PATHOLOGIC CHANGES IN LYMPHOID TISSUES IN EARLY TRANSPLANTATION (RUNT) DISEASE IN MICE

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Despite intensive studies, the pathologic sequelae and cause of death in graft-versus-host reactions are poorly understood.[1] The immunogenetic basis of acute transplantation disease is, however, well established. When two inbred strains or individuals possess one or more different strong histocompatibility genes and antigens, injection of immunologically competent adult cells from one strain into newborn recipients of another strain usually leads to a fatal runting syndrome. The features regularly associated with such runt disease in various species are inhibition of growth, diarrhea, emaciation, hepatomegaly, splenomegaly and disappearance of lymphoid tissue.[1-5] Among other factors, the severity and course of runt disease have been affected by the species-strain combination tested, by the type and number of cells injected, and by the age of the recipients.

Although most transplantation disease studies have involved the inoculation of mixed populations of adult lymphoid cells derived from spleen or lymph nodes, it is now clear that purified small lymphocytes from peripheral blood[6] or thoracic duct lymph[7] are capable of producing acute runt disease. Donor spleen cells may persist in hosts for many days, but small lymphocytes alone derived from C57BL/6 mice persist for only 2 days or less after injection into newborn A/Jax mice.[8] That these lymphocytes promptly attack antigenically disparate newborn hosts and then rapidly disappear is surprising, since overt symptoms of runt disease are not evident until 8 days of age or later. The apparently long latent period between the initial damage presumably done by these lymphocytes and discernible disease suggested that a study of very early changes in host lymphoid tissues could be especially revealing. Our previous findings might be explained if injected small lymphocytes homed on the thymus of the newborn to produce an "immunologic thymectomy." Conversely, an attack on the spleen and lymph nodes might be expected to cause rapid thymic depletion associated with con-

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current splenomegaly. The latter possibility has been inferentially supported by recent findings of Miller and colleagues.[9,10]

To test the hypothesis of an immunologic thymectomy, concurrent pathologic changes in thymus, spleen and lymph nodes of neonatal recipients have been evaluated in the present chronologic study of the early phases of acute runt disease. For comparative purposes, both adult spleen cells and purified small blood lymphocytes were employed as sources of immunologically competent donor cells.

Material and Methods

Two inbred strains of mice differing at the strong H-2 locus were employed. Adult donor cells were harvested from C57BL/6 (H-2^b) mice for injection into A/J (H-2^a) recipients less than 20 hours old. Donor spleen cells and purified small lymphocytes were prepared by methods previously described in detail.[8] The cell viability in these preparations was about 90 per cent for the spleen cells and 98 per cent for the small lymphocytes as assessed by eosin-Y exclusion. The newborn recipients were given injections by the intracardiac route. Half the mice in each litter, with tail tips cut off, were left without injections as littermate controls.

Two experimental and two littermate control animals were sacrificed at random 1, 2, 4, 7, 10, 13 and 16 days after individual injections of 2.4 million spleen cells. An identical series of litters was evaluated after individual injections of 3.2 million small blood lymphocytes. Thus a total of 56 animals were assayed. Total body weight and weights of thymus and spleen were obtained on each animal. Concurrent quantitative assessments of changes in lymph node sizes were determined from inspection of 8 step-cut sections through the cervical regions of all animals. The longitudinal and transverse diameters of the largest cervical node in each animal were measured in arbitrary units, using an ocular micrometer at a magnification of 100 times. The product of these diameters was taken as a relative indication of lymph node size whereby experimental and control animals might be compared. In addition, 12 to 15 transverse sections were made through selected animals, so that representative sections of most organs were available from each experimental group at each time period.

