The Histological Changes in Immunologically Tolerant Lymphoid Tissue

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SUMMARY

The histological features of the regional lymph node draining a skin homograft have been examined in normal and tolerant recipients. The response of this node was morphologically identical in normal and specifically tolerant hosts, the most important feature being the appearance of medullary cords packed with intensely pyroninophilic cells. Furthermore, a similar response was observed in the regional lymph nodes of (DA×Lewis) F_1 hybrids bearing DA skin grafts of which they were "genetically tolerant". It was concluded that the failure of graft rejection in tolerant rats could not be attributed to an *absence* of reactivity to the grafts on the part of the lymphoid tissue of the host.

INTRODUCTION

Although functional modifications of lymphocytes have been extensively studied in animals that are immunologically tolerant of homografts, little attention has been paid to the morphological features of the lymphoid tissue of tolerant animals. In the current investigation lymph nodes draining skin grafts in tolerant rats have been examined histologically. It was hoped that some indication of the anatomical features of this lymphoid tissue might assist in the interpretation of its function. For example, if a tolerant animal fails to reject a graft because it is incapable of recognizing the graft as foreign, then one might expect its lymphoid tissue to be as quiescent as that which is draining an isograft.

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Alternatively, if homograft acceptance in tolerance resulted from *modification* of the response to a tissue which was still recognized as being different from self rather than the *absence* of a response due to non-recognition, then this might be reflected histologically in the activity of the local lymphoid tissue.

Argyris (1963) investigated tolerance of C3H mice for CBA mouse tissues. In this strain combination, tolerance is spontaneously lost after several months and chronic graft rejection ensues. Two months after grafting examination of the lymph node draining a CBA graft revealed an increase in the frequency of germinal centres in the cortex and of plasma cells in the medulla. This histological evidence of an immune response appearing in the axillary lymph nodes of mice bearing seemingly healthy grafts of two months' standing was interpreted as a stage in the rejection which was to occur spontaneously several months after grafting.

Voisin, Kinsky and Maillard (1968) reported that the lymphoid system, and especially the spleen, of highly tolerant mice was in a state of immune reactivity which resembled that of an immunized animal more closely than that of a normal, non-immunized animal.

The present experiments were performed in such a way as to exclude the possibility that any lymph node responses observed in tolerant rats were a prelude to graft rejection. Thus, each tolerant rat bore two homografts of identical skin. One graft, together with its local lymph node, was removed from the live rats for examination while the remaining skin graft was left *in situ* so that its fate could be followed. The histological response of graft-draining lymph nodes in tolerant recipients was compared with that of draining nodes in normal recipients of either isografts or homografts. In a further experiment lymph nodes draining skin grafts were examined histologically at the same time as the loss of tolerance that follows the receipt of normal (non-tolerant) lymphocytes. Finally, the response of the lymph nodes draining a semi-allogeneic graft was examined in "genetically tolerant" F_1 hybrid recipients.

MATERIALS AND METHODS

Rats used in these experiments were from the inbred DA strain and also (DA × Lewis) F_1 hybrids.

Immunological tolerance of DA rats for (DA × Lewis) F_1 hybrid tissues was induced by the intravenous injection of from 5×10^7 to 10^8 F_1 hybrid type bone marrow cells on the day of birth. Confirmation that tolerance had been achieved was obtained by grafting with F_1 hybrid skin in the

second month of life.

Sensitization of DA rats against (DA×Lewis) F_1 hybrid tissues was effected by the intraperitoneal injection of 2×10^8 F_1 hybrid spleen cells 1 week before the sensitized rats were to be grafted.

Operative procedures.

Skin grafts of 4 cm^2 in area, which were to be removed for histological examination, were placed on the right lateral thoracic wall under sterile conditions. At the time of graft excision, the homolateral superficial axillary lymph node, which is constantly a single node lying just lateral to the margin of the *Pectoralis major*, was also removed for examination. Lymph nodes lying more deeply in the axilla were not removed. In the case of tolerant rats (Groups (3) and (5)), skin grafts and nodes were removed from live rats. The rats in these two groups were maintained indefinitely following removal of one graft, so that the subsequent course of the remaining graft, originally placed on each rat to confirm that it was tolerant, could be followed. Thoracic duct cannulation was performed to obtain lymphocytes by Gowans' (1959) modification of the technique of Bollman, Cain and Grindlay (1948).

