated growth of this field: prior to 3/15/62 there were 68 known non-twin kidney homotransplants (2); 54 new non-twin homografts were performed between 3/16/62 and 3/15/63 (2); from 3/16/63 to 3/15/64 the number of new homografted patients recorded was 231 (4); during the year ending on 3/15/65 the new patients with non-twin kidney homografts were 273 (4). Ninety per cent of all recorded kidney homotransplants have been performed in the last three years. The most recent tabulation is based on the experience with over 700 transplants in 672 patients (4). Statistical analysis of this data by actuarial methods has been used to estimate survival (5,6).

*Table I. Survival Data of Kidney Transplantation**

Type of Donor	*Total Cases*	*Fraction Surviving*					
		6 mos.	*1 yr.*	*2 yr.*	*3 yr.*	*5 yr.*	*7 yr.*
Identical Twin	36	.89	.89	.85	.85	.85	.68
Living Relative	300	.60	.53	.42	.42	.37	.37
Unrelated Living Donor	95	.17	.14	.09			
Cadaver	241	.27	.21	.14			

*Based on data in ref. 5.

Further analysis revealed there was no significant difference between groups receiving transplants from unrelated living or cadaver donors. However, transplants from related living donors appeared to be far superior. The difference at 12 months being highly significant ($P<0.0001$).

Table II. Local Experience with Kidney Grafts

Patient	Age-Race-Sex	Donor	Kidney Graft Date	Kidney Graft Place	Survival in Days	BUN	Cause of Death
[redacted].	10 WF	Identical twin sister	[redacted]/64	Dallas	> 444	16	-
[redacted]	15 WF	Mother	[redacted]/63	Denver	>1218	7	-
[redacted].	28 WM	Cadaver	[redacted]/65	Dallas	16	-	No function; infected perinephic hematoma
[redacted].	40 WF	(1) Cadaver	[redacted]/65	Dallas	-	-	No function.
		(2) Cadaver	[redacted]/65	Dallas	108	11*	GI bleeding; bronchopneumonia
[redacted]	22 WF	Cadaver	[redacted]/65	Dallas	208	66*	Hypertension, subarachnoid hemorrhage

*BUN during final admission

[redacted] had a first non-functioning transplant removed and a second kidney grafted which functioned very adequately for 108 days. The patient died from GI bleeding and necrotizing bronchopneumonia. She was receiving Imuran and Prednisolone. Her demise was probably a consequence of the toxic effects of these medications. In spite of apparent good renal function there was histologic evidence of progressing rejection.

[redacted] was followed for over six months. She was azotemic and hypertensive throughout most of her course. Post-transplant period was complicated by marked reduction in creatinine clearance, increased sodium retention and multiple infections. The final episode was was due to massive intracranial hemorrhage. Blood pressure was 240/140. Spinal fluid grossly bloody. Permission for autopsy was not obtained.

[redacted] who received a kidney graft from her twin sister more than a year ago is doing well. Since the girls are genetically identical, rejection does not occur.

[redacted]. (Case [redacted] 17, University of Colorado School of Medicine). This 15 year-old girl received a homotransplant from her mother for treatment of terminal renal disease due to chronic pyelonephritis. Two and a half years have passed since the original operation in Denver. There was an initial rejection crisis at about 40 days after transplantation which was controlled with Prednisone. Since then the course has been uneventful. Patient remains on Imuran 125 mgm and Prednisone 2.5 mg.

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2. EXPERIMENTAL TRANSPLANTATION: IN DOGS AND HUMANS

A great part of the information about the behavior of kidney homotransplants comes from the work performed in dogs. A kidney has never been homotransplanted into a healthy non-uremic human.

Homografts in dogs usually cease to function between 4 to 8 days after grafting (7,8,9).

Renal homografts performed for acute renal failure in humans have tended to last longer. A good example is that of a 16 year-old boy who had his only kidney removed because of hemorrhage due to trauma. Michon and associates (10) performed a graft of a kidney from his mother. The homografted kidney functioned until the 22nd day when it suddenly ceased.