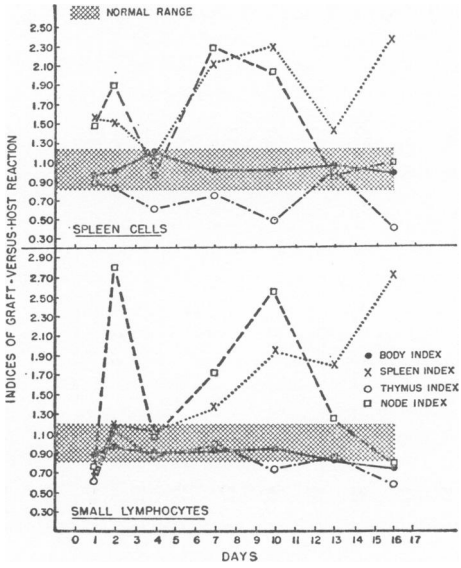
Mean body weights and mean relative spleen and thymus weights expressed in gm. per 100 gm. body weight were determined for each experimental and control group. Mean node sizes in arbitrary units of the largest cervical nodes were similarly recorded. From these data, indexes of graft-versus-host reaction were calculated as follows: index = experimental mean body or relative organ weight or size/control mean body or relative organ weight or size. Thus indexes close to 1.00 (i.e., 0.80 to 1.20) signified that the mean experimental group weight and the respective weight of littermate controls were similar and probably did not differ significantly.[6,11] Indexes less than about 0.75 indicated substantial depression of body or organ weight in comparison with controls, whereas indexes greater than 1.25 reflected conspicuous organ enlargement relative to controls. It is important for controls to be littermates because there is considerable variation in these values between litters and much less within any given litter. In certain strain combinations, the incidence of runt disease appears to be significantly lower in small litters than in large litters.[12]

Results

Quantitative Indexes of Reaction as a Function of Time

Indexes of graft-versus-host reaction at 1 to 16 days after injection of 2.4×10^6 adult C57BL/6 spleen cells into A/J newborns are detailed

in Table I and Text-figure 1. The whole body weight indexes revealed little or no inhibition of weight gain in experimental animals relative to their control littermates over this entire early period. However, significant spleen and lymph node enlargement associated with depression of thymic weight was evident in experimental neonates as early as 1 day after injection. This same interrelationship was even more striking after 2 days. Although profound thymic weight loss to about half the control value was found after 4 days, the spleen and lymph node indexes were essentially normal at this time, suggesting that excessive cell pro-



TEXT-FIG. 1. Indexes of graft-versus-host reaction at 1 to 16 days after injection of adult C57BL/6 spleen cells or small blood lymphocytes into A/J newborns.

liferation in these tissues had been temporarily curtailed. At 7 and 10 days, however, conspicuous enlargement of both spleen and nodes was once again evident, while the thymus index remained depressed. The experimental thymus and lymph node sizes returned to control levels at 13 days, but moderate splenomegaly persisted. After 16 days, which is within the range of median survival times for this strain combination,[6] the greatest thymic atrophy was observed in conjunction with maximal splenomegaly. Nevertheless, the lymph node index remained normal at this time.

Comparable data including indexes of graft-versus-host reactions at 1 to 16 days after injection of 3.2×10^6 adult C57BL/6 small blood lymphocytes into A/J newborns are summarized in Table II and Text-figure 1. The weight-size changes in host lymphoid tissues following

TABLE I

INDEXES OF GRAFT-VERSUS-HOST REACTION AT 1 TO 16 DAYS AFTER INJECTION OF 2.4×10^6 ADULT C57BL/6 SPLEEN CELLS INTO A/J NEWBORNS

Host age (days)*	E or C†	Mean body wt. (gm.)	Whole body index‡	Mean spleen wt. (gm./100 gm. body wt.)	Spleen index‡	Mean thymus wt. (gm./100 gm. body wt.)	Thymus index‡	Mean node area, largest cervical node (arbitrary units)	Node index‡
1	E	1.604	0.92	0.355	1.52	0.243	0.84	0.83	1.46
	C	1.745		0.233		0.289		0.57	
2	E	1.776	0.96	0.324	1.49	0.294	0.80	0.75	1.87
	C	1.840		0.218		0.386		0.40	
4	E	3.271	1.17	0.584	1.11	0.234	0.58	1.85	0.93
	C	2.785		0.527		0.402		2.00	
7	E	4.207	0.97	1.313	2.07	0.323	0.71	4.50	2.25
	C	4.339		0.635		0.451		2.00	
10	E	5.598	0.97	1.425	2.25	0.277	0.45	7.00	2.00
	C	5.756		0.634		0.616		3.50	
13	E	8.268	1.02	1.085	1.37	0.502	0.95	9.00	0.92
	C	8.095		0.790		0.530		9.80	
16	E	8.167	0.94	1.355	2.33	0.817	0.38	9.65	1.07
	C	8.679		0.581		0.490		9.00	

* Two experimental neonates and two littermate controls (no injections) were assayed at random on each day indicated.