Histology.

Sections of all tissues were fixed in Carnoy's fluid, embedded in paraffin and stained with haematoxylin and eosin or with methyl green-pyronin.

RESULTS

Seven groups, each of 4 rats, were grafted with skin as described in Methods. At intervals of 3 days thereafter the freshly placed grafts, together with their regional lymph nodes, were removed for histological examination. The histological features of skin and lymph node sections will be described individually for each group. Details of lymph node weights and the frequency of pyroninophilic cells in imprints prepared from lymph nodes are presented at the end of this section.

1. Normal DA recipients of skin from normal DA donors.

Examination of tissues from the recipients in this group provided a 'control' for the healing in of a graft and the response of a draining lymph node in a host incapable of mounting an immunological response to the graft. The most characteristic feature of the transplanted skin on both the 3rd and 6th days after placement was dermal oedema. On the 6th day some infiltration of polymorphonuclear leucocytes and macrophages into the dermis had occurred. By the 9th day the oedema had lessened

but macrophages containing hemosiderin were prominent in the dermis. After 12 days, as fur reappeared on the graft, the dermis contained numerous hair follicles and other epidermal appendages (Fig. 1(a)).

The appearance of the regional lymph node differed only marginally from that of an unstimulated node on the 3rd day. At this time, and also at 6 days, a small number of primary nodules and germinal centres were present in the cortex. By the 9th and 12th days germinal centres had become even less prominent (Fig. 2(a)). Although isolated pyroninophilic cells were present in the medulla, at no time was there any suggestion of the formation of organized cords of such cells.

As skin donor and recipient were isogeneic, these minimal changes observed in the regional lymph node were considered to represent the "background" response occurring in the absence of stimulation by histoincompatibility and attributable to the grafting procedure itself. Accordingly, the lymph node responses observed in the following 6-groups of rats have been compared with the response of this first group.

2. Normal DA recipients of skin from normal (DA×Lewis)F_1 hybrid donors.

This combination of donor and recipient was selected to provide an example of the histological features of graft rejection by a non-sensitized host for comparison with the lymph nodes of other groups. On the 3rd and 6th days after their placement such skin grafts resembled the isografts of Group (1) showing oedema and macrophage infiltration. However, by the 9th day homografts differed markedly from isografts. Although dermal oedema had decreased, there was a notable lack of any epidermal appendages and very little of the epidermis itself remained intact. The graft bed was heavily infiltrated with mononuclear leucocytes. By the 12th day the graft was necrotic, and viable epidermis and epidermal appendages were both absent (Fig. 1(b)).

Apart from the presence of a few germinal centres, the axillary node appeared comparatively unchanged on the 3rd day. There was little increase in the number of germinal centres after 6 days, but the medulla contained a number of well-organized cords of large, intensely pyroninophilic cells. These cords became progressively more marked on the 9th and 12th days (Fig. 2(b)). Dilated blood capillaries became evident in the cords by the 12th day. Germinal centres were not prominent in the cortex. The histological changes observed in the lymph nodes of this group were used as an example of the response of the normal lymphoid system to foreign tissue for comparison with later groups.

3. (DA × Lewis) F_1 hybrid-tolerant DA recipients of skin from normal (DA × Lewis) F_1 hybrid donors.

The recipients in this group were DA rats in which immunological tolerance of (DA × Lewis) F_1 hybrid tissues had been induced by means of the neonatal injection of bone marrow cells of this type and confirmed by the prolonged survival of similar skin grafts placed in adult life. Fresh grafts of (DA × Lewis) F_1 hybrid skin were placed and were then removed, together with their draining lymph nodes, at intervals thereafter. The long-standing graft on each rat was allowed to remain in place. The lymph nodes from this group were examined to indicate the response of the lymphoid system of tolerant animals to tolerated tissues. After biopsy of the fresh graft and its node the prolonged retention of the original skin graft provided confirmation that the host had remained tolerant.

On the 3rd and 6th days after grafting the transplanted skin showed marked oedema of the dermis together with some infiltration of macrophages and polymorphonuclear leucocytes into the graft bed. By the 9th day this oedema was subsiding and regenerating epidermal appendages were prominent. This trend continued with the graft appearing healthy and indistinguishable from the isografts in Group (1) by the 12th day (Fig. 1(c)). Thirteen months following the removal of the fresh skin graft and its draining axillary lymph node the original skin grafts remained intact and healthy in all of these tolerant rats.