Similar and perhaps even better is the experience in humans with chronic uremia. Hume et al (11) reported 9 cases the best of which survived 37, 47, 99 and 176 days.

Mannick et al (12) studied the effect of azotemia on the rejection of renal homografts in dogs:

	No. dogs	*Survival after transplant*
Azotemic	4	15-21 days
Normal	4	7 days

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3. IMMUNOLOGY OF TRANSPLANTATION

a. Rejection as an immune response

Medawar (13) established that rejection of a homograft has most of the features of a classical immune response: latent period, specificity, the "second-set phenomenon" (memory), participation of lymphoid tissue and of humoral antibodies.

b. The terminology of tissue transplantation (14)

Old Terminology	*New Terminology*	*New Adjective*	*Definition*
Autograft	Autograft	Autologous	Graft in which donor is also recipient
Isograft	Isograft	Isogeneic	Graft between individuals identical in histocompatibility antigens
Homograft	Allograft	Allogeneic	Graft between genetically dissimilar members of same species
Heterograft	Xenograft	Xenogeneic	Graft between species

c. Cellular immunity

The predominant role of sensitized cells in the rejection of skin homografts is manifest by (reviewed in 14):

--a mononuclear infiltrate early in the rejecting graft;

--characteristic histologic changes in the local lymph nodes;

--inhibition of rejection by ablation of the local lymph nodes;

--transfer of second-set rejection by injection of sensitized cells;

--inability to transfer second-set rejection with serum;

--protection from rejection by cell-impermeable but serum-protein permeable Millipore filters (Algire chambers).

These characteristics have led many to believe tha allograft rejection is related to delayed hypersensitivity.

Testing of this hypothesis led to the discovery of the *Direct and Transfer Reactions of Brent, Brown, and Medawar (15).*

These reactions constitute the background for the *Normal Lymphocyte Transfer Test* which will be discussed in relation to Histocompatibility Typing.

d. Circulating antibodies

During allograft rejection antibodies are produced. These can be detected by a variety of methods such as hemagglutination (16,17) or cytotoxicity tests (18). In most instances, it has been impossible to demonstrate that circulating antibodies participate in the rejection of solid tumors or skin grafts (19). Humoral antibodies do play a role in the rejection of several kinds of normal or tumoral cells derived from myeloid or lymphoid tissues and in a special form of skin graft rejection: the "white graft" (20,21). In the latter antibodies appear to injure the graft vessels in such a way that the grafted skin never recovers from ischemia. As will be seen, vascular injury plays a significant role in many kidney homografts and gamma globulin that can be eluted with acid buffer and that binds complement *in vitro* has been, in fact, demonstrated by immunofluorescence in the vessels of grafted dog kidneys (22).

Serum C^{1hu}_{2} complement levels appeared to fall in relation to episodes of attempted rejection in 4 patients (23).

Under special circumstances serum antibodies have been shown to delay the rejection of allograft (or enhance the growth to tumors (24)).

e. Special features of the kidney graft

Excision of the local lymph nodes prolongs skin grafts but has no effect on kidney homografts (25). The grafted kidney is connected to the circulation, and antigens released are offered into the blood. The skin graft, however, makes contact with the local lymphatics and requires about 3 days to establish adequate perfusion through vascular channels.

Uremia was shown to produce a marked and multifacetic alteration of the immune response. This encompassed inhibition of the ability to produce antibodies against typhoid antigens, to manifest delayed hypersensitivity and impairment of skin and kidney homograft rejection (26,27,28). Peripheral effector mechanisms were preserved. Absolute lymphopenia in a high proportion of uremics and abnormal histology of the thymus in 11 cases studied was reported (27).