† E: experimental animals; C: littermate controls.

‡ Index = Experimental mean body or relative organ weight or size/Control mean body or relative organ weight or size. Indexes less than 0.75 indicate substantial depression of body or organ weight in comparison with controls, whereas indexes greater than 1.25 reflect conspicuous organ enlargement relative to controls (cf. Hildemann *et al.*[6]).

TABLE II

INDEXES OF GRAFT-VERSUS-HOST REACTION AT 1 TO 16 DAYS AFTER INJECTION OF 3.2×10^6 ADULT C57BL/6 SMALL BLOOD LYMPHOCYTES INTO A/J NEWBORNS

Host age (days)*	E or C†	Mean body wt. (gm.)	Whole body index‡	Mean spleen wt. (gm./100 gm. body wt.)	Spleen index‡	Mean thymus wt. (gm./100 gm. body wt.)	Thymus index‡	Mean node area, largest cervical node (arbitrary units)	Node index‡
1	E	1.550	0.89	0.215	0.69	0.210	0.61	0.43	0.76
	C	1.752		0.313		0.342		0.57	
2	E	2.156	0.96	0.562	1.20	0.457	1.14	1.68	2.80
	C	2.244		0.469		0.401		0.60	
4	E	2.405	0.91	0.613	1.16	0.343	0.89	2.05	1.08
	C	2.640		0.528		0.387		1.90	
7	E	4.064	0.92	1.086	1.39	0.432	1.00	8.00	1.71
	C	4.400		0.784		0.432		4.68	
10	E	5.614	0.94	1.478	1.97	0.398	0.72	12.40	2.58
	C	5.952		0.752		0.552		4.80	
13	E	7.038	0.81	0.953	1.80	0.450	0.84	11.75	1.26
	C	8.684		0.530		0.533		9.35	
16	E	7.198	0.73	1.485	2.73	0.311	0.57	8.35	0.79
	C	9.874		0.544		0.541		10.50	

* Two experimental neonates and two littermate controls (no injections) were assayed on each day indicated.

† E: experimental animals; C: littermate controls.

‡ Index = Experimental mean body or relative organ weight or size/Control mean body or relative organ weight or size. Indexes less than 0.75 indicate substantial depression of body or organ weight in comparison with controls, whereas indexes greater than 1.25 reflect conspicuous organ enlargement relative to controls (cf. Hildemann *et al.*[9]).

injection of purified lymphocytes differed in some respects from those obtained after inoculation of the mixed population of spleen cells although the over-all directions of change were quite similar (Text-fig. 1). The experimental groups showed essentially normal weight gains at 1 to 13 days of age, but at 13 to 16 days conspicuous runting was evident (Table II). Spleen, thymus and node indexes were all depressed 1 day after inoculation. Although nearly normal thymus and spleen weights were found after 2 days, substantial lymph node enlargement was evident. Slight thymic atrophy was observed at 4 days, while spleen and node indexes were not significantly elevated at this time. After 7 days, experimental and control thymic weights were identical; both spleen and node indexes revealed substantial hypertrophy of these tissues in the experimental mice. By 10 days, splenomegaly and striking lymph node enlargement were found in association with thymic atrophy in the experimental group. With increasingly severe runt disease at 13 and 16 days, thymic atrophy and splenomegaly remained pronounced; the lymph nodes were transformed from an enlarged to an atrophic condition. It should be noted that the cervical nodes on which measurements are given were indicative of the condition of lymph nodes in general. In other words, there was no apparent disparity in the relative sizes of lymph nodes in particular mice observed at a given time.

