Immunologic Enhancement of Rat Renal Allografts

I. Comparative Morphology of Acutely Rejecting and Passively Enhanced Grafts

A. K. Abbas, MBBS, J. M. Corson, MD, C. B. Carpenter, MD, E. G. Galvanek, MD, J. P. Merrill, MD and G. J. Dammin, MD

The acute unmodified rejection of (Lewis × Brown Norway) F_1 to Lewis renal allografts is characterized by an early and progressive lymphoid cell infiltrate, glomerular necrosis, necrotizing arteritis and ischemic cortical necrosis leading to graft destruction. A single low dose of enhancing antiserum given at the time of transplantation prolongs graft survival by abrogating the necrotizing lesions in glomeruli and arteries and the subsequent cortical necrosis. Passive enhancement in this model is interpreted as representing predominantly a block in the humoral antibody-mediated rejection response. It is suggested that the block is effected mainly, peripherally, *ie*, at the level of the transplanted kidney itself (Am J Pathol 75:255–270, 1974).

THE PROLONGED SURVIVAL OF TUMORS or normal tissue grafts induced by specific alloantibody directed against their antigenic determinants is termed "immunologic enhancement". Enhancement of renal allografts in inbred strains of rats has been achieved by treatment of recipients with a combination of donor antigen and anti-donor alloantiserum,[1] or antigen alone [2] or alloantiserum alone.[3] Since these early reports, much work has been done on the mechanism of enhancement, and the topic has been reviewed recently by Feldman.[4,5] However, there is little information on the morphologic alterations which occur either in enhanced or in unmodified acutely rejecting renal allografts in the rat, and considerable dispute exists regarding the pathogenesis of the lesions reported. Guttmann, Lindquist, *et al* [6] found acute rejection of unmodified (Lewis × Brown Norway) F_1 to Lewis kidney transplants to be characterized by an intense early mononuclear cell infiltration (commencing at 2 days) and late occurring arterial necrosis (2 to 3 weeks postgrafting). In related studies, Lindquist *et al* found no clear evidence of parenchymal destruction mediated by these cells,[7]

From the Departments of Pathology and Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Mass.

Supported by Grants HL-01771, HL-05274 and AM-15579 from the US Public Health Service.

Accepted for publication December 17, 1973.

Address reprint requests to Dr. A. K. Abbas, Department of Pathology, Peter Bent Brigham Hospital, 721 Huntington Ave, Boston, MA 02115.

and the mild glomerular lesion which they observed was attributed to immune complex deposition.[8,9] On the other hand, Feldman and Lee,[10] studying Brown Norway and DA to Lewis allografts, who raised the possibility of infiltrating cells damaging renal tubules, found no significant glomerular or arterial lesions and no role of immune complexes in the rejection reaction. Various workers have described alterations in enhanced renal allografts as representing "diminished rejection,"[2] diminished cellular infiltration [11] or a pattern essentially similar to acute unmodified rejection, with a delay in the time sequence of events.[12]

The present study was designed to compare the morphology of unmodified acutely rejecting and passively enhanced kidney allografts. Inbred rat strains were used as kidney donors and recipients because of technical convenience, and because enhancement can be induced consistently in this model. A single low dose of enhancing antiserum was used to achieve passive enhancement, to examine the changes in the simplest possible system. Sequential changes in acutely rejecting grafts were compared with the early changes in enhanced grafts by histologic and by immunohistochemical methods.[13] A report on the lesions in long surviving transplants will be published later. The same series of recipients were also examined for *in vitro* lymphocytotoxicity by a ^{51}Cr release assay, as well as for levels of cytotoxic antibody in their sera. These studies are described in detail elsewhere.[14]

Materials and Methods

All rats used in this study were adult males weighing 250 to 350 g (Microbiological Associates, Inc, Walkersville, Md). Renal transplants were performed across a major histocompatibility barrier from (Lewis × Brown Norway) F_1 hybrid (AgB1, 3) to bilaterally nephrectomized Lewis (AgB1) rats by a standard microvascular surgical technic.[15] Enhancing serum was raised in Lewis rats by a single skin graft from brown Norway (BN) to Lewis rats, followed by seven intraperitoneal injections at 2-week intervals of 10^7 to 10^8 pooled BN lymph node, spleen, thymus and bone marrow cells. Rats were bled 2 weeks after the final injection, and the serum pooled and stored at −70 C. The same pool of serum was used to enhance animals through the entire study. This serum had a cytotoxicity titer of 1:850 (50% lysis of BN cells) in the presence of rabbit complement.[14,16] A group of untreated (control) renal allograft recipients all died of acute rejection within 9 to 11 days (15 of 15 animals). Another group of recipients were given 0.5 ml of the enhancing antiserum (*ie*, hyperimmune Lewis anti-BN serum) intravenously into the dorsal vein of the penis immediately before or after completion of skin sutures following transplantation. They showed consistently prolonged survival up to more than 4 months unless sacrificed earlier (these will be referred to as "enhanced" or "passively enhanced"). Renal function was monitored by sequential blood urea nitrogen (BUN) measurements (Table 1), further details of which are described elsewhere.[14,16] Renal isografts were also performed from Lewis to Lewis rats, and these received no treatment. Isograft recipients, as well as untreated (control) and treated (enhanced) allograft recipients, were sacrificed at defined inter-

vals, kidneys were hemisected and half of each fixed in 10% formalin for light microscopic study. Tissues were embedded in paraffin, sectioned at 4 μ and stained routinely with hematoxylin and eosin and periodic acid–Schiff (PAS), and in selected cases with: Verhoeff–van Gieson elastic tissue stain, Mallory's trichrome and the Fraser-Lendrum stain for fibrin. Tissue was also quick frozen for immunohistologic studies, which are the basis for the companion report.[13]

Kidneys from the following groups of animals have been studied by light microscopy: a) Isografts—one each at daily intervals from days 1 through 7 posttransplantation (total of 7); b) Control (untreated) allografts—minimum of 3 and maximum of 8 each, at daily intervals from days 1 through 9 posttransplantation (total of 49); and c) Enhanced (treated) allografts—3 animals in each group (and 4 in 2), sacrificed at days 1, 3, 4, 5, 6, 7, 9, 12, 14 and 21 posttransplantation (total of 32). Technical failures, or animals found to have hydronephrosis at the time of sacrifice, were excluded from the study.

