penal institution for mentally defective delinquent adults, 1:15; in a penal institution for unselected delinquent adults, 1 : 12; and in a mental hospital for the criminally insane, 1:8. The comparable incidence of sex chromosome errors among tall men at large is estimated to be 1:80, if one assumes that 20 percent of American males attain a height of 6 feet or over (*5*), that sex chromosome errors result in extreme body height, and that the incidence of 47,XYY is 1 : 2000 (*6*) and of 47,XYY is 1 : 500 (*7*) adult males.

The results of this limited survey appear to confirm British observations that gross chromosomal errors contribute, in small but consistent numbers, to the pool of antisocial, aggressive males who are mentally ill and who become institutionalized for criminal behavior. Our data show, furthermore, that these men are to be found in general prisons as well as in mental hospitals for the "hard to handle."

To this we would add the observation that despite good physical care and much psychiatric attention throughout repeated incarcerations, these individuals are not being identified in the institutions we have surveyed. The implications of gross chromosomal errors for the intellectual, emotional, physical, and social development of the individual, for his legal status before the law (*8*), for the psychiatrist who treats him, for the society that must provide either care or parole are fundamental and deserve serious attention by professionals in many related disciplines.

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Pathogenesis of a Local Graft versus Host Reaction: Immunogenicity of Circulating Host Leukocytes

Abstract. *A local invasive-destructive reaction typical of that seen in allograft rejection occurs when Lewis rat spleen cells are inoculated under the capsule of Lewis kidney freshly grafted into F_1 hybrid hosts. Thus the donor lymphoid cells can be immunogenically stimulated by circulating host leukocytes and the interaction of these two cell populations results in nonspecific damage to kidney parenchyma. The results indicate that passenger leukocytes in organ allografts may be important immunogenic agents.*

Lymphocytes from normal adult parental strain rats give rise to a local invasive-destructive lesion when inoculated under the kidney capsule of genetically tolerant F_1 hosts (*1*). The local lesion is a massive one which depends on immunologically specific activation of donor cells (*1*, *2*) and is marked by their continuing proliferation for periods in excess of 1 week (*2*). In terms of time course and histopathology this local graft versus host reaction mimics that of the acute rejection of primary renal allografts (*1*, *3*), hence one could surmise that the infiltrating mononuclears are engaged in an immunological attack on the renal parenchyma.

However, when hosts that had previously been exposed to total body irradiation were employed, it was found that the graft versus host reactions were progressively inhibited in proportion to the dose of radiation administered (*4*). The donor lymphoid cells appeared to be powerless to generate an invasive-destructive lesion in allogeneic kidney when the host was profoundly leukopenic. One of several possible explanations for this phenomenon would be that host leukocytes rather than kidney were necessary to provide an immunogenic stimulus to the donor lymphoid cells. In order to study whether the invasive-destructive process depended upon the antigenicity of the renal parenchyma, or whether, on the other hand, the immunogenic stimulus could be provided by host leukocytes, we sought to confront the donor cells with isogeneic kidney that was perfused by allogeneic blood.

Lewis (L) rat kidneys were transplanted orthotopically by the microvascular surgical technique of Fisher and Lee (*5*) into genetically tolerant (L/BN) F_1 hybrid hosts. Within 24 hours 50 million spleen cells (*6*) from L, BN, and F_1 donors (*7*) were inoculated under the capsule of the graft, and the results were assessed by histologic examination on the 8th day. When Lewis spleen cells were employed the kidney parenchyma was of course nonantigenic, but circulating host leukocytes or free subcellular transplantation antigens of the F_1 hybrid host could provide the necessary immunogenic stimulus.

Typical invasive-destructive lesions were observed under these circumstances, as shown in Table 1 and Figs. 1 and 2. Therefore, it is reasonable to conclude that the kidney need not provide the stimulus. Moreover, because the ability of inocula of whole blood to induce transplantation immunity resides exclusively in its leukocyte fraction (*8*), it seems likely that the donor lymphocytes were stimulated by circulating host leukocytes. Polymorphonuclear leukocytes are but rarely noted in the interstitial infiltrate or in the peritubular capillaries within the reaction site by either light or electron microscopy (*1*, *9*), so the host cells involved are probably lymphocytes or monocytes or both.

The role of circulating leukocytes as the effective source of antigen in local graft versus host reactions was first un-

Table 1. Induction of graft versus host reactions in antigenically relevant and irrelevant kidney grafts from Lewis donors in genetically tolerant (L/BN) F_1 hosts.

Derivation of spleen cell inoculum	No.	Histologic evaluation*			Kidney relevant?	Blood leukocytes relevant?
		No. pos.	No. equiv.	No. neg.		
L	4	4	0	0	—	+
BN	3	3	0	0	+	+
(L/BN) F_1	5	0	1	4	—	—

* Positive = mononuclear cell invasion through cortex at least to depth of peripheral glomeruli, and distinct signs of tubule degeneration. Equivocal = sparse mononuclear cell interstitial infiltrate, no sign of tubule destruction. Negative = no infiltration or destruction of outer cortex.

covered by Ramseier and Billingham (*10*) in their analysis of the normal lymphocyte transfer test in hamsters, and our confirmation and extension of their findings with a different system suggests that this is not a parochial phenomenon but one which may have general import in the field of transplantation immunology.