Histologic Changes

The microscopic alterations were largely confined to the lymphoid system. The final morphologic appearance was similar or identical in mice given "spleen cell" as compared to those receiving "peripheral lymphocyte" injections, but some differences were evident during the early period preceding clinical manifestations of runt disease. Following allogeneic spleen cell injection, the neonatal host spleens displayed some increase in hematopoiesis after 1 and 2 days, but this had subsided by the seventh day. Thymic changes were first noted in 2-day-old hosts. These consisted of moderate cortical thinning over the superior pole, increased numbers of mitotic figures and reticuloendothelial cell proliferation in the thymic medulla. Similar thymic changes were also present on the fourth day. Despite very early lymph node enlargement, no distinct microscopic lesions were discernible until the fourth day. At this time a slight increase in cellularity and reticuloendothelial cell proliferation were seen, despite the decrease in total area indicated by nodal indexes (Text-fig. 1).

In neonates injected with small lymphocytes, no splenic or thymic microscopic alterations were seen through and including 4 days. Lymph node changes were more marked, however, than in animals that received

spleen cells. By the second day, an increase in the cellularity of nodes and reticuloendothelial proliferation were evident. These features were quite distinct by the fourth day, again on this day being paradoxically accompanied by a decrease in total area. From the seventh day on, changes in lymphoid tissues of recipients of spleen and small blood lymphocytes were nearly parallel. Splenic changes generally tended to be more severe in "spleen cell"-injected mice, whereas lymph node changes were consistently more severe in neonatal recipients of purified lymphocytes.

By the seventh day there was distinct reticuloendothelial proliferation along the fibrous septums of the spleen and, indeed, throughout the entire white pulp. The follicular and germinal-center pattern was obscured. The reticuloendothelial cells were medium to large size, with a single oval, occasionally folded nucleus and a moderate amount of cytoplasm; they appeared to be differentiating towards histiocytoid or monocytoid cells. There was also scattered fatty infiltration in the spleen. These splenic changes progressed steadily as visualized on the tenth, 13th and 16th days post-injection, until by the 16th and final day of the present study, 60 to 75 per cent of the spleen was composed of proliferating RE cells of the type described above.

Thymic changes during the seventh to 16th days consisted of progressive cortical thinning over the superior pole and accentuation of the medulla (Figs. 1 and 2). The medulla in addition exhibited the accumulation of considerable numbers of fairly well differentiated acidophilic histiocytoid cells.

Progressive lymph node changes were quite striking. Beginning on the seventh day there was a noticeable blurring and loss of corticomedullary distinction accompanied by RE cell proliferation and gradual transformation or replacement (nearly complete by the 13th day) of almost the entire lymphocyte population by acidophilic histiocytoid cells (Figs. 3 and 4). There was also a fine diffuse fibroplasia and a tendency toward a whorling cell pattern, to the extent that an actual epithelioid cell transformation was suggested.

In addition to the alterations in lymphoid tissues, we noted irregular RE cell proliferation in the liver. This was first seen on the tenth day, and was rather prominent by the 16th day in both groups of experimental animals. Occasional interstitial RE cell proliferation in the lungs was discernible by the 13th to 16th days. Detailed examination of the heart, kidney, adrenals, pancreas, brain, muscle, gastrointestinal tract, genital organs and joints revealed no convincing differences between experimental and control groups. In particular, no connective tissue changes comparable to those seen in so-called "collagen diseases" were encountered.

Discussion

The concept of an early "immunologic thymectomy" as a primary cause of acute transplantation disease was supported by the interdependent changes in lymphoid tissues of neonatal hosts observed in the present experiments. Thus, prior to the onset of clinical manifestations, the weight of the thymus declined in association with spleen and lymph node enlargement. In view of the diverse manifestations of runt disease, however, one may well question the specificity and consequences of the suggested relationship in the light of recent findings. Considering the known variability in the time course of transplantation disease,[6] the quantitative differences in the indexes of graft-host reaction at successive time intervals might be questioned because of the small number of neonates sampled at each time interval. Nevertheless, a consistent pattern of early thymic atrophy in conjunction with hypertrophy of spleen and lymph nodes emerged with respect to donor inoculums of both spleen cells and purified small lymphocytes. Several lines of recent evidence have a direct bearing on this reciprocal lymphoid weight relationship.