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4. MECHANISMS OF KIDNEY HOMOGRAFT REJECTION

The two major recognized mechanism of kidney graft rejection lead to ischemic damage through attack on the kidney vessels.

a. "graft rejection cells"

The early manifestation of rejection is an infiltrate comprised of mononuclear cells. The most striking is a large pyroninophilic cell with dark cytoplasm full of ribosomes but without the abundant rough endoplasmic reticulum characteristic of a plasma cell. Such cells have been described in the regional lymph node during rejection and infiltrating skin allografts (29). They have been called "graft rejections cells."

b. disruption of peritubular capillaries

Electron microscopic studies have shown that such cells marginate and attach to the endothelial cells in peritubular capillaries. This is followed by disruption of the capillary walls, spilling of inflammatory cells into the interstitium and necrosis of the tubules (30, 31).

c. late vascular changes

In transplants prolonged by the use of immunosuppressive agents, arterial and arteriolar lesions become prominent (32). These consist of fibrinoid necrosis and progressive fibrous intimal thickening leading to vascular occlusion.

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5. *MEANS OF MODIFYING THE REJECTION PHENOMENON*

a. Immunosuppression with drugs

The single most important factor responsible for the advancement of kidney homografting was the discovery of the immunosuppressive effect of antimetabolite drugs (33) and the demonstration that 6-mercaptopurine prolonged survival of homografts of skin (34,35) and kidney (36,37). Azathioprine (Imuran) was found equally effective and somewhat easier to handle (38). Other drugs were useful in conjunction with azathioprine. These were actinomycin C, azaserine, corticosteroids (39,40,41,42) and others (43). The mechanism by which these drugs exert their effect is not known; cited are: inhibition of antigen uptake, inhibition of mitosis, inhibition of synthesis of DNA, RNA, or protein, alteration of nucleic acid bases and cell destruction (44).

6-mercaptopurine was shown to inhibit antibody production in man (45) and in dogs receiving renal homografts (46). It was thought to produce a partial specific immune tolerance in recipients of renal homotransplants (47). In other experiments it was found to be a direct inhibitor of the inflammatory response in rabbits (48).

Imuran was shown to inhibit the destructive reaction of sensitized lymphoid cells against target cells *in vitro* (49).

b. Removal of lymphoid tissue

Removal of the thymus did not seem to influence the end result of renal homografts in dogs treated with drugs (50).

Lymphocyte depletion by thoracic duct drainage has been shown to prolong the survival of first set homografts in rats (51,52) and in humans (53).

Evidence for a possible benefit from splenectomy in human renal transplantation is inconclusive (54).

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6. HISTOCOMPATIBILITY AND OTHER FACTORS

Both the experimental and clinical experience demonstrates that histocompatibility is the most important factor in determining the survival of grafts. When histoincompatibility is strong grafts are rejected in spite of most modifying procedures. Successful long-term survival of grafts is obtained in animals when histoincompatibility is weak. Similarly, in humans, living relatives have been found to be superior donors (discussed above).

a. Histocompatibility testing for donor selection

The relevant transplantation antigens of humans remain unknown. The observance of cross reactions suggests that unrelated human subjects may share tissue transplantation antigens (55). These experiments also illustrate the complexities of the problem. Many different techniques have been proposed for histocompatibility testing. At a recent conference and workshop (56) on this subject, 10 different test methods were discussed. None of them was satisfactory.

--Leukoagglutinins and lymphotoxins

This procedure, as several others, is based on the assumption that relevant tissue transplantation antigens are represented on the surface of circulating WBC.

A complex body of data is developing from these studies (57,58). An attempt was made to correlate the results of lymphocyte typing with the clinical and pathological course of long-term kidney homograft survivors (59). The results are not convincing.

--*The normal lymphocyte transfer test* suggested by Brent and Medawar (60) on the basis of their previous experiments in guinea pigs. Evaluation of this test in humans has been rather disappointing (61), it was impaired by uremia (62), poorly reproducible (63) or at most of limited value (64).

--*Third party skin grafting* is based on active immunization of an indifferent recipient, involving multiple skin grafting (65,66).