The response of a lymph node in a tolerant host to a graft of tissue from the appropriate, tolerated donor was compared with the response of the lymph nodes of normal rats to isografts and homografts. In contrast to the skin grafts which resembled isografts (Group (1)), the histological response of the local lymphoid tissue was very similar to that of a node draining a homograft (Group (2)). Thus, by the 6th day after placement of the fresh graft there were numerous pyroninophilic cells in the medulla of the local lymph node. On the 9th day the medullary cords were packed with pyroninophils and some germinal centres were evident in the cortex. These features were even more striking by the 12th day by which time the cords of pyroninophils were very well organized (Fig. 2(c)) and contained numerous dilated blood vessels (Fig. 3). Germinal centres had become more conspicuous and contained large numbers of pyroninophils. Thus, although the fresh skin graft had been accepted by the tolerant host as successfully as the long-standing graft, the draining lymph node had responded in a manner indistinguishable from that of a node involved in homograft rejection.

4. Specifically sensitized DA recipients of skin from normal (DA×Lewis) F_1 hybrids.

DA rats, which had been injected with (DA×Lewis) F_1 spleen cells previously, as described in Methods, were grafted with skin from normal (DA×Lewis) F_1 hybrid rats in order to compare the response of lymphoid tissue of a sensitized host during graft rejection with the response of the nodes in the three preceding groups. Examination of skin grafts at various times after placement failed to reveal any features not present during graft rejection by a non-sensitized host (Fig. 1(d)), although necrosis of the graft occurred slightly earlier. As regards the draining lymph nodes, no distinction could be made from the nodes examined in Groups (2) and (3) (Fig. 2(d)).

5. DA rats tolerant of (DA×Lewis) F_1 hybrid tissues simultaneously grafted with (DA×Lewis) F_1 hybrid skin and injected with lymphocytes from normal DA rats.

Comparison of the lymph nodes of Groups (2) and (3) has indicated that the histological response of lymphoid tissue to a homograft is similar, irrespective of whether the recipient is normal or specifically tolerant of the graft. However, whereas the skin graft evoking this response is rejected in the former situation, it survives and heals in the latter. If a tolerant rat is injected intravenously with sufficient lymphocytes from a *normal*, isogeneic donor, the tolerant state is abrogated as indicated by graft rejection. The present group of experiments examined the response of lymphoid tissue draining a skin graft in such a situation. DA rats, tolerant of (DA×Lewis) F_1 hybrid tissues, were grafted with skin of this type, as was Group (3), and were simultaneously injected intravenously with 4×10^8 thoracic duct lymphocytes from normal (nontolerant) DA donors. The 4 rats in this group were examined on the 6th, 9th, 12th and 15th days after lymphocyte injection to ensure that the lymph node response associated with the episode of graft rejection was witnessed.

In this situation, the fresh graft appeared healthy and the oedema was resolving on the 9th day. However, by the 12th day partial breakdown of the graft had occurred, and at 15 days there were large areas of necrosis. The remainder of the graft had again become oedematous and infiltrated with mononuclear cells. The most notable feature of the axillary lymph nodes was their weight which was from two to three times greater than that of the nodes in any of the preceding groups at similar times after grafting. Histologically, pyroninophilic cells had accumulated in the medulla of the axillary lymph node by the 6th day. On the 9th day there were numerous, well-organized medullary cords packed with

pyroninophils and containing dilated blood vessels. Germinal centres containing pyroninophils were frequent in the cortex. These germinal centres had become profuse by the 12th day while the medullary cords of pyroninophils extended out through cortical sinuses to the peripheral sinus (Fig. 4(b)). Fifteen days after grafting and the injection of lymphocytes most of the sinuses had been obliterated by expansion of the medullary cords of pyroninophils. These cells also filled the peripheral sinus (Fig. 4(b)). Few germinal centres remained.

6. Normal (DA × Lewis) F_1 hybrid rats grafted with skin from normal DA rats.

In view of the florid response of the local lymph node to a homograft in a rat in which specific homograft tolerance has been induced, the response of lymph nodes of rats manifesting a naturally occurring tolerance to semiallogeneic tissues was examined. Normal (DA × Lewis) F_1 hybrid rats were grafted with skin from normal DA donors.