Axelrad and van der Gaag[13] determined that the thymus of normal C_3Hf/Bi mice grows rapidly to about 30 times its original size during the first 2 weeks after birth. The maximum number of thymic cells per lobe in young mice was reached at around 15 days of age. From our own present data, it is apparent that the thymus of the normal A/J mouse increases 8 to 10 times in weight from 1 to 16 days of age, while the spleen increases about 12-fold in weight during this same period. In contrast, A/J neonates developing acute transplantation disease showed only a 4- to 6-fold increase in thymic weights coupled with a profound 20- to 32-fold increase in spleen weights between 1 and 16 days of age. Thus the normal growth of thymus and spleen was altered in opposite directions as a consequence of graft-versus-host reactions.

It might be argued that these lymphoid tissue changes were merely a nonspecific result of "stress." Quite recently, Schlesinger and Mark[14] found that a single injection of hydrocortisone acetate into neonatal mice induced a wasting syndrome similar to runt disease and the post-thymectomy syndrome. Although thymic atrophy was apparent within 1 day after injection of hydrocortisone, they found marked reductions in the weights of both thymus and spleen. While it is clear that general lymphoid tissue atrophy is produced by excessive doses of adrenal corticosteroids, the splenomegaly and lymph node hypertrophy found in transplantation disease appear to be distinctive. Neonatal runting as such can, of course, be produced by a variety of deleterious agents. Host susceptibility to runting induced by polyoma virus has even been shown

to have a clear-cut genetic basis.[15] Similarly, splenomegaly alone is often associated with infections, notably so in the case of Friend leukemia virus infection in susceptible mouse genotypes.[16] We are not aware, however, of any particular infections or other host insults that mimic the spectrum of pathologic changes in lymphoid tissues found in early, acute transplantation disease.

If immunologically competent donor lymphocytes directly or indirectly mediate a functional thymectomy in neonatal hosts of different H-2 genotypes, the localization and fate of the injected cells must be positively correlated with the early pathologic changes. A recent study by Gowans and Knight[17] of the distribution of tritiated adenosine-labeled small lymphocytes injected into the blood of isogenic rats is revealing in this connection. The labeled lymphocytes "homed" rapidly and in large numbers into the lymph nodes, white pulp of the spleen and Peyer's patches of the intestine. Few such cells were found in other host tissues. Although no labeled small lymphocytes were detected in the thymus of adult recipients, such cells from adult donors did pass in small numbers into the deep thymic cortex of newborn hosts. Since this evidence is almost certainly applicable to the allogeneic situation as well, it is probable that the allogeneic host thymus is depleted in the process of restitution of rapid damage to spleen and lymph nodes by injected donor cells. Until more definitive evidence is available, the possibility of a direct immunologic attack on the neonatal host thymus must remain in doubt. The cellular or humoral role of the thymus in the development and maintenance of immunologic competence might be further clarified by determining whether isogenic thymic grafts in cell-impermeable diffusion chambers are capable of mitigating transplantation disease in otherwise vulnerable hosts.[18]

The magnitude of the lymphoid tissue weight changes in the present study, especially those up to and including the fourth day, are not easily explained in terms of histologic changes, for lesions were not always impressive during this early period. In the thymus the loss of lymphoid cells was evidently not sufficiently compensated by histiocytoid conversion to offset the gradual weight loss. In the spleen and lymph nodes, however, the histiocytoid transformation subsequent to the fourth day was so extensive and rapid as to offset the loss of lymphocytes, and indeed to lead to weight gains. Histologically, the thymus and lymph nodes appeared to change qualitatively in a similar manner for about 7 days after donor cell inoculation; i.e., both gradually accumulated large numbers of histiocytoid cells in the medulla. Thereafter, the nodes and the spleen in addition became progressively more committed to, or transformed by, such cells than the thymus. The decreasing weights of

the nodes by the 13th and 16th days indicated a developing involutional or atrophic change following an almost complete histiocytoid transformation. This stage had not yet been reached in the spleen by the termination of the study at 16 days. Progressive histiocytosis in the spleen and lymph nodes associated with a disappearance of lymphoid cells has been previously described by Gorer and Boyse,[19] among others, following injection of allogeneic spleen cells.