--*In vitro stimulation of lymphocytes.* Bain and Lowenstein (67, 68) noted that mixtures of peripheral blood leukocytes from non-related subjects were stimulated to produce large basophilic cells and mitosis. Similar *in vitro* stimulation of lymphocytes by homologous cells were observed by others in humans (69) and in experimental animals (70,71). This reaction has been proposed as a possible test for donor selection (72,73). Chapman and Dutton (70) point out that the response to homologous cells resembles the secondary response of cell suspensions from rabbits previously immunized with an antigen. Rapaport and Chase (74,75,76) have recently presented evidence that group A streptococci and staphylococci can induce in the guinea pig a state of altered reactivity to skin homografts similar to that resulting from sensitization with homologous disease.

b. Blood group antigens

Many kidney transplants with donor-recipient ABO blood groups differences have been performed. The permissible missmatches appear to be the same as for blood transfusions (77) (0 universal donor, AB universal recipient). In one series, 5 non-acceptable missmatches were recorded (78); 3 of them failed acutely. ABO antigens are known to be present in renal parenchymal and vascular cells (79,80,81). Rh antigens appear to be manifest only on red cells (82).

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7. CLINICAL MANAGEMENT

a. "Transplantation disease"

The status of renal transplantation in clinical medicine is reflected in recent reports by the groups that have the largest series of such patients (83,84,85,86). The current attitude is one of guarded optimism.

"Transplantation disease" is a multifacetic iatrogenic disorder which involves not only the kidney undergoing rejection but rather has a wide spectrum of clinical manifestation including the early and late rejection crises, the results of drug toxicity: aplasia and sepsis, connective-tissue-like manifestations, thromboembolic and hemorrhagic phenomena, growth of inadvertently transplanted neoplasms, and occasionally, the development in the grafted kidney of the primary disease affecting the host.

b. "the rejection crisis"

Eighty to ninety per cent of patients develop an early rejection crisis after a variable period of good renal function despite continuous immunosuppressive treatment. This new illness develops from 18 hours to 42 days post-op (average 13 days) (86). It is characterized by malaise, anorexia, fever, renal failure, tenderness over the area of the transplant, sometimes severe hypotension.

Diagnosis of attempted rejection may be difficult. Several laboratory tests have been proposed for this purpose:

--presence of lymphocytes in the urine (87, 88).

--increase in urinary and serum LDH and urinary acid phosphatase (88,89).

--increase in urinary lysozyme was claimed to be related to tubular damage and to precede azotemia (90).

--fall in serum-trypsin inhibitor (91).

--measurement of renal blood flow (92).

--objective evidence of change in renal size, by x-ray visualization of silver clips (93).

Late rejection (85,86) 2-4 months after transplant or later. Insidious failure, swollen and tender homograft, edema and hypertension. Vascular changes in the graft and fibrosis.

c. connective-tissue-like manifestation

Waller and associates (94) observed the appearance of positive rheumatoid factor tests in 14/21 recipients of kidney homografts.

[redacted] developed arthralgias, an olecranon bursitis and 1 frank synovitis resembling rheumatoid arthritis. [redacted] had lesions resembling erythema nodosum and [redacted] developed symptoms indicative of peripheral neuropathy.

Similar complications have been observed recently in a few patients at other institutions.

d. development in the graft of the primary renal disease of the host

The development of glomerular lesions in grafted kidneys is not frequent but its occasional occurrence has led to several lines of interpretation. For one series of 17 identical twins, glomerulonephritis was said to have developed in 3 (95). In another series, nephritis allegedly ensued in 5/25 identical twin transplants (96). These cases were interpreted to represent instances of transmission of the primary disease of the host to the transplant. However, similar lesions have been observed in a few homotransplants in dogs (97). Recently, Hamburger (98) reported two cases developing the clinical and histological picture of glomerulonephritis in kidneys homografted into hosts whose original disease was not glomerulonephritis. This was associated with proteinuria, hematuria, increase in blood pressure and decrease in renal function. In addition, hypergammaglobulinemia and splenomegaly were also present.

The development of membranous glomerulonephritis in human renal homografts has also been reported by other observers (99, 100). Focal deposits of finely granular hyaline material on the glomerular capillary basement membranes were found in 4/8 biopsies obtained two years after homografting in the Denver series (101). These were thought to resemble the appearance of glomeruli in both human nephritis and experimental nephritis produced by the deposition of antigen-antibody complexes.

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