RENAL HOMOTRANSPLANTATION IN RATS

I. Allogeneic Recipients*

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Techniques of microsurgery have been recently developed so that organ transplantations can be achieved in rats with a fairly reasonable frequency of success (1, 2). Homografting in this type of laboratory animal is advantageous because the genetic disparity is constant between highly inbred strains which are commercially available. Such constancy of genetic differences yields reproducible results, i.e., an invariable rejection of the homografted kidney proceeding at a reproducible pace. There need be no uncertainty about the antigenic relationship of donor and recipient, as there is concerning transplants between human beings, and between dogs. The rejection process may therefore be followed in a series of animals from its beginning to final destruction of the grafted kidney, with reliance upon the reproducibility of the phenomena.

The events which occur in homologous renal grafts have been studied after transplantation into allogeneic recipients, into allogeneic recipients tolerant of the tissues of the kidney donor, and into F_1 recipients. The first paper of the series presents the temporal sequences of morphologic changes which developed in homologous renal transplants, as observed by light, fluorescence, and electron microscopy.

Materials and Methods

Male Lewis rats[1] ranging in weight from 250 to 450 g were recipient hosts for all renal transplants. Donors were either BN[1] or DA[2] (3) males of similar size, although no attempt was made to match precisely donor and recipient according to weight. Orthotopic transplants of the right kidney were done as described by Lee (1, 2). Total ischemic time of the grafted organ

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[1] Purchased from Microbiological Associates, Inc., Bethesda, Md.

[2] Generously provided by Dr. Willys Silvers and Dr. Darcy Wilson, University of Pennsylvania School of Medicine, Philadelphia, Pa.

was 30–35 min. The host's left kidney and ureter were not manipulated and served as one type of morphologic control.

From 3 hr to 7 days after transplantation, both donor and host kidneys were removed and tissues were taken for light, fluorescence, and electron microscopy (Table I). A complete

TABLE I

Data from Renal Homografts and Recipients, Unpaired Series

Animal No.	Duration of transplant	Source of donor kidney	Kidney weight at autopsy				Characteristic lesion in	
			Donor	Per cent difference from mean*	Host	Per cent difference from mean‡	Kidney	Ureter
			g		g			
Recipients								
1	3 hr	BN	1.05	+2.9	1.35	+3.0	±	−
2	6 "	BN	0.96	−5.7	1.24	−5.4	+	−
3	24 "	BN	1.54	+51.0	1.74	+32.8	+	+
4	24 "	BN	1.61	+57.8	1.49	+13.7	+	−
5	2 days	BN	1.79	+75.5	0.81	−38.1	+	n.e.§
6	2 "	BN	1.02	0.0	1.25	−4.6	+	+
7	2 "	DA	1.21		1.48	+13.0	+	−
8	2 "	DA	0.85		0.97	−25.9	+	−
9	3 "	BN	1.41	+38.2	1.42	+8.4	+	+
10	3 "	DA	2.13	+33.3	1.15	−12.2	+	−
11	4 "	BN	1.36	+33.3	1.10	−16.0	+	+
12	4 "	DA	3.50		1.26	−3.8	+	−
13	4 "	DA	2.33		1.40	+6.9	+	+
14	6 "	BN	4.50	+341.2	1.20	−8.4	+	n.e.
15	6 "	BN	—		—		+	n.e.
16	7 "	BN	3.54	+247.0	1.11	−15.3	+	n.e.
Control recipients								
17	3 days	Le	1.78	+35.9	1.75	+33.6	−	−
18	4 "	Le	1.88	+43.5	1.15	−12.2	−	−
19	5 "	Le	1.55	+18.3	1.45	+10.7	−	−
20	6 "	Le	1.34	+2.3	1.35	+3.0	−	−
21	7 "	Le	1.54	+17.5	1.19	−9.2	−	−

* Mean kidney weight of BN rats, 1.02 ± .03 g.

‡ Mean kidney weight of Lewis rats, 1.31 ± .02 g.

§ n.e., not examined.

autopsy was done on all recipients; ureters, bladders (both transplanted and recipients'), pieces of spleen, liver, et al. were processed for light microscopic examination. No rats were included in this series in which complications such as infarction, peritonitis, pyelonephritis, etc. had occurred. However, some dilatation of the renal calyces, the pelves, and segments of the ureter was found in the gross in most of the transplants, and it seemed that this type of alteration was an almost inevitable accompaniment of the surgical procedure. Such dilatation

did not interfere with the rejection process nor complicate the interpretation of the morphologic changes. In addition, control isografts provided a baseline by which to evaluate the results of surgery since they, too, exhibited mild changes of calyceal, pelvic, and ureteric dilatation after transplantation.

TABLE II

Animal No.	Duration of transplant	Time killed after ink	Source of donor kidney	Kidney weight at autopsy				Characteristic lesions in	
				Donor	Per cent difference from mean*	Host	Per cent difference from mean*	Kidney	Ureter
A. Data from renal homografts and recipients, paired series									
	hr	*min*		*g*		*g*			
22	6	60	BN	1.22	+19.7	1.20	−5.5	+	−
23	6	60	Le	1.52	+16.0	1.18	−7.1	−	−
24	7	120	BN	1.36	+33.3	1.22	−3.9	−	−
25	7	120	Le	1.26	−3.8	1.19	−6.3	−	−
26	24	60	BN	1.15	+12.7	1.05	−17.3	+	+
27	24	60	Le	1.31	0.0	1.21	−4.7	−	−
28	24	20	BN					+	−
29	24	20	Le	1.37	+4.6	1.15	−9.4	−	−
30‡	24	10	BN	1.45	+42.1	1.22	−3.9	+	+
31‡	24	10	Le	1.52	+16.0	1.20	−5.5	−	−
32	24	20	BN	1.08	+5.9	1.28	+0.8	+	−
33	24	20	Le	1.40	+6.9	1.36	+7.1	−	−
34	48	20	BN	1.39	+35.3	1.08	−15.0	+	−
35	48	20	Le	1.32	+0.7	1.29	+1.6	−	−
B. Data from renal homografts and preimmunized recipients, paired series									
36	6	—	BN	1.18	+15.7	1.10	−13.4	+	−
37	6	—	Le	1.29	−1.5	1.38	+8.7	−	−
38	24	—	BN	1.48	+45.1	1.38	+8.7	+	−
39	24	—	Le	1.25	−4.6	1.38	+8.7	−	−
40	24	—	BN	1.36	+33.3	1.30	+2.4	+	−
41	24	—	Le	1.60	+22.1	1.35	+6.3	−	−
42	48	—	BN	1.95	+91.2	1.35	+6.3	+	−
43	48	—	Le	1.55	18.3	1.15	+9.4	−	−

* Mean kidney weight of BN rats, 1.02 ± .03 g; of Lewis rats, 1.31 ± .02 g.
‡ Ferritin injected.