When graft versus host reactions are induced by the systemic administration of lymphoid cells, the most impressive lesions are characteristically found in the lymphoreticular organs, skin, and intestines of the host (*11*). These, of course, are sites in which large numbers of lymphocytes occur normally, and in which transfused exogenous lymphocytes may be expected to settle and interact with their host counterparts. This interaction can be related to the pathogenesis of the ensuing systemic disease (*12*). Hitherto the local renal graft versus host reactions appeared to provide the clearest example of a direct and destructive immune attack by an immunologically competent graft on nonlymphoid tissue, but it now appears that here also the significant interaction occurs between two populations of genetically diverse lymphoid cells. It is possible that host lymphoid cells are immunogenically more potent than parenchymal tissues, such as kidney. Hence host irradiation would be inhibitory by virtue of its ability to eliminate the former source of immunogen. In this connection it is interesting that mouse lymphoid cells have proved to be a more abundant source of extractable H-2 transplantation antigens than liver or kidney (*13*).

In the reactions elicited by Lewis spleen cells in Lewis kidney grafts the mononuclear cells which infiltrated the interstitium could only be isogeneic (spleen cell donor type) or genetically tolerant (host-type) with respect to the renal blood vessels and parenchyma; and therefore these latter cannot serve as antigenic targets for the infiltrating cells. Thus it is most unlikely that specific immune products, for example, cell-bound antibody, are directly responsible for the local kidney damage. Rather, the destruction of kidney tissue is apparently a nonspecific consequence of an immunologic, undirectional interaction between donor and host mononuclear cells (*1, 2*). A likely locale where this interaction might take place would be in and about the peritubular capillaries and small venules of the cortex. Indeed, many such vessels

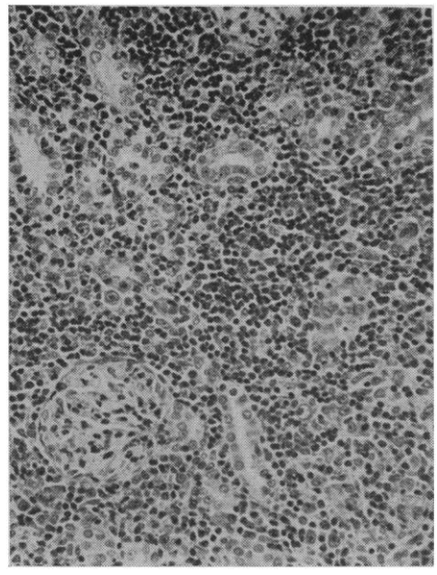

Fig. 1. Invasive-destructive reaction resulting from inoculation of Lewis spleen cells under capsule of Lewis kidney graft in (L/BN) F_1 host. (× 180)

appear to be plugged with mononuclear cells (*1*), and it is probable that the tubular epithelium suffers ischemic damage as a consequence. It is also possible that there is a direct, although nonspecific, cytotoxic effect of immunologically activated, infiltrating cells on the tubules (*14*).

The results of the experiment here reported suggest that the rejection of solid organ grafts, a process which is characteristically heralded by development of perivascular mononuclear cell infiltrates, might frequently be initiated by an immune interaction between host lymphocytes and reticuloendothelial or lymphoid cells which are passengers in the capillaries or perivascular interstitium of the graft. Thus rigorous attempts to eliminate such cells might be of value in clinical practice (*15*). Steinmuller has indeed provided evidence that even skin grafts may bear adventitious cells capable of sensitizing host mice (*16*), and it has long been known that allogeneic tissues enclosed in cell impermeable membranes do not sensitize their hosts (*17*). The immunogenic stimulus provided by such passengers could be delivered in the graft itself or in the regional lymph nodes, or both, and would be marked by transformation and proliferation of host lymphocytes in these sites. It is very probable that the "mixed lymphocyte reaction" in vitro represents a cognate phenomenon (*2*).

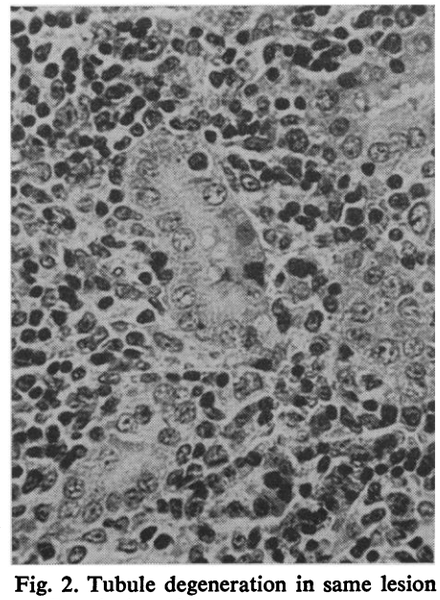

Fig. 2. Tubule degeneration in same lesion as Fig. 1. (× 400)

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