Diverse pathologic changes have been observed and described in association with transplantation disease in several species under certain conditions. Particular hematologic abnormalities produced in adult mice[20] and cutaneous lesions induced in adult rats[21] have been considered as models of similar human disease thought to have an autoimmune basis. In the present study involving strong H-2 differences that led to acute disease in neonatal hosts, no histologic evidence for processes resembling autoimmune phenomena were discerned. No connective tissue changes similar to those encountered in "collagen diseases" were seen in the heart, kidney, joints or elsewhere. Such changes may be more prevalent in adults and may depend upon more chronic disease.

Summary

Evidence of an early "immunologic thymectomy" as a primary cause of acute transplantation disease was supported by the inverse changes observed in lymphoid tissues of neonatal hosts in the present experiments. Substantial spleen and lymph node enlargement associated with depression of thymic weight was evident as early as 1 to 2 days after injection of adult C57BL/6 lymphoid cells into A/J newborns. This interrelationship characterized the early period of induction of transplantation disease 1 to 10 days following inoculation of both spleen cells and purified small blood lymphocytes.

Other recent evidence indicates that the particular lymphoid tissue changes observed are not merely nonspecific consequences of "stress" reactions, such as those mediated by adrenal corticosteroids. Following injection of immunologically competent lymphocytes, it is probable that the neonatal host thymus is depleted in the process of restitution of rapid damage to spleen and lymph nodes. A direct immunologic attack on the host thymus by infiltrating small lymphocytes may also be involved.

The progressive disappearance of lymphoid cells from thymus, spleen and lymph nodes was associated with a histiocytoid conversion of these tissues. Although this process appeared to be so extensive in spleen and nodes as to produce organ weight gains, it was insufficient to offset persistent weight loss in the thymus. The final histologic pattern was es-

sentially the same in mice given spleen cells as compared to those receiving peripheral lymphocytes, although some differences were apparent during the early period preceding clinical manifestations of runt disease. Splenic enlargement tended to be more severe in spleen cell-injected mice, whereas lymph node changes were consistently more severe in neonatal recipients of small blood lymphocytes.

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LEGENDS FOR FIGURES

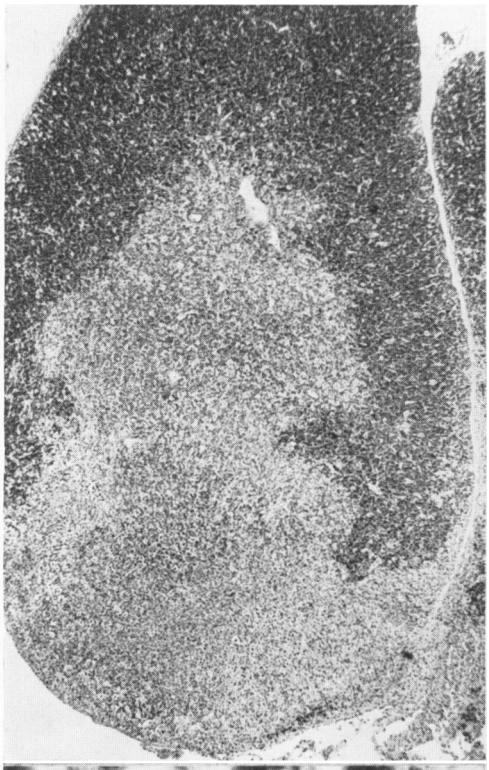
Photomicrographs were prepared from sections stained with hematoxylin and eosin.

FIG. 1. Thymus of 7-day-old mouse given spleen cell injections at birth. Enlarged medulla and cortical thinning, especially over the superior pole (at bottom in photograph) are apparent. × 80.

FIG. 2. Control thymus to illustrate normal architecture in 7-day-old mouse. × 80.

FIG. 3. A cervical lymph node, 13 days after an injection of lymphocytes. The normal lymphoid population is entirely replaced by proliferating histiocytoid cells. × 350.

FIG. 4. Cervical lymph node, 16 days after injection with spleen cells. The node is almost entirely replaced by histiocytoid cells, with some fibroplasia. × 120.



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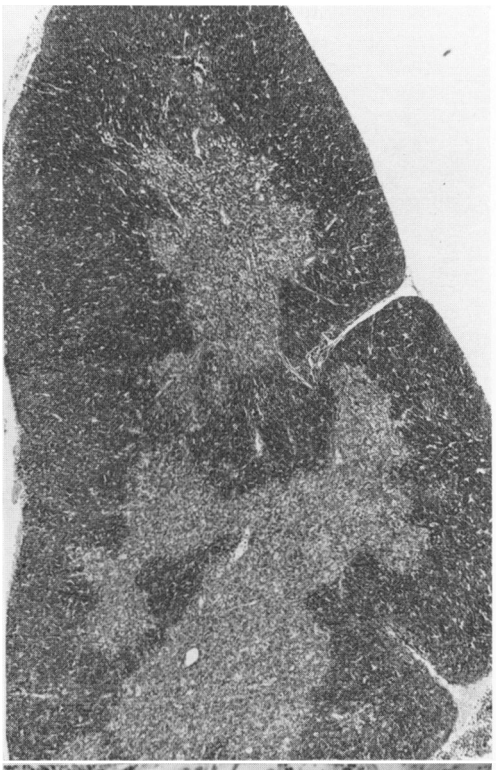

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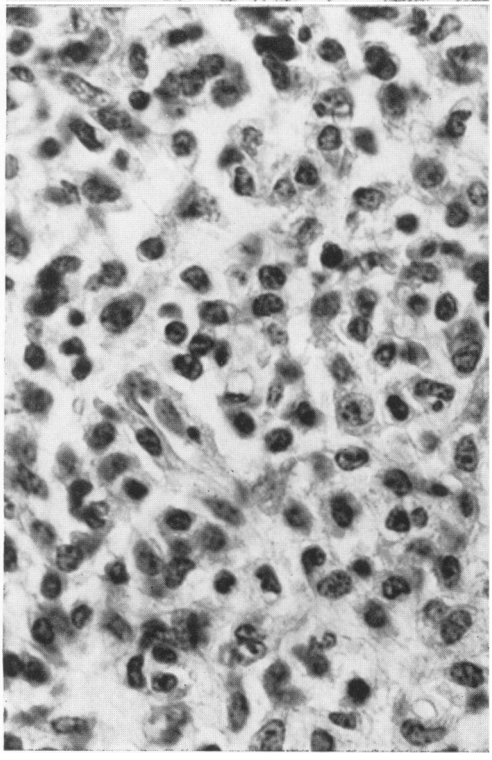

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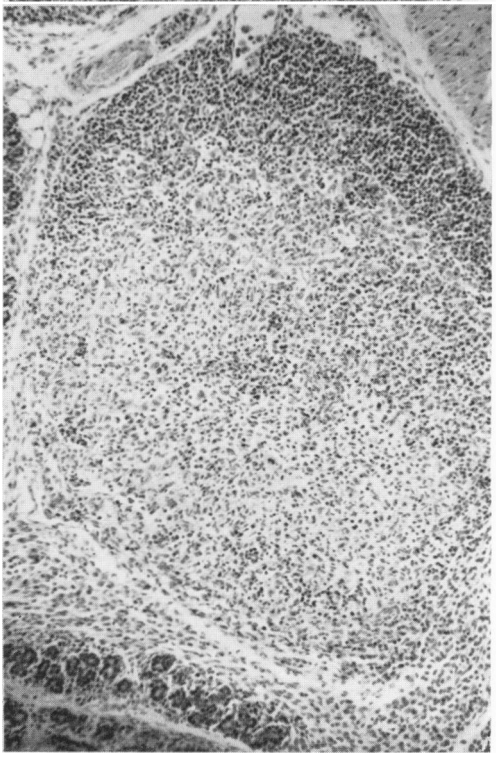

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