To examine the integrity of the vascular bed of the grafted organs, transplants of urinary tract tissue were made in allogeneic and syngeneic pairs (Table II A). From 10 min to 2 hr before killing, and at varying time intervals after surgery, India ink[3] or ferritin[4] was injected

[3] Pelikan No. C11/14312 purchased from J. Henschel & Co., Inc., Farmingdale, N. Y.
[4] Nutritional Biochemicals Corp., Cleveland, Ohio.

into the tail veins of the host rats. At autopsy pieces of tissue were taken for histologic and ultrastructural study.

To examine the effects of prior immunity to BN tissue, a group of Lewis rats was homografted with BN skin, and additionally, in some instances, by intraperitoneal injection of 30×10^6 viable BN spleen cells, 2–3 wk after the skin grafts were placed (Table II B). 15–20 days after skin rejection or the intraperitoneal administration of BN spleen cells, BN or Lewis kidneys were transplanted to the immunized Lewis hosts. Before closure of the abdomen, blood flow to the transplanted kidneys was observed for 15 min after circulation was reestablished. At the time intervals shown in Table II B, the recipients were autopsied as described above. Each pair represented an allogeneic and syngeneic transplant performed within 1.5 hr of each other.

Radiation was used to study the rejection process in rats in which the immune response was depressed and their lymphoid tissues depleted of cells. A series of Lewis recipients received 550 R total body irradiation 1 hr prior to homo- or isotransplantation. Mortality in both experimental and control hosts was high, due to hemorrhages at suture lines.

All grafted and host kidneys, from all groups, were examined in the fluorescence microscope for the presence of Lewis IgG, IgM, β_{1C}-globulin, and fibrin, using rabbit antibodies specific for these blood proteins. The fluor reagents were prepared according to the method of Riggs et al. (4) by labeling, with fluorescein isothiocyanate, the γ-globulin fraction which was separated from antisera by precipitation with 50% ammonium sulfate and which was further fractionated by electrophoresis in Pevikon (5). The fluor reagents yielded single precipitin bands when reacted against whole rat serum and the bands gave a reaction of identity with known purified IgG, IgM, β_{1C}, and fibrin. Aliquots of the fluor reagents, when absorbed with their specific antigens, no longer precipitated in agar with whole rat serum, nor did they stain diseased renal tissue known to contain the serum proteins being studied.

RESULTS

Light and Electron Microscopy.—The earliest certain morphologic manifestation of renal rejection was observed 6 hr after the circulation was reestablished in the graft. It consisted of the accumulation of mononuclear cells in the major connective tissue septa carrying the large interlobular vessels and their branches. Characteristically, these aggregates of cells were adjacent to, or contiguous with, large thin-walled vessels which were contained in the septa or formed a part of their boundaries (Fig. 1). The accumulation of lymphoid cells was progressive in numbers and in distribution over the period of 1–7 days. The spread of the infiltrate was centrifugal and appeared around thin-walled vessels accompanying the smaller branches of the interlobular arteries, the arterioles, and finally, around intertubular vessels. At 24 hr after surgery, the increase and advance of cells were almost entirely limited to the septa (Fig. 3). At 72 hr small accumulations of cells appeared between cortical tubules (Fig. 4). Beyond 3 days the spread of infiltrating cells was inexorably progressive, dispersed, and accompanied by destruction of parenchyma. Arterial lesions appeared between days 5 and 7; thrombi were not present at any time.

The composition and ultrastructural characteristics of the cellular aggregates changed from day to day. In the light microscope, the majority of cells at 6 to 24 hr after homologous trasplantation appeared to be lymphocytes; in the

electron microscope, however, the clusters were composed of both lymphocytes and monocytes, roughly in proportions of 2 to 1 (Fig. 5). At 48 hr in the light microscope, the mononuclear elements were larger than at preceding intervals and occasional mitoses were seen. Ultrastructurally, there were many transitional forms between lymphocytes and blast cells, and also a small number of typical blast elements (Fig. 8). Monocytes were diminished in relative number but macrophages, i.e. monocytes with phagocyted material, were present in force. At 72 hr the cellular infiltrate was composed predominantly of large cells with abundant cytoplasm, and mitoses were numerous (Fig. 6). At this time, an occasional cell was found with the morphologic appearance of a young plasma cell. In the electron microscope, the cell aggregates were a mixture of blast cells, macrophages, lymphocytes, and plasma cells, in order of decreasing numbers. In addition, polymorphonuclear leukocytes were more frequently recognized than in material of earlier time intervals. The composition and cytology of the expanding infiltrate up to 7 days remained much the same as described above.

Parenchymal changes were most prominent in the cortical tubular areas. Within the first 24 hr, the tubular epithelium of allogeneic and syngeneic grafts was vacuolated, swollen, and smudgy, an alteration which was quite focal and limited to relatively small parts of the cortex. Beyond 24 hr, homografts (but not isografts) showed progressive focal destruction of tubules and segments of their basement membranes, accompanied by the increasing pressure of infiltrating cells, until at 7 days, large areas of the cortex were destroyed. It was not possible to ascertain by morphologic examination whether these tubular changes were effected by contact with host cells, or whether they were secondary to a slowly-developing ischemic process. For the most part glomeruli were unaffected.

Mononuclear cell infiltration of the ureteric wall was first observed one day after grafting and was found in about 25% of all allogeneic transplants (Table I). The inflammatory process was spotty and not as severe nor as constant as that occurring within the kidney (Fig. 7).