Such a graft was very oedematous 6 days after transfer. However, by the 12th day the DA skin graft appeared healthy, with numerous hair follicles in the process of regeneration. Despite this ready acceptance and healing of the graft, the local lymph node was as active as nodes involved in homograft rejection (Group 2). Thus, by 9 days medullary cords (Fig. 4(c)) and germinal centres, both packed with pyroninophils, were prominent features. Pyroninophilic cells floating free in sinuses were conspicuous after 12 days.

7. Normal (DA × Lewis) F_1 hybrid rats grafted with skin from DA rats tolerant of (DA × Lewis) F_1 hybrid tissues.

It is possible, although unlikely, that the marked response of the lymphoid tissue of the F_1 hybrid recipients of Group (6) could have been a consequence of a graft-versus-host reaction mounted by "passenger lymphocytes" of parental type in the DA skin graft. To circumvent this type of reaction, the F_1 hybrid recipients in the present group were grafted with skin from DA rats *tolerant of (DA × Lewis) F_1 hybrid tissues.* Lymphocytes from such tolerant DA donors are unable to produce graft-versus-host reactions in F_1 hybrid recipients.

As in the preceding groups, grafts had healed in after 12 days. Examination of the local lymph node in this group disclosed a reaction similar to that seen during homograft rejection. By the 12th day there were prominent medullary cords packed with pyroninophils (Fig. 4(d)) and similar cells were plentiful in the germinal centres. Pyroninophils were not found floating free in the sinuses as in the preceding experiment, but, apart from this, the nodes were similar.

The superficial axillary lymph nodes from the rats in the preceding 7 groups were weighed, and an imprint was prepared from the cut surface of each before the tissue was fixed. The results of these examinations are summarized in Table 1. The maximum node weight observed in each group is recorded. The time at which maximum enlargement occurred varied from 6 to 15 days after grafting in different groups. The lymph node weights do not correspond well in all groups with the vigour of the node response indicated by histological examination of the nodes. In particular, the low weights recorded in nodes draining homografts in the presensitized (Group 4) and tolerant (Group 3) recipients are surprizing in view of the florid response observed histologically in these nodes. The deep axillary nodes, the weight of which was not recorded, may have been proportionally larger in these rats. If the significant histological finding in these two groups of experiments had been the absence of reactivity in the nodes examined, the possibility that the weights of these nodes had not been influenced on account of the placing of homografts would have to be considered. However, in view of the marked histological features of these nodes, this would not be a satisfactory explanation for their size. It may be relevant that some of the homograft-draining nodes examined by Scothorne and McGregor (1955) in their study were not significantly larger than nodes draining autografts.

Imprints were prepared from the cut surface of the superficial axillary nodes of the various groups and stained with methyl green and pyronin. It is apparent that any correlation between the frequency of

Table 1. Features of lymph nodes draining skin grafts: weight and pyroninophil frequency in imprints

Skin graft transfer	Peak weight of superficial axillary node (mg)*	Peak frequency of pyroninophilic cells in imprints ($\times 10^{-3}$)†
(i) DA→DA	30	10
(ii) F_1 →DA	42	21
(iii) F_1 →Tolerant DA	28	21
(iv) F_1 →Sensitized DA	34	24
(v) F_1 +DA T.D.L.→Tolerant DA	78	25.5
(vi) DA→F_1	63	14
(vii) Tolerant DA→F_1	57	10

T.D.L.=Thoracic duct lymphocytes.
F_1=(DA×Lewis)F_1 hybrid.
*Mean weight of superficial axillary node in 8 ungrafted DA rats 23 ± 1.5 mg
†Mean frequency of pyroninophilic cells in imprints from superficial axillary lymph nodes of ungrafted DA rats—$4.5/10^3$.

pyroninophilic cells in sections and imprints prepared from a node will be determined by the ease with which these cells detach from the cut surface of the node. With this qualification, there is a reasonable concordance between the occurrence of prominent medullary cords of pyroninophilic cells in sections and the presence of an increased number of pyroninophilic cells in smears, with the exception of Groups 6 and 7 (Table 1). In these experiments the increased number of pyroninophilic cells which might have been predicted from the sections was not observed in smears.