Table 1—BUN (mg % ± SD) in Lewis Rats Receiving (Lewis × Brown Norway) F_1 Renal Allografts

	Days after transplantation							
	1	3	5	7	9	11	13	21
Controls	29 ± 18	36 ± 31	61 ± 24	221 ± 95	327 ± 157	—	—	—
Enhanced	25 ± 2	86 ± 48	20 ± 10	49 ± 43	98 ± 127	99 ± 57	126 ± 47	97 ± 42

At least two microscopic sections of each hemisected kidney were examined and the following morphologic features were selected for detailed study: a) interstitial mononuclear cell infiltration into the graft, and the invasion of these cells into tubular epithelium; b) glomerular cell necrosis; c) inflammatory and necrotizing lesions in arteries, and d) coagulative necrosis of cortical tubules, which was probably a consequence of vascular compromise. Each of these histologic parameters was then scored independently by two observers (JMC and AKA) without knowledge of the day posttransplantation or the treatment given. Scoring was quantified as follows.

Mononuclear Cell Infiltration. 1+, Small perivascular aggregates of mononuclear cells; 2+, cells spreading focally into intertubular and periglomerular areas; 3+, diffuse infiltration, but underlying renal architecture distinctly visualized; and 4+, widespread severe infiltration with blurring of the parenchymal architecture.

Glomerular Cell Necrosis. 1+, 1 to 25% of glomerular mass involved (glomerular mass being assessed on the basis of number of glomeruli as well as proportion of each glomerulus involved by the necrotizing lesion); 2+, 26 to 50% of glomerular mass involved; 3+, 51 to 75% of glomerular mass involved; and 4+, more than 75% of glomerular mass involved.

Necrosis of Arteries. 1+, 1 to 15% of arteries show necrotizing lesions; 2+, 16 to 30% of arteries show lesions; and 3+, greater than 30% of arteries show lesions.

Cortical Tubular Necrosis. 1+, 1 to 15% of cortex necrotic; 2+, 16 to 30% of cortex necrotic; 3+, 31 to 50% of cortex necrotic; and 4+, more than 50% of cortex necrotic. The histologic scores of each parameter in control and treated allografts were summed, and the arithmetic means plotted against days posttransplantation. The scores recorded by the two observers were compared by correlation coefficients, and showed a highly significant correlation ($P < 0.01$ in all groups of paired scores except one, in which P was < 0.05).

Results

Isografts

At 1 day postgrafting, occasional arcuate and interlobular arteries contained small PAS-positive deposits in the media. These were not associated with necrosis or inflammation, and were not present at any other time. All the other isografted kidneys appeared morphologically normal.

Allografts

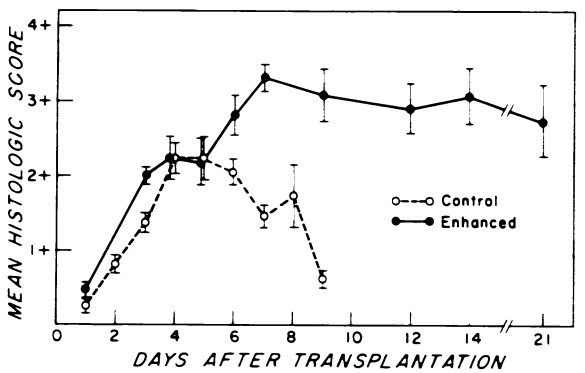
Mononuclear Cell Infiltration

In *control grafts,* aggregates of cells were seen around small veins and arteries in the cortex at day 1. These cells initially consisted of a mixed population of small and large lymphocytes, but by day 2 there were increasing numbers of the large lymphoid cell with large nuclei and nucleoli, and abundant amphophilic or basophilic cytoplasm. The infiltrate rapidly increased in amount and spread into peritubular and periglomerular areas, reaching its peak at day 5. Lymphocytes could be identified infiltrating through the basement membranes and into the epithelium of renal tubules. After day 5 the infiltrate receded, and by day 9 it was composed largely of a few small lymphocytes aggregated around cortical vessels. (At this time, all animals were severely uremic.)

In *passively enhanced grafts* (*ie,* from recipients who had received 0.5 ml of enhancing serum intravenously at the time of transplantation), a comparable sparse mononuclear infiltrate was present in perivenous areas at day 1 (Figure 1). This increased progressively and spread, peaking at day 6 or 7 (Figure 2). At this time, the infiltrate was greater than the peak in untreated control allografts; the cell population was more variable, with numerous small as well as large lymphoid cells; and lymphocytes were seen actively infiltrating renal tubules (Figure 3). In both control and enhanced allografts, the infiltrate was localized predominantly in the cortex and tended to obscure peritubular capillaries. Small numbers of plasma cells, often in aggregates, were seen after day 6. In contrast to the control grafts, the cellular infiltrate in enhanced kidneys persisted, with minimal diminution through day 21 posttransplantation and a gradual increase in the proportion of small lymphocytes. (Enhanced animals showed varying degrees of nitrogen retention, but none were severely uremic.)

A comparison of the mononuclear cell infiltration in control and enhanced animals (Text-figure 1) showed no significant differences in

the early stages (through day 4). In enhanced animals the peak was delayed by 2 days, but the degree of infiltration was greater and persisted longer. The extent to which these mononuclear cells were invading renal tubules could not be readily quantified, but no significant differences were apparent between untreated and enhanced grafts in the early stage, and invasiveness appeared to parallel the number of infiltrating cells.



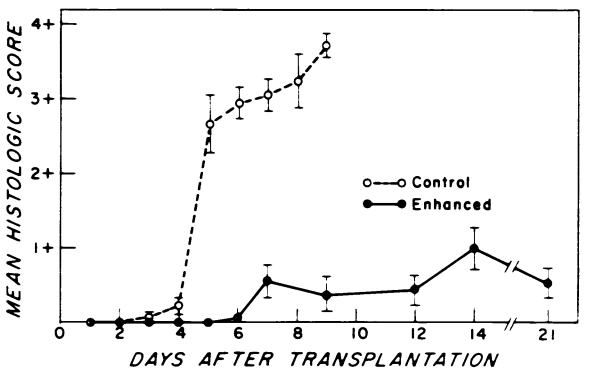
TEXT-FIG 1—Comparison of interstitial mononuclear cell infiltration in control (untreated) and enhanced (treated) allografts. Vertical lines represent standard errors of the means.