The rejection process in the bladder was difficult to interpret, since the histologic picture was complicated by the presence of sutures, the accompanying acute reaction to foreign material, focal necrosis of the donor bladder wall, and occasional small hemorrhages. There were several instances, however, in which dense aggregates of lymphoid cells were dispersed in the mucosa and, occasionally, in the muscularis of the donor bladder, and these were considered to be the manifestations of graft destruction.

Control renal isografts (Lewis to Lewis transplants) also revealed evidence of minor septal changes, especially in those transplants of short duration (Figs. 2 and 11). The alterations consisted of edema, i.e. by comparison of the width and texture of the connective tissue septa of the unmanipulated left host kidney, a scattering of single mononuclear and polymorphonuclear leukocytes in the

areolar mesh, and swelling of some of the fixed elements of the connective tissues. Host kidneys were morphologically unaffected and served as a baseline for comparisons.

Surgical manipulation, per se, caused the transplanted renal isograft to increase in weight. The average weight of one Lewis kidney from intact, normal rats (100 measured) was 1.31 ± 0.02 g or 3.73 ± 0.04 mg per 1 g body weight.[5] Isotransplanted kidneys increased in weight, averaging 1.37 ± 0.03 g or 4.26 ± 0.19 mg per 1 g body weight of the donor when resident in recipients up to 24 hr (9 measured); and 1.57 ± 0.08 g or 4.71 ± 0.22 mg per 1 g body weight when kept in situ for 2–7 days (7 specimens). The latter increase was significant and represented a 20% enlargement over the mean weight of controls. The cause of this increase in isografts has not been determined. The allogeneic transplants increased in weight much more than the syngeneic kidney grafts, and it was likely that such enlargement, which was progressive, was due not only to surgical manipulation but also to the inflammatory process which was developing in the homotransplants. A single normal BN kidney averaged 1.02 ± 0.03 g or 2.74 ± 0.05 mg per 1 g body weight (25 measured). During the first 7 hr after grafting, there was a mean increase to 1.15 ± 0.22 g (5 specimens); at 24 hr, to 1.42 ± 0.08 g (6 measured); and between 2 and 7 days, to 2.28 ± 0.47 g (7 measured). Occasionally, DA tissues were homografted into Lewis recipients. We did not keep a record of DA body and kidney weights, but the DA rat is generally smaller than the BN and its kidneys are correspondingly small, of a similar size or less than those of BN strain. Increases in renal weight of DA homotransplants were of similar magnitude as those for BN transplants (Table I).

Soon after homologous transplantation of the kidney, mononuclear cells migrated from the vascular tree, apparently at the level of large venules. To examine this locus more closely, a group of paired homografted and isografted recipients was injected with India ink and, in one instance, with ferritin. The temporal details of this study are shown in Table II A. In all transplanted kidneys, isografts, and homografts, no vessel was stained by carbon, nor was there evidence of unusual leakage of particles at any level of the vascular tree. Aggregation of carbon or ferritin against the basement membranes of venules, which has been described to occur after administration of histamine and/or serotonin (6, 7), was not found. That carbon particles could accumulate along the basement membranes of other vessels damaged by surgery was demonstrated by the presence of large aggregates in the walls of bladder vessels near sutures. In transplanted allogeneic kidneys, there were more cells in the lumens of the large thin-walled vessels than in the vessels of syngeneic grafts. Most of these elements were mononuclear and were close or adherent to the endothelium.

[5] Feldman, J. D. Unpublished observations.

Three times as many cells were lined up against the vessel walls in homografts as were found in isografts (Figs. 10 and 11). The majority of these were macrophages, some were lymphocytes, and a few were neutrophiles. The thin-walled vessels within or adjacent to the septa in homologous renal transplants exhibited ultrastructural evidence of focal injury as early as 6 hr after grafting and were progressively damaged with passage of time. The lesions consisted of segmental swelling of endothelial cytoplasm and avulsion of endothelium from its basement membrane, which, in these loci, was frayed (Fig. 9). Infrequently circulating cells traversed vessels at sites where the eudothelium was separated from the wall or its neighbor, and also migrated across vessels that appeared morphologically normal (Fig. 12). 3 days and later after homografting, many thin-walled vessels were so distorted that it was difficult to identify them.

Fluorescence Microscopy.—Fluorescent stains for IgG and IgM were consistently negative in all transplanted allogeneic and syngeneic kidneys and in host kidneys of all groups. From 3 hr to 7 days after grafting, no unequivocal specific coloration of vessels, tubules, or glomeruli was observed. Glomeruli frequently exhibited a mesangial pattern of staining, i.e. a pattern of arborization without visualization of peripheral capillary walls, which we regarded as of no immunological significance. Of interest but without any explanation, the cells of the infiltrate were rarely stained by either anti-IgG or anti-IgM, despite the presence of numerous typical plasma cells identified in both the electron and light microscopes. Although anti-β_{1C} antiserum lightly stained segments of some basement membranes surrounding proximal convoluted tubules, the staining was not considered to be immunologically meaningful since it was observed in control as well as homografted kidneys. In allogeneic renal grafts only, fibrin formed a network or droplet deposit in perivascular zones containing cellular infiltrates.

Preimmunized and Irradiated Hosts.—Neither the pace of rejection nor the light, fluorescent, and electron microscopic alterations were significantly affected by preimmunization of hosts. Irradiation of five hosts with allogeneic and three with syngeneic transplants was complicated by focal hemorrhages, either around the renal pelvis and/or in the donor bladder at suture sites, generally more severe in the homologous tissues. Characteristic cellular infiltration was first observed between 4 and 5 days after grafting, i.e., the rejection process was delayed. At 5–6 days, the extent of mononuclear cell accumulation in the renal septa was equivalent to that seen in nonirradiated recipients at 24 hr, and at 10 days appeared to be equivalent to the severity observed in nonirradiated hosts at 4 days after surgery.

DISCUSSION

The morphologic manifestations and their temporal sequences in first-set renal homografts between inbred strains of rats have suggested that the phenomena of rejection comprise several simultaneous and self-perpetuating proc-

esses. The trigger event remains unknown, but we have considered allogeneic inhibition, or some mechanism akin to it, as a reasonable concept to explain the early events of graft destruction (8, 9, 10). There was some circumstantial evidence to support the point of view that recognition of foreign antigen might be operative as an initiating event in these renal homografts. First, the rapidity of the development of the morphologic lesion, within 6 hr of placing the homotransplant, was consonant with the temporal aspects of such recognition in vitro. Secondly, the earliest host response appeared in and around large thin-walled vessels, most probably veins. In such vascular spaces, blood flow was likely to be slower than the flow in arteries and capillaries. Consequently, contact of some duration between circulating host cells and target endothelium could occur. Thirdly, there was aggregation of hematogenous elements to the walls of these thin-walled vessels, manifested by the sticking of mononuclear cells in relatively large numbers. The primary event that provoked endothelial stickiness and cellular adherence was not ascertained; nonspecific injury, perhaps, as a result of iscehmia during transfer of the kidney, might have been responsible, to some extent, since cellular adherence to vessel walls was seen to a slight degree in control renal isografts. Once host cells aggregated on the luminal surface of vessels and were not removed by the swiftness of blood flow, the hematogenous elements could initiate and perpetuate a local injury of the type described as occurring in vitro. Lastly, by fluorescence microscopy, we were unable to detect humoral factors in the renal homotransplants that would suggest an immunologic process. The latter negative observations have not excluded the possibility that antibody against renal components might appear later in the rejection process. Indeed, Milgrom et al. (11) have reported the presence of kidney-fixing antibodies in the circulation of patients transplanted with kidneys, and Kolker et al. (12) have isolated antibodies which bind to vessels of dogs with renal transplants. Such antibodies have been found only after the homotransplants were in residence for a considerable time.

Recently Chase and Rapoport have reported accelerated destruction of skin grafts in animals previously primed with bacterial antigens (13, 14). The implication was that some ubiquitous bacteria might have antigenic components similar or identical with antigenic components in host tissues. The possibility cannot be excluded that the rapid development of lesions in rat renal allografts might have been the result of prior exposure to ubiquitous antigens immunologically similar to tissue components.

Once the process of rejection has been triggered, the evolution of the pathology terminating in a necrotic, functionless kidney was self-perpetuating and comprised several activities proceeding simultaneously. There was, first, local and focal destruction, possibly due to the activities of the lymphoid cells which aggregated against endothelium and outside the vascular tree. If recognition of foreign antigen by lymphoid cells led to injury of target tissue, then the

continued influx and local proliferation of hematogenous cells would have produced progressive damage with time. In vitro, analogous destruction of target cells and proliferation of attacking cells has been described when antigenic differences existed between the two populations (15–17).

Accompanying the local and focal destruction occurring between cell and cell, there was probably ischemia which became more extensive and severe during the period of observation. We have not measured in any objective way the ischemic process, but it was apparent from morphologic examination that vascular injury was at first restricted to large thin-walled vessels, then spread to intertubular thin-walled vessels, and finally reached the arteries and arterioles. In dogs, ischemia has been measured by direct recording of blood flow and was demonstrated to begin on day 3 after transplantation and to advance until renal destruction terminated function (18, 19). It should be emphasized that the vascular lesions we and others have described were nonspecific, i.e., the focal alterations seen in the electron microscope were elicited by several kinds of nonimmunologic stimuli. Of even greater interest was the fact that, despite the movement of cells across their walls, carbon and ferritin did not accumulate against the basement membranes of these vessels nor in the interstitial spaces in which the mononuclear elements aggregated. The dissociation of leukocyte migration and increased permeability to fluids, proteins, and marker particles was emphasized by Hurley and Spector (20) and Hurley (21). The mediators of this type of delayed and selective vascular injury have yet to be identified.

Finally, along with allogeneic inhibition and ischemia, there was most likely a good deal of nonspecific inflammation, i. e., the inflammation attendant upon necrobiotic and necrotic tissue. Evidence of this kind of process was provided by the presence of numerous macrophages laden with cellular debris and unidentifiable substances, and of increasing numbers of neutrophiles, especially in the later periods of rejection, also filled with ingested material.

Kidney function as determined by urine output and proteinuria was not studied in this investigation, for several reasons. First, the inflammatory and hemorrhagic reaction in the bladder during the first 3–4 days after surgery would have falsified any measure of protein leakage from the kidney. Secondly, since the recipient retained one functioning kidney, ureter, and distal bladder, measurement of urine volumes would not have shown whether the transplanted kidney was functioning or not. In a subsequent paper of this series, urinary studies have been carried out on tolerant recipients holding a single homotransplanted kidney.

The effects of radiation on the rejection process were ephemeral, merely delaying by several days the onslaught of destruction. Such a delay might have been effected by simple quantitative reduction of lymphocytes in the lymphoid organs and circulation of the host. When a sufficient number of lymphoid cells had been regenerated, the process of rejection was initiated and at 5 days after

grafting, the lesion resembled that seen 6–24 hr after transplantation in non-irradiated rats.

Preimmunization of recipient rats had little noticeable influence on the rejection process. Since a characteristic lesion developed within 3 to 6 hr in first-set renal grafts, it would have been difficult to observe an acceleration of these morphologic phenomena in grafts residing in preimmunized hosts. Nor did prior immunization of Lewis rats by BN skin homografts and spleen cell injections uncover any humoral factors that might have played an immunologic role in homograft rejection.

Cellular infiltration around and in the ureter and bladder did not keep pace with the incidence and extent of rejection occurring in the kidney. Only a fourth of the ureters showed evidence of early invasion by mononuclear cells. A similar disparity of the rejection process between renal and skin homografts has been noted (22, 23). It has been proposed that antigenic differences of the various tissues such as skin and kidney might explain these observations. On the other hand, acceptance or rejection of a graft might depend on the quantity and quality of its blood supply. The ureter in rat transplants is supplied with blood from a branch of the renal artery which is frequently disturbed by the surgical procedures. At best, there was no clear explanation for the difference in incidence and intensity of rejection between ureter and kidney. In most instances, the piece of bladder was so altered by nonspecific inflammation for several days after transplantation as to obscure the histologic manifestations of rejection.