DISCUSSION

The response of the axillary lymph node to specifically tolerated skin grafts has been examined. When the lymph node response to an isograft was adopted as a "baseline" indication of changes attributable to non-immunological effects of grafting, the most typical histological features of a homograft response were the presence of large numbers of pyroninophilic cells in the medullary cords, and, to a lesser extent, the appearance of germinal centres in the cortex. The regional lymph nodes draining a healing homograft in a tolerant animal were indistinguishable from those draining homografts in the course of rejection by normal, non-tolerant recipients. The lymph node response of an animal in which tolerance was being abrogated with normal isogeneic lymphocytes was similar to, but more florid than, that seen in a homografted normal rat. In a situation of "genetic tolerance", the regional lymph node draining a healing, semi-allogeneic graft was as reactive as a regional node in an animal rejecting a homograft. A close correlation was not obtained, in all groups, between the intensity of nodal response as indicated by examination of lymph node sections, imprints and weights. However, the features evident in sections were considered to be sufficiently marked to justify discussion on their own.

An increased frequency of germinal centres in the cortex and of plasma cells in the medulla was noted in the regional lymph nodes of C3H mice, tolerant of CBA tissues, *two months* after skin grafting (Argyris, 1963). As these changes did not become apparent until this interval after grafting, and as tolerance is spontaneously lost in this strain combination, these lymph node responses were attributed to the increasing severity of a host-versus-graft reaction which was to culminate in graft rejection.

Group (3) of the present experiments, in which DA rats tolerant of (DA$\times$Lewis) F_1 hybrid tissues were grafted with F_1 hybrid skin, differ from the experiments of Argyris in two features. In the first place, the

response described in the nodes occurred during the *2 weeks* after grafting. A reaction as marked as that observed to accompany homograft rejection developed in the lymph nodes of grafted, tolerant rats during this period. The second difference occurred in the subsequent fate of the skin grafts in the two investigations. Whereas Argyris (1963) found that the C3H mice were beginning to lose tolerance at the time of observation, 2 months after grafting, the DA rats in the current experiment remained completely tolerant. As the hosts were not killed at the time of axillary node examination, and as only one of the two skin grafts on each rat was removed, it was possible to follow the fate of the remaining graft on each of the tolerant recipients. These grafts have remained intact for longer than 13 months after lymph node biopsy at the time of writing. There is no possibility that the lymph node responses observed represented loss of tolerance.

Voisin and his colleagues (1968) interpreted the increased immune reactivity apparent throughout the lymphoid system of tolerant mice as indicating that immunological tolerance to living cells entails an active immunological reaction rather than a state of primary immune paralysis. Their histological examination was based on methyl green pyronin staining and immunofluorescence of lymph node and splenic imprints. The present investigation differs from that of Voisin *et al.* (1968) in that examination was specifically directed to the lymph node draining a freshly applied homograft rather than to the lymphoid system in general. The two investigations lead to a common conclusion, namely, that tolerance is not a state of primary non-reactivity.

It is difficult to reconcile the highly reactive state of the lymphoid tissue draining a tolerated homograft with any explanation of tolerance based on inability to recognize such a graft as foreign. If the morphological appearance of a lymph node bears any relation to its immunological activity, then it would be justifiable to infer that the lymph nodes of the DA rats in the Groups (2) (normal) and (3) (tolerant) were both reacting in recognition to a homograft in distinction to the regional nodes draining an isograft (Group (1)). This inference can be reconciled with the differing fates of the grafts in Groups (2) (rejection) and (3) (acceptance) if the modification of responsiveness in the tolerant animal is conceived of as an *alteration of the response* to a homograft which can still be recognized as foreign, rather than an *inability to recognize* the graft as foreign. As an alternative explanation, it could be postulated that the graft-bearing rats were not tolerant of all antigenic determinants on the graft. The histological response of the host's lymph node would then be attributed to a

reaction to non-tolerated antigens which, as a result of the nature of these antigens, did not lead to graft rejection. It is not possible to exclude this objection experimentally. We consider it improbable.

The histological features of lymph nodes during the *abrogation* of tolerance by transferred normal lymphocytes were similar to those seen during homograft rejection or the acceptance of grafts by tolerant hosts. The greater enlargement of the lymph nodes and their more florid morphological changes during the abrogation of tolerance may reflect an attack by the transferred normal DA lymphocytes on (DA×Lewis) F_1 hybrid lymphocytes in the chimaeric lymph node.

The response of the regional nodes of (DA×Lewis) F_1 hybrid rats to grafts of DA skin closely resembled the lymph node response of homografted rats and was completely different from the response to isografts. The possibility that the response of the axillary node in this situation represented a graft-versus-host reaction mounted by "passenger" lymphocytes transferred with the graft was excluded when skin grafts from DA rats *tolerant* of (DA×Lewis) F_1 hybrid tissues were found to evoke similar responses. The relationship of the "genetic tolerance" of F_1 hybrid rats for parental tissues to the neonatally induced form of tolerance is as uncertain, experimentally, as is the relation of the latter to "self tolerance". It has been suggested that F_1 hybrids are able to recognize and react against 'recognition units' on parental strain lymphoid cells (Ramseier and Lindemann, 1969). Conceivably, such a reaction could produce the response observed in these experiments. Of considerable interest is a report that parental strain skin grafts *fail* to survive indefinitely on F_1 hybrid recipients (Eichwald, Wetzel and Lustgraaf, 1965). These observations are in conflict with the accepted concept that F_1 hybrid recipients accept parental strain grafts as isografts. Certainly, the response of the lymph nodes of F_1 hybrid rats grafted with parental skin suggests that structural changes in lymphoid tissue correlate better with the occurrence of confrontation between dissimilar cells than with concurrent acceptance or rejection of the grafts.

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EXPLANATION OF FIGURES

Fig. 1. Haematoxylin and eosin stained sections of skin grafts removed 12 days after placement. Magnification × 15.

(a) Skin from normal DA rat grafted on normal DA recipient.

(b) Skin from normal (DA × Lewis) F_1 hybrid rat grafted on normal DA recipient.

(c) Skin from normal (DA × Lewis) F_1 hybrid rat grafted on DA recipient tolerant of (DA × Lewis) F_1 hybrid tissues.

(d) Skin from normal (DA × Lewis) F_1 hybrid rat grafted on DA recipient which had been sensitized 7 days previously by the injection of spleen cells from a (DA × Lewis) F_1 hybrid rat.

Fig. 2. Methyl green-pyronin stained sections of axillary lymph nodes removed 12 days after placement of skin grafts in the area drained by this node. Magnification × 33.

(a) Node from normal DA recipient of graft from normal DA rat (regional node of graft in Fig 1(a)). Note absence of medullary cords.

(b) Node from normal DA recipient of graft from normal (DA × Lewis) F_1 hybrid rat (regional node of graft in Fig. 1(b)). Note well developed medullary cords.

(c) Node from (DA × Lewis) F_1 hybrid-tolerant DA recipient of graft from normal (DA × Lewis) F_1 hybrid rat (regional node of graft in Fig. 1(c)). Note prominent pattern of medullary cords.

(d) Node from DA rat, pre-sensitized against (DA × Lewis) F_1 tissues, after grafting with skin from normal (DA × Lewis) F_1 hybrid donor (regional node of graft in Fig. 1(d)). Note development of medullary cords.

Fig. 3. Methyl green-pyronin stained sections of medulla of axillary node removed from (DA × Lewis) F_1 hrbrid-tolerant DA rat 12 days after placement of (DA × Lewis) F_1 hybrid skin graft in area drained by this node. (Higher magnification of node shown in Fig. 2(c), draining graft in Fig. 1(c)).

(a) Magnification 430 ×. Note organization of medullary cords and dilated blood vessels.

(b) Magnification 1,075 ×. Note uniformity of cells in cords. All were intensely pyroninophilic.

Fig. 4. Methyl green-pyronin stained sections of axillary nodes removed after placement of a skin graft in the area drained by this node. In the case of (a), (c) and (d) the nodes were removed 12 days after grafting, while the node in (b) was removed 15 days after grafting. Magnification 33 ×.

(a) Node from (DA × Lewis) F_1 hybrid-tolerant DA recipient of graft from normal (DA × Lewis) F_1 hybrid rat. 4×10^8 thoracic duct lymphocytes from a normal (nontolerant) DA rat were injected intravenously into the recipient at the time of skin grafting. Note extensive medullary cords.

(b) Node from recipient similar to that in (a). Note obliteration of sinuses by expansion by medullary cords and packing of cells in peripheral sinus of node.

(c) Node from normal (DA × Lewis) F_1 hybrid rat in receipt of skin graft from normal DA donor. Note profuse medullary cords.

(d) Node from normal (DA × Lewis) F_1 hybrid rat in receipt of skin graft from DA rat which was tolerant of (DA × Lewis) F_1 hybrid tissues. Note extensive medullary cords.

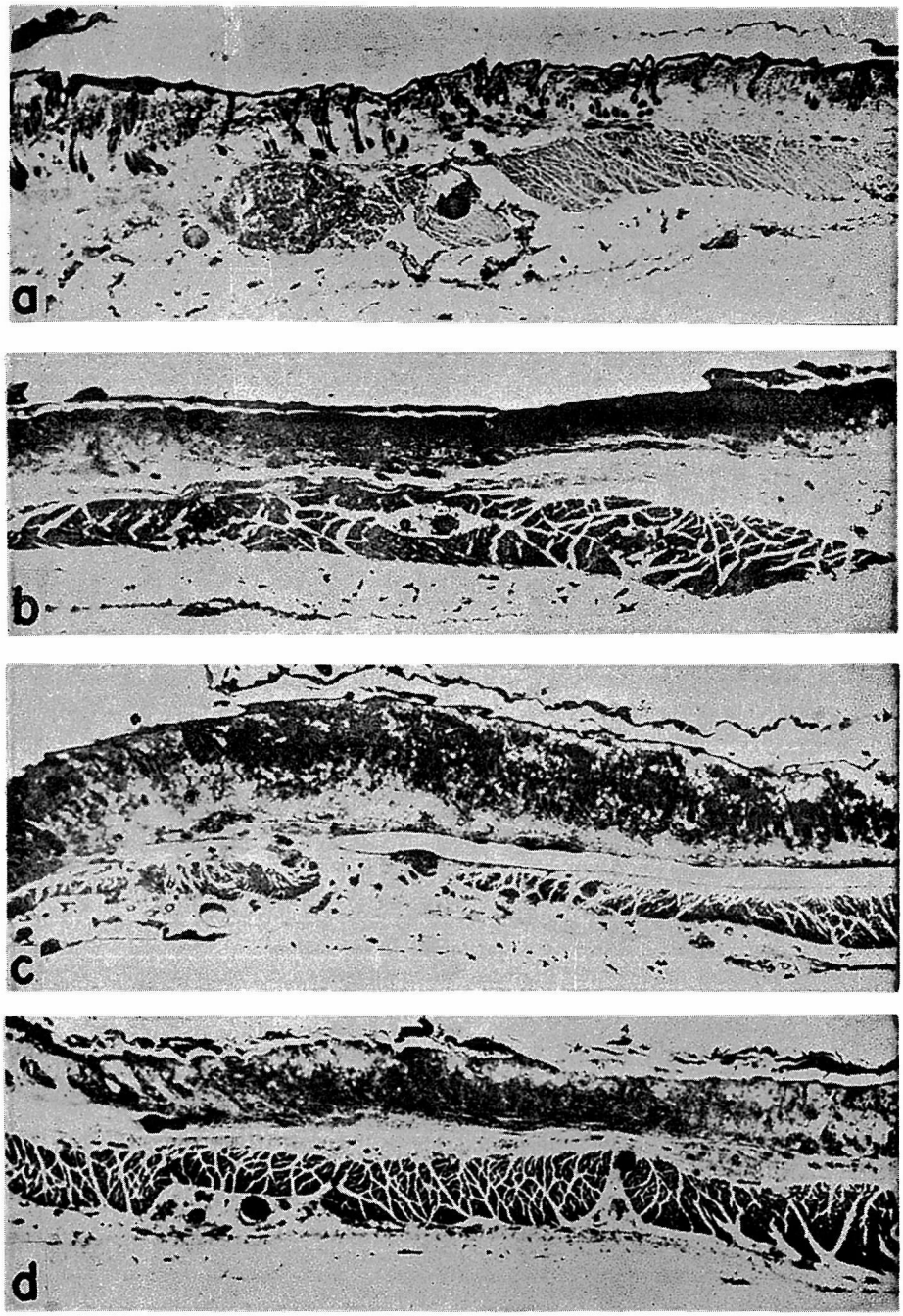