Glomerular Lesions

Glomeruli in *control animals* were congested but otherwise unremarkable until day 4. At this time, a lesion appeared in portions of some glomeruli which became widespread and severe at day 5. Most of the glomeruli were hypocellular (Figure 4), and the capillary lumens were filled with an amorphous eosinophilic PAS-positive material (Figure 5). Endothelial cells were extensively lysed, and occasional pyknotic and fragmented cell nuclei were present (Figure 5). Neutrophilic infiltration was trivial and focal. Electron microscopy revealed that the amorphous material consisted mainly of large numbers of granulated and degranulated platelets and small amounts of fibrin.[17] The glomerular cell necrosis and associated deposition of eosinophilic material (probably representing platelet-fibrin thrombi) progressively involved more of the glomerular mass, and by day 9 virtually all glomeruli showed almost complete endothelial cell lysis.

Passively enhanced allografts, in contrast, showed only small foci of necrosis in glomeruli starting at day 6 or 7, and this persisted through day 21 without significant increase. At day 6 some glomeruli were mildly hypercellular, as a result of intrinsic cell proliferation and/or the presence of lymphocytes in the tufts. This slight hypercellularity was noted through day 21, but widespread endothelial cell lysis was never seen (Figure 6).

A comparison of the glomerular cell necrosis in the untreated and treated groups (Text-figure 2) revealed a highly significant abrogation of this lesion in the enhanced allografts. The amount of eosinophilic material deposited in the capillaries paralleled cell necrosis in both groups.



TEXT-FIG 2—Comparison of glomerular cell necrosis in control and enhanced allografts. Vertical lines represent standard errors of the means.

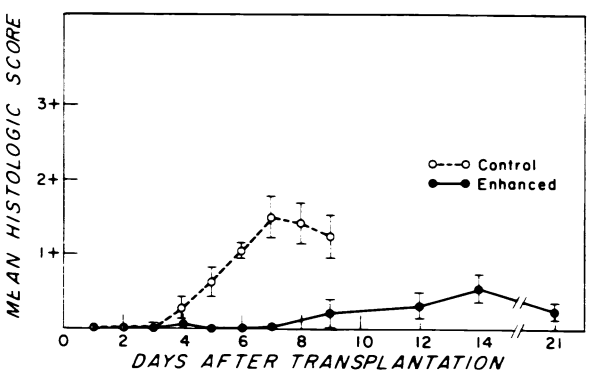
Vascular Lesions

Beginning on day 2, *control allografts* showed hypertrophy and hyperplasia of endothelial cells in arteries and arterioles. Circulating lymphoid cells were adherent to and occasionally lying under the endothelium, and by day 5 small areas of endothelium had been lysed, leaving denuded arterial intima. Starting at day 3 and progressing rapidly, necrotizing lesions appeared in the media of medium-sized arteries. Vessels involved were typically of the order of arcuate and interlobular arteries, and necrosis was most prominent at sites of arterial branching. Lesions were characterized by disruption of the internal and external elastic laminae, pyknosis, fragmentation and lytic necrosis of smooth muscle nuclei, mild or absent neutrophilic infiltration and minimal deposition of fibrin (Figure 7). Increasing numbers of vessels showed this type of necrotizing arteritis, and in some grafts at day 9 the lesions were widespread, but no occlusive thrombosis was observed. From days 5 through 7 posttransplantation, occasional large cortical veins contained "polypoid" nonocclusive venous thrombi attached to their walls, composed of large numbers of aggregated large lymphoid cells and little fibrin. The degree of mononuclear infiltrate so obscured the peritubular capillaries that it was impossible to evaluate injury at this level of the vascular system.

Enhanced allografts showed a comparable degree of endothelial cell hyperplasia in arteries at day 2 and later. However, significant endo-

thelial cell lysis was not observed at any stage. Necrotizing arteritis was seen in rare arteries from day 9 onwards. It was qualitatively similar to the arterial medial lesions in control allografts, but never attained a comparable intensity. Polypoid venous thrombi were extremely rare and appeared later (at days 7 and 9), and peritubular capillaries could not be accurately evaluated because of the intense interstitial cellular infiltrate.

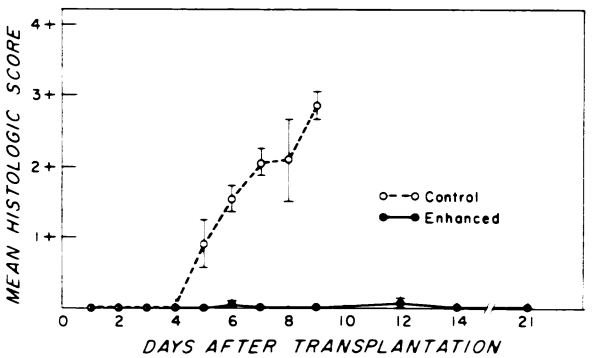
A comparison of necrotizing arteritis in the two groups of allografts (Text-figure 3) showed a marked reduction and delayed appearance of this lesion in the enhanced animals. There was no significant difference in the reactive proliferation of arterial endothelium.



TEXT-FIG 3—Comparison of necrotizing arteritis in control and enhanced allografts. Vertical lines represent standard errors of the means.

Cortical Tubular Necrosis

At day 5, control allografts showed a patchy coagulative necrosis of outer cortical (subcapsular) tubules, which was preceded and accompanied by extensive lipid-negative basal vacuoles in tubular epithelial cells. The necrosis was characterized by fragmentation and loss of cell nuclei, increased eosinophilia and often granularity of the cytoplasm, indistinct cell borders and a sparse focal neutrophil accumulation in the interstitium (Figure 8). This necrosis became progressively confluent, and by day 9 a large portion of the renal cortex was destroyed. The initial subcapsular distribution and the appearance of this coagulative tubular necrosis indicate that the underlying cause was cortical ischemia. In *enhanced allografts*, cortical necrosis of this type was not seen at any stage, and a comparison of the lesion in the two groups of allografts (Text-figure 4) showed a highly significant difference. Thus, treatment with enhancing serum appeared to abrogate ischemic cortical tubular necrosis completely.



TEXT-FIG 4—Comparison of coagulative necrosis of cortical tubules in control and enhanced allografts. Vertical lines represent standard errors of the means.

Discussion

Unmodified acute rejection of (Lewis × Brown Norway) F_1 hybrid to Lewis kidney allografts is characterized by an early mononuclear cell infiltration, as noted by other investigators.[6,10] This infiltrate rapidly increases, peaks about 5 days posttransplantation and subsequently recedes. Glomerular cell necrosis and the associated platelet fibrin thrombi appear suddenly at about day 5 and increase rapidly. Necrotizing arteritis is apparent at day 4, and involves progressively increasing numbers of arteries. Cortical tubular necrosis appears at day 5, presumably as a result of arterial compromise related to the necrotizing arteritis. Although no arterial occlusion was observed, allograft arteritis is known to lead to ischemia, possibly due to local release of vasoactive amines and vasoconstriction.[18] Progressive cortical necrosis leads to eventual destruction of the graft. Single low dose treatment with enhancing serum modifies this sequence of events in a consistent and characteristic manner. There is a significant abrogation of glomerular necrosis, necrotizing arteritis and subsequent coagulative necrosis of cortical tubules. Cellular infiltration of the graft is not diminished, but maximal infiltration appears to be delayed by 2 days. These same animals show a similar 2-day delay in the attainment of peak lymphocytotoxicity of splenic lymphocytes as studied by the *in vitro* ^{51}Cr release assay.[16]

The rejection of solid organ grafts has been considered to be a predominantly cell-mediated phenomenon,[19] and the morphologic hallmark of cellular rejection is the infiltration of lymphoid cells (presumably cytotoxic) into the graft. Passive enhancement in our model does not abrogate the cellular rejection. However, peak lymphocytotoxicity as well as peak cell infiltration are delayed in the enhanced recipients. The significance of these observations is unclear without direct evidence about the functional populations in the infiltrate and the immune reactivity

of the cells. Hence, the mechanism and significance of alterations in cellular rejection induced by enhancing antiserum remain to be elucidated.

The role of circulating antibody in mediating allograft rejection has been appreciated only quite recently.[20] Considerable evidence has accumulated that cytotoxic antibody causes lesions of hyperacute and acute rejection in man,[18,21,22] dog,[20] rabbit [23] and other species. The lesions are essentially those of arteritis, glomerulitis and cortical necrosis in all the species studied. It has proved difficult to induce humoral antibody-mediated rejection in the rat kidney allograft system. However, rejection has been induced in rat renal allografts by the additional administration of large volumes of heterospecific complement,[24] resulting in glomerular and cortical necrosis with vascular thrombosis. Perfusion of donor Fischer rat kidneys by allogeneic Wistar anti-Fischer serum followed by isografting into Fischer recipients has also been shown to lead to hyperacute rejection characterized by cortical necrosis and fibrin deposition in glomeruli.[25] Perfusion of *in situ* kidneys with cell-free allogeneic antiserum leads to cell infiltration with fibrinoid necrosis and endothelial hyperplasia in arteries.[26] It appears, therefore, that humoral antibody participates as a mediating agent in the rejection of rat kidney allografts. More importantly, as in other species this humoral rejection is characterized by inflammatory and/or necrotizing lesions in glomeruli and arteries, which may be accompanied by cortical necrosis. Hence, it can be reasonably concluded that the necrosis of glomeruli, arteries and cortical tubules seen in the unmodified (Lewis × Brown Norway) F_1 to Lewis kidney grafts are the peripheral manifestations of humoral antibody mediated rejection. Two further observations from the current study support this view, namely, a) the deposition of IgG and β1C globulin in the arteries of untreated allografts,[13] and b) the absence of infiltrating mononuclear cells in arterial media prior to the appearance of necrosis.

Passively enhanced allografts differ from untreated controls most significantly in the relative absence of glomerular, arterial and cortical necrosis in the former. It appears, therefore, that single low-dose treatment with enhancing antiserum effectively abrogates the humoral rejection response, the peripheral effect being manifested predominantly in arteries and glomeruli. This abrogation is highly significant and probably crucial to graft survival. It is not, however, absolute, since mild glomerular and arterial lesions are seen in enhanced allografts also, and some functional impairment persists.[14] Abrogation of humoral rejection may be the result of either a central block in antibody production or a peripheral block in the deposition of antibody and the toxic

immunologic reaction that follows. Although measurement of circulating cytotoxic antibody by *in vitro* methods does not necessarily reflect the level of antibody that is cytotoxic *in vivo,* it has been shown in several allograft systems that titers of circulating antibody as assayed by *in vitro* lymphocytotoxicity correlate well with graft survival, and especially in man and dogs, high titers are associated with acute and/or hyperacute rejection (reviewed by Busch *et al*).[17] The passively enhanced animals in our study were found to have titers of cytotoxic antibody that were quite comparable to controls; in fact, antibody was detected earlier in the treated group. Thus, in control recipients, mean titers of lymphocytotoxic antibody (assayed in the presence of rabbit complement) were 0 on day 5 and 1:65 on day 6, while in enhanced recipients mean titers were 1:35 on day 5 and 1:25 on day 6. The subsequent course was similar in both groups.[14] It appears, therefore, that enhancing factor(s) do not have an antiimmunogenic effect so as to prevent the formation of antibody. It is, of course, possible that these factor(s) induce a qualitative change in the nature of antibodies formed in the enhanced recipient which is not reflected in the *in vitro* assay. On the other hand, enhancing antibody may act at the level of the transplanted kidney itself and prevent the circulating cytotoxic antibody from mediating its injurious effects. This would be consistent with the demonstration that enhanced kidney grafts show reduced uptake of additionally administered IgG, suggesting that enhancing antibody localizes in the kidney itself.[27] If true, then there must be an important qualitative difference between the early antibody made upon exposure to the graft and the "enhancing" antibodies made by hyperimmunization. Although both are highly lymphocytotoxic by *in vitro* assays, *in vivo* the former damages the graft while the latter protects against injury. Such a difference may relate to classes of immunoglobulin or subclasses of IgG, but there is as yet no direct evidence for such an hypothesis. In any event, abrogation of humoral rejection processes is a critical mechanism whereby enhancing antibodies induce prolonged graft survival, despite evidence of continuing cell-mediated rejection.

References

1. Stuart FP, Saitoh T, Fitch FW: Rejection of renal allografts: specific immunologic suppression. Science 160:1463–1465, 1968
2. Kim JP, Shaipanich T, Sells RA, Maggs P, Lukl P, Wilson RE: Active enhancement of rat renal allografts with soluble splenic antigen. Transplantation 13:322–329, 1972
3. French ME, Batchelor JR: Immunologic enhancement of rat kidney grafts. Lancet 2:1103–1106, 1969

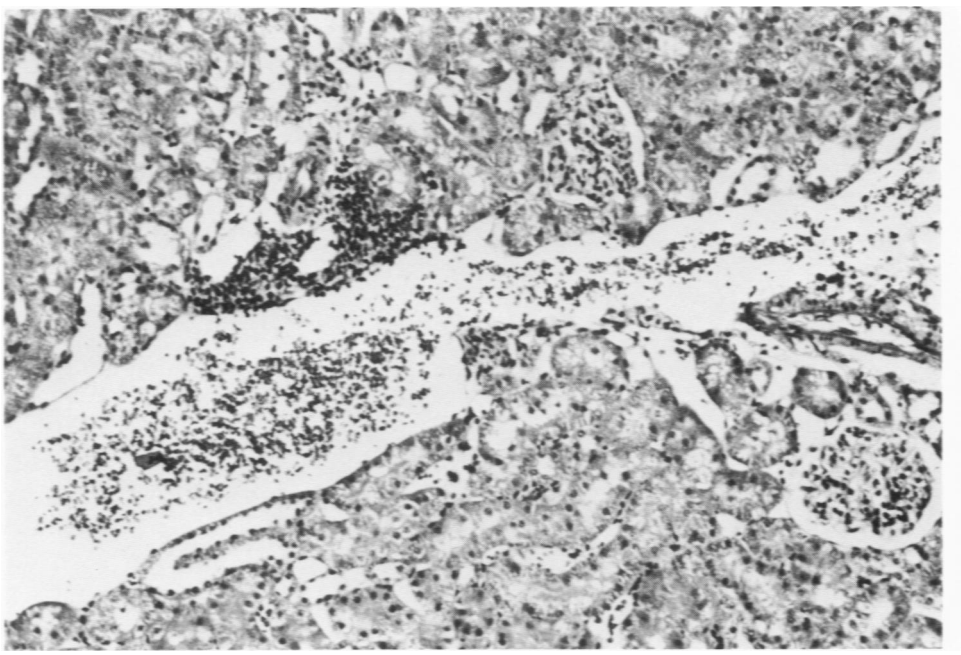
4. Feldman JD: Immunologic enhancement: a study of blocking antibodies. Adv Immunol 15:167–214, 1972
5. Feldman JD: Immunologic enhancement of normal tissue grafts. Pathol Ann 7:19–44, 1972
6. Guttmann RD, Lindquist RR, Parker RM, et al: Renal transplantation in the inbred rat. I. Morphologic, immunologic and functional alterations during acute rejection. Transplantation 5:688:681, 1967
7. Lindquist RR, Guttmann RD, Merrill JP: Renal transplantation in the inbred rat. VI. Electron microscopic study of the mononuclear cells accumulating in rejecting renal allografts. Transplantation 12:1–10, 1971
8. Lindquist RR, Guttmann RD, Merrill JP: Renal transplantation in the inbred rat. II. An immunohistochemical study of acute allograft rejection. Am J Pathol 52:531–545, 1968
9. Lindquist RR, Guttmann RD, Merrill JP: Renal transplantation in the inbred rat. VII. Ultrastructure of the glomerulus during acute renal allograft rejection. Transplantation 11:1–9, 1971
10. Feldman JD, Lee S: Renal homotransplantation in rats. I. Allogeneic recipients. J Exp Med 126:783–794, 1967
11. Lucas ZJ, Markley J, Travis M: Immunologic enhancement of renal allografts in the rat. I. Dissociation of graft survival and antibody response. Fed Proc 29:2041–2047, 1970
12. Ockner SA, Guttmann RD, Lindquist RR: Renal transplantation in the inbred rat. XIII. Modification of rejection by active immunization with bone marrow cells. Transplantation 9:30–38, 1970
13. Abbas AK, Corson JM, Carpenter CB, et al: Immunologic enhancement of rat kidney allografts. II. Immunohistologic study of acute rejection and passive enhancement. Am J Pathol 74:271–284, 1974
14. Garovoy MR, Strom TB, Carpenter CB, Merrill JP: Cellular and humoral immunity during allograft rejection and enhancement. (Unpublished data)
15. Fisher B, Lee S: Microvascular surgical techniques in research, with special reference to renal transplantation in the rat. Surgery 58:904–914, 1965
16. Garovoy MR, Strom TB, Carpenter CB, Merrill JP: Cellular and humoral immunity during allograft rejection and enhancement. Fed Proc 32:225, 1973 (Abstr)
17. Galvanek EG: Unpublished observations
18. Busch GJ, Reynolds ES, Galvanek EG, Braun WE, Dammin GJ: Human renal allografts: the role of vascular injury in early graft failure. Medicine (Balto) 50:29–83, 1971
19. Billingham R, Silvers W: The Immunobiology of Tissue Transplantation. Englewood Cliffs, NJ, Prentice Hall, 1971, pp 102–121
20. Winn HJ: Humoral antibody in allograft reactions. Transplant Proc 2:83–91, 1970
21. Corson JM: The pathologist and the kidney transplant. Pathol Ann 7:251–292, 1972
22. Dammin GJ: Renal transplants: correlation of histologic pattern with function, The Kidney, International Academy of Pathology Monograph No 6. Baltimore, Williams & Wilkins Co, 1966
23. McDowall RAW, Batchelor JR, French ME: Hyperacute rejection and enhancement of rabbit-kidney allografts. Lancet 2:797–801, 1973

24. French ME: The early effects of alloantibody and complement on rat kidney allografts. Transplantation 13:447–451, 1972
25. Collste LG, Falk RE, Ericson JLE: Hyperacute cortical necrosis after antibody pretreatment of syngeneic rat kidney transplants. Scand J Urol Nephrol 4:58–65, 1970
26. Straus A, Straus F, Roseman D: Allogeneic "rejection" of in situ kidney using humoral antibody. Transplant. Proc 3:570–572, 1971
27. Morris R, Lucas ZJ: Immunologic enhancement of rat kidney grafts: evidence for peripheral action of homologous antiserum. Transplant Proc 3:697–700, 1971

Acknowledgments

The excellent technical assistance of Agnes Heafy, Susan Washington and Peter Coren and the excellent secretarial assistance of Frances Cascio and Margo LeVesque are gratefully acknowledged.

Dr. Abbas is a training fellow supported by Grant HL-05275 from the US Public Health Service. Dr. Carpenter is an investigator with the Howard Hughes Medical Institute.



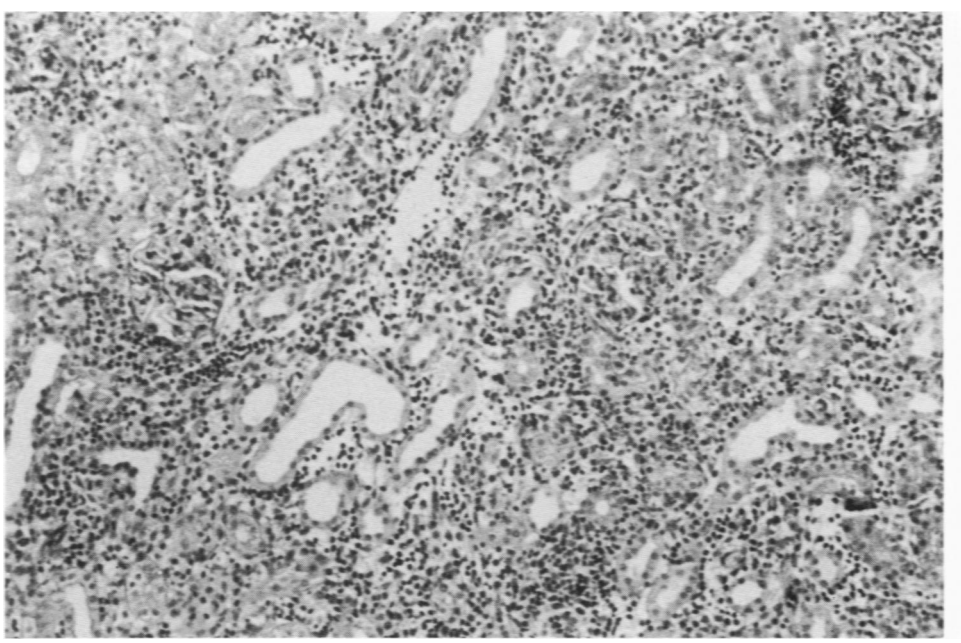
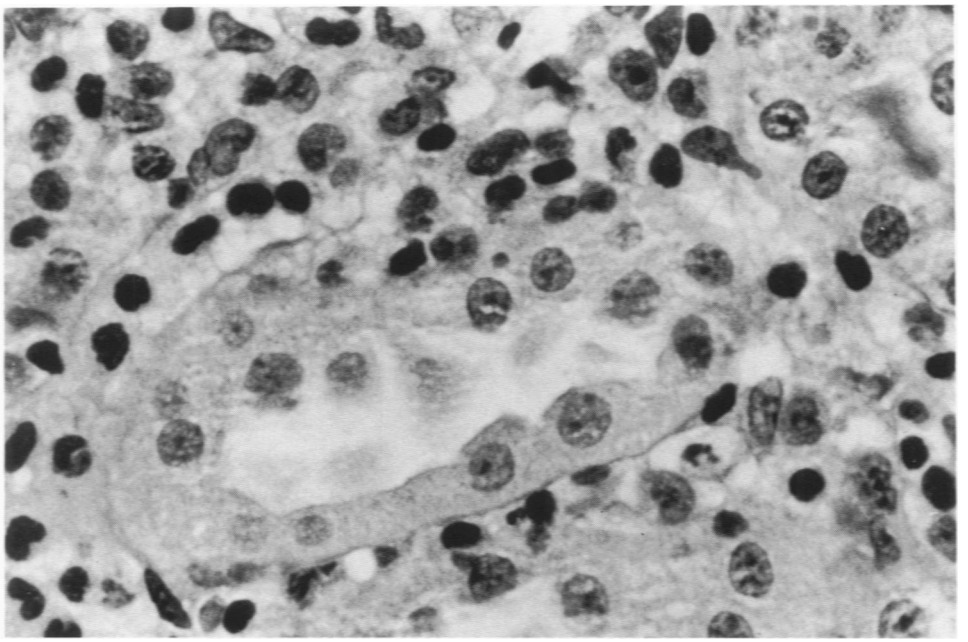


Fig 1—One-day enhanced allograft. Small perivenous aggregate of lymphocytes in the cortex (H&E, × 48). **Fig 2**—Six-day enhanced allograft. Intense diffuse interstitial lymphocytic infiltrate, with "blurring" of the underlying cortical architecture (PAS, × 48).

3



4

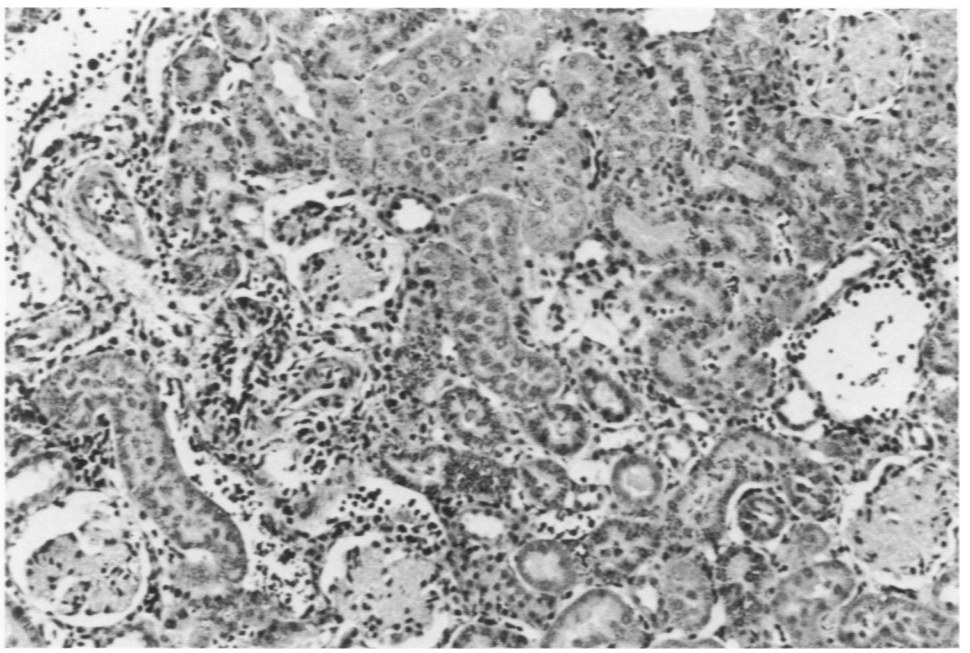
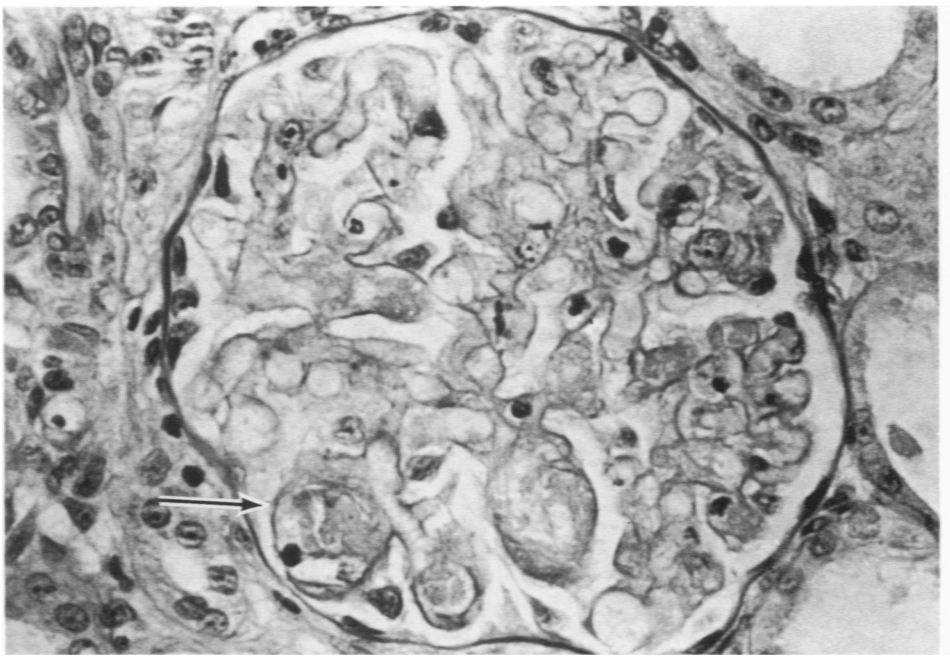
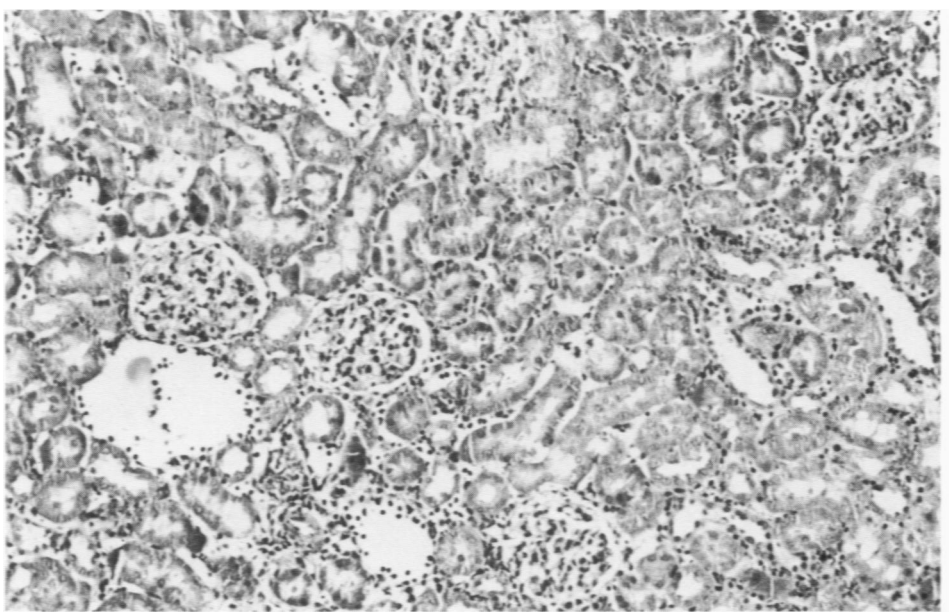


Fig 3—Six-day enhanced allograft. Lymphocytes invading through the basement membrane of a tubule into the epithelium (PAS, × 320). **Fig 4**—Five-day control allograft. Hypocellular glomeruli, with partial replacement of the tufts by an eosinophilic material. Compare with normal glomeruli in Figure 1 (H&E, × 48).

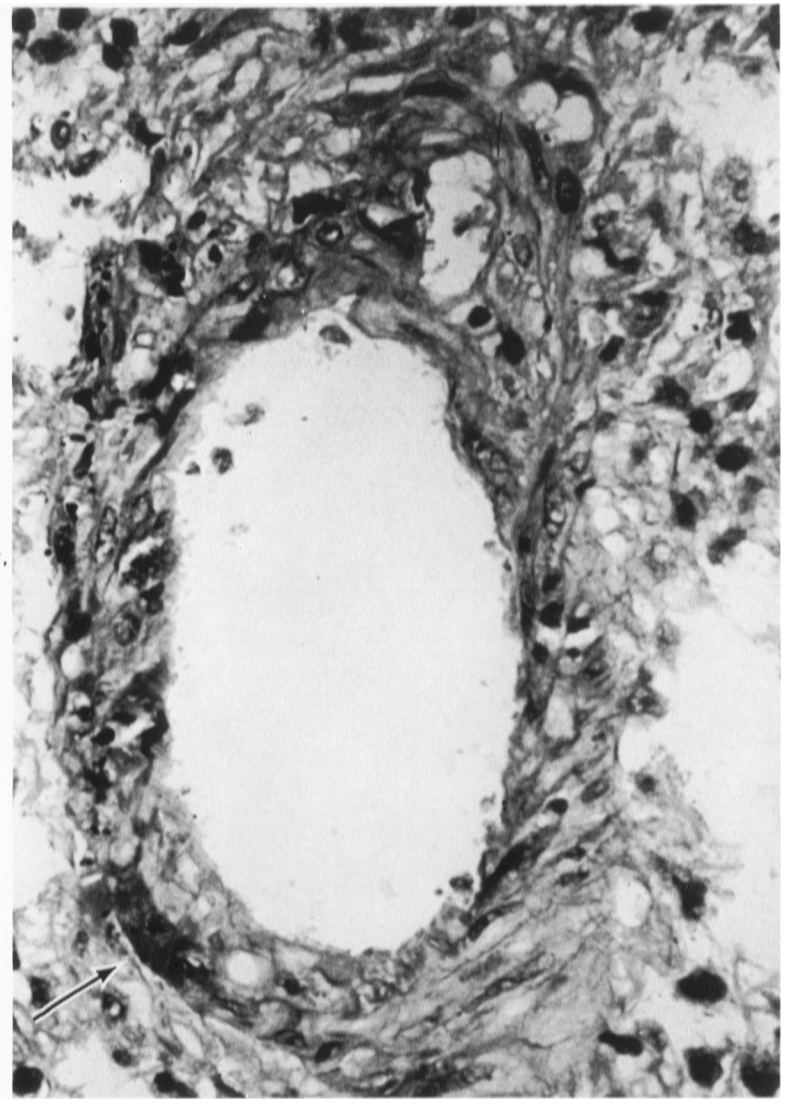


5



6

Fig 5—Nine-day control allograft. Glomerulus with lytic necrosis of endothelial cells, focal deposition of amorphous material (*arrow*), occasional fragmented nuclei and neutrophils is seen (PAS, × 200). **Fig 6**—Six-day enhanced allograft. Normocellular or mildly hypercellular glomeruli with no cell necrosis. Compare with hypocellular glomeruli in control allograft, Figure 4. (Interstitial infiltrate is unusually mild in this area of the graft) (H&E, × 48).



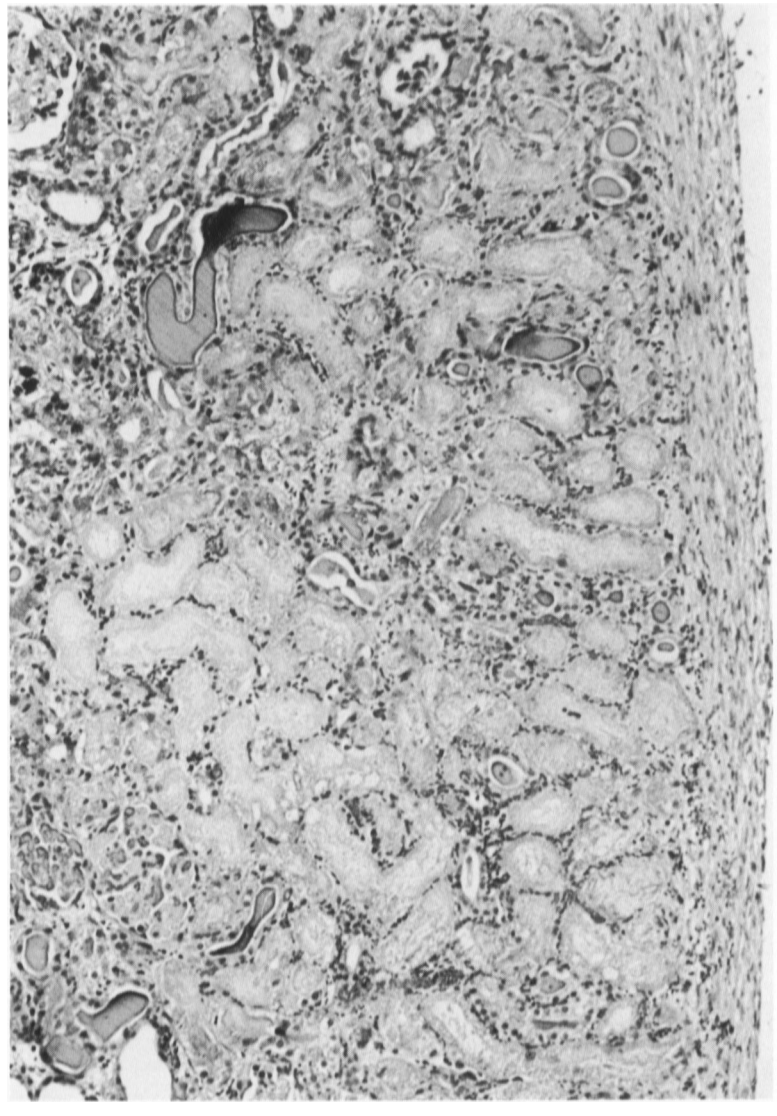


Fig 7—Six-day control allograft. Necrotizing arteritis involving an arcuate artery, with nuclear pyknosis and fragmentation, occasional neutrophils, destruction of elastic laminae and small fibrin deposit (*arrow*) (PAS, ×200).

Fig 8—Nine-day control allograft. Focal coagulative necrosis of tubules in the outer (subcapsular) cortex (H&E, × 48).