SUMMARY

Within 3–6 hr after the reestablishment of the circulation, a characteristic pathology developed in renal homotransplants. Blood monocytes and lymphocytes adhered to large thin-walled vessels of the septa carrying interlobular arteries, traversed their walls, and aggregated in the connective tissue spaces around them. Within 3 days, the number and size of the extravascular cells markedly increased, filling the septa completely and spreading from them centrifugally to occupy the intertubular spaces throughout the cortex. The composition of these aggregates at first was a mixture of lymphocytes and monocytes, and later consisted of large blast cells, macrophages, a few plasma cells, and polymorphonuclear leukocytes. Mitotic activity was seen 2 days after surgery among the large blast cells and increased to a maximal level a day later. Coevally with these changes, the thin-walled septal vessels, intertubular veins and capillaries, and finally, arteries and arterioles, in that order, were damaged. Focal injury of tubules was slight 24 hr after homografting; widespread cortical necrosis had developed 5–7 days later. At no time up to 7 days were concentrations of immunoglobulins detected by fluorescence microscopy in the transplanted kidneys.

The morphologic manifestations and temporal sequences of renal homograft

destruction suggested that several mechanisms acted synergistically to eliminate the transplant. The initial injury appeared to be the result of an interaction between host lymphoid cells and target endothelium, a phenomenon akin to allogeneic inhibition; followed by spreading ischemia; additional contact injury to tubules; and nonspecific inflammation associated with necrobiotic tissue.

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EXPLANATION OF PLATES

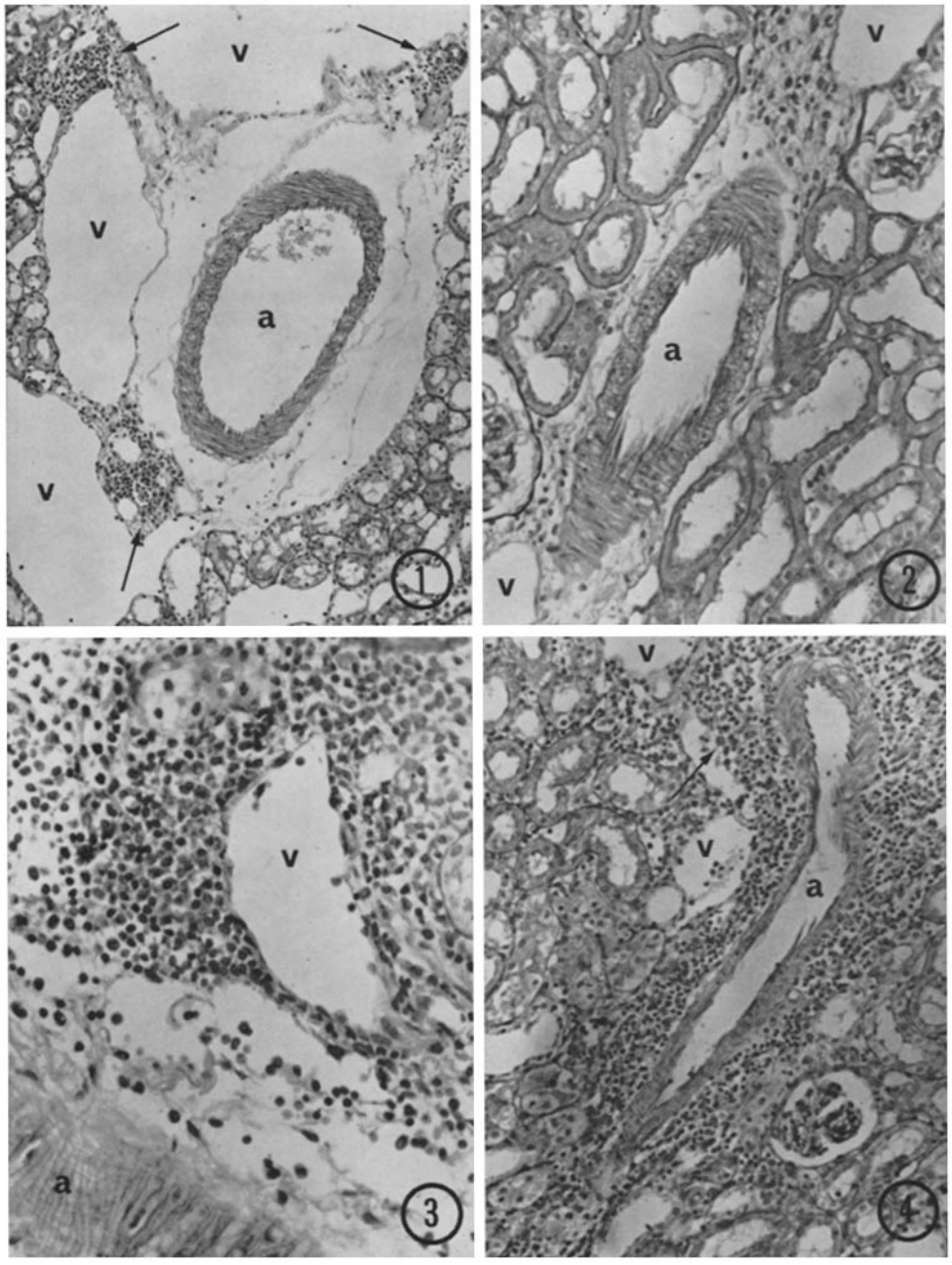
PLATE 55

FIG. 1. 6-hr renal homograft. In the septum there are three aggregates of mononuclear cells (arrows) adjacent to large thin-walled vessels (v). An interlobular artery (a) is embedded in edematous areolar tissue. × 110.

FIG. 2. 24-hr renal isograft. A few mononuclear cells are dispersed in the connective tissues carrying an intertubular artery (a). The cells are close to thin-walled vessels (v) and represent as severe an inflammatory response as is seen in isografts. Compare with Fig. 3. × 200.

FIG. 3. 24-hr renal homograft. The mononuclear cell aggregate around thin-walled vessel (v) is larger and denser than at 6 hr and is composed primarily of small cells. Wall of interlobular artery (a) is unaffected. Compare with Fig. 6. × 315.

FIG. 4. 3-day renal homograft. A dense agglomeration of cells in the septum ensheathes an interlobular artery (a). A segment of the wall of a thin-walled vessel is overrun by infiltrating elements (arrow). There is also an increase of cells between cortical tubules. × 150.



(Feldman and Lee: Renal homotransplantation in rats. I)

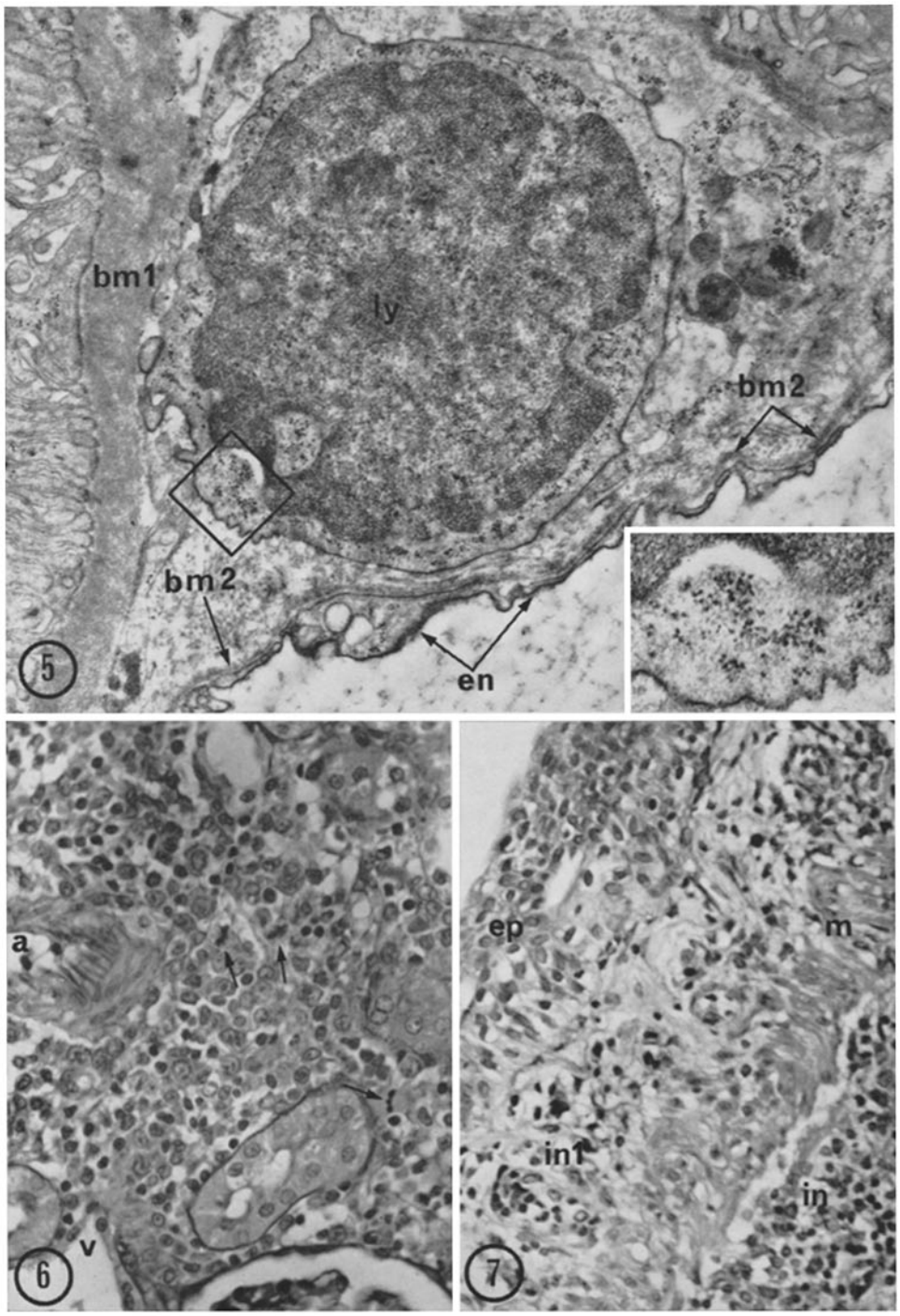
PLATE 56

FIG. 5. 6-hr renal homograft. An extravascular lymphocyte (ly), adjacent to the basement membrane (bm 1) of a tubule, has a scanty cytoplasm which contains relatively few ribosomes and polyribosomes. At this level the endothelium (en) appears normal; it is thin, fenestrated, and intimately apposed to its basement membrane (bm 2), which is intact. × 19,000.

Inset: Enlargement of boxed area to show arrangement of ribosomes. × 95,000.

FIG. 6. 4-day renal homograft. The mononuclear cell aggregate around an artery (a) and vein (v) is composed chiefly of large cells (compare with Fig. 3). Three mitoses (arrows) are seen. × 360.

FIG. 7. 4-day renal homograft. A small segment of ureter shows a typical infiltrate of mononuclear cells in the adventitial connective tissues (in) and few elements in the subepithelial connective tissues (in 1). ep, epithelium; m, muscle. × 210.

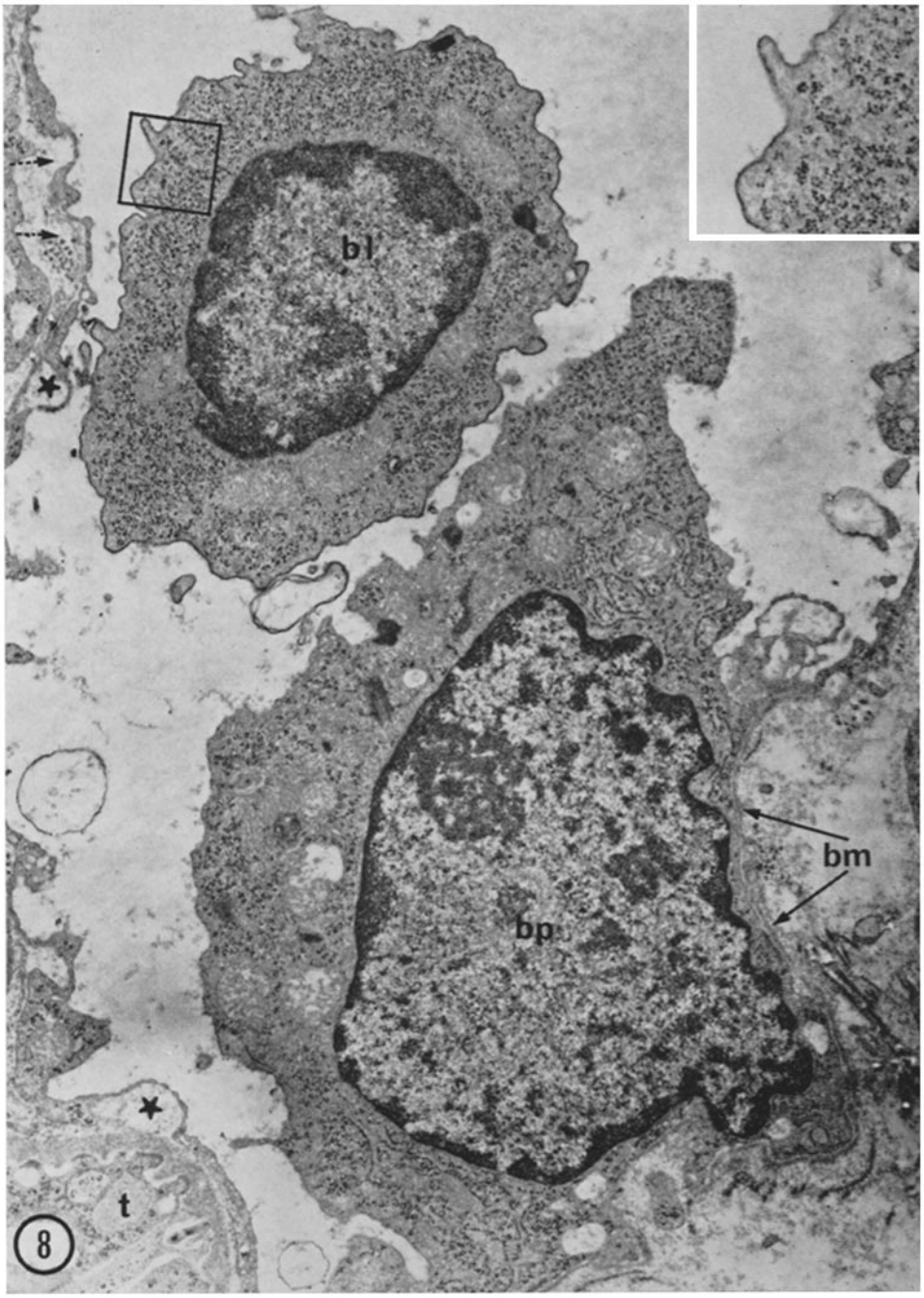


(Feldman and Lee: Renal homotransplantation in rats. I)

PLATE 57

FIG. 8. 3-day renal homograft. In this thin-walled intertubular vessel, the cell on the left (bl) is either a blast cell or a transitional form between lymphocyte and blast. It is characterized by numerous polyribosomes in a moderately abundant cytoplasm; its nucleus retains some features of a lymphocyte. The cell to the right (bp) is either a blast cell or an immature plasma cell. It rests directly on the basement membrane (bm) of the vessel. The endothelium is lifted away from its basement membrane at several sites (star) and at one locus the basement membrane is missing (broken arrows). t, tubule. × 11,000.

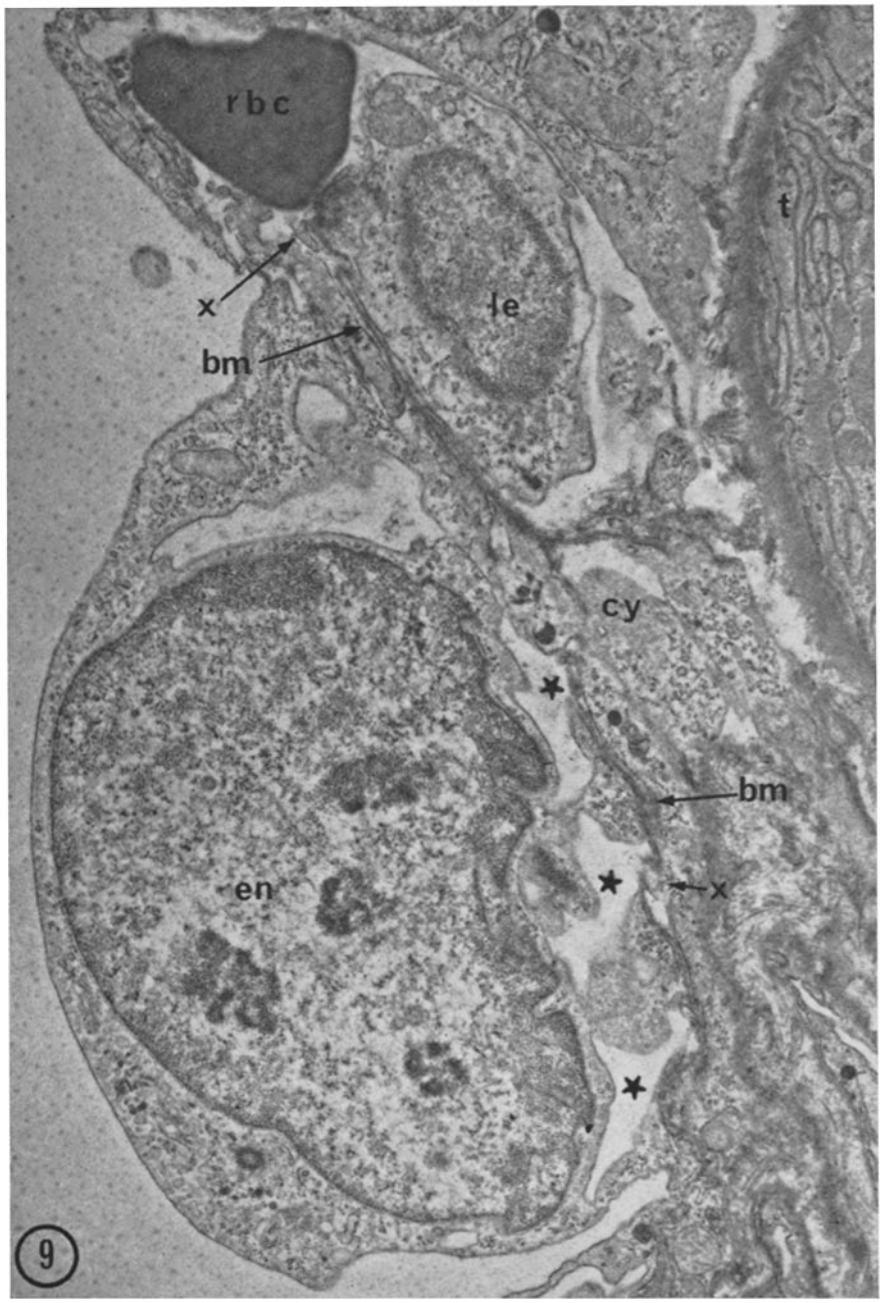
Inset: Enlargement of boxed area to show arrangement of polyribosomes. × 55,000.



(Feldman and Lee: Renal homotransplantation in rats. I)

PLATE 58

FIG. 9. 24-hour renal homograft. A small segment of a large thin-walled vessel illustrates the following alterations: (*a*) endothelium (en) is lifted away, in part, from its basement membrane (star); (*b*) the basement membrane (bm) is missing at several sites (x); (*c*) cytoplasm of a cell extends from endothelium to extravascular space (cy); (*d*) a leukocyte (le) and erythrocyte (rbc) are located between vessel and tubule (t). × 13,000.



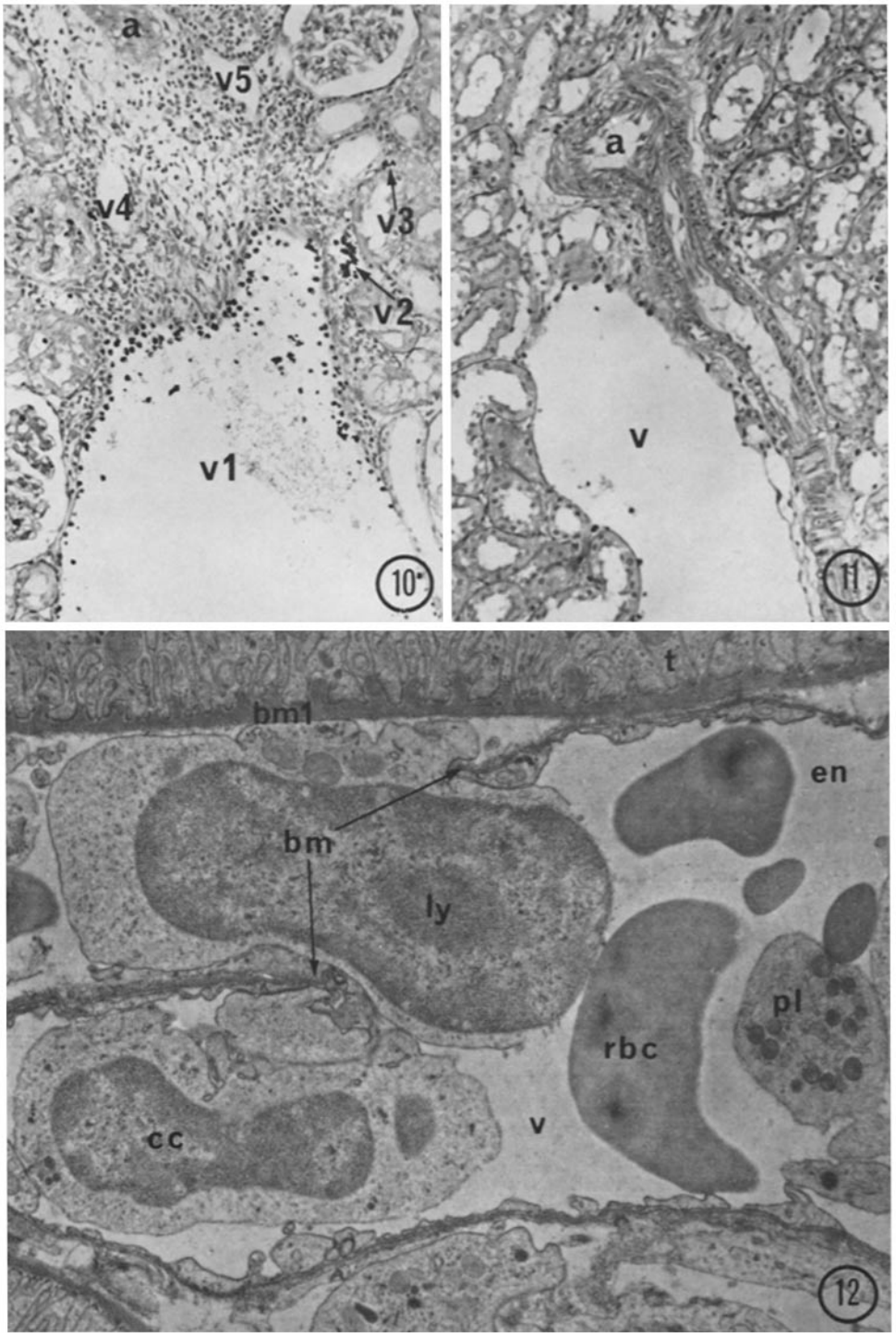
(Feldman and Lee: Renal homotransplantation in rats. I)

PLATE 59

FIG. 10. 1-day renal homograft. Hematogenous cells, many laden with carbon, are close or adherent to wall of large vessel (v1) and extend into smaller vessels between tubules (v2 and v3). Mononuclear cell aggregates are present in septum and surround veins (v4 and v5) near an artery (a). × 175.

FIG. 11. 1-day renal isograft. Relatively few hematogenous cells line up against wall of a large vessel (v) which is close to an artery (a). Compare with Fig. 10. The connective tissues around the artery are free of infiltrating inflammatory cells. × 175.

FIG. 12. 24-hour renal homograft. A lymphocyte (ly) traverses the wall of a large vessel (v) cutting through its basement membrane (bm). The endothelium (en) appears normal. rbc, erythrocyte; pl, platelet; cc, circulating cell; t, tubule; bm 1, tubular basement membrane × 9700.



(Feldman and Lee: Renal homotransplantation in rats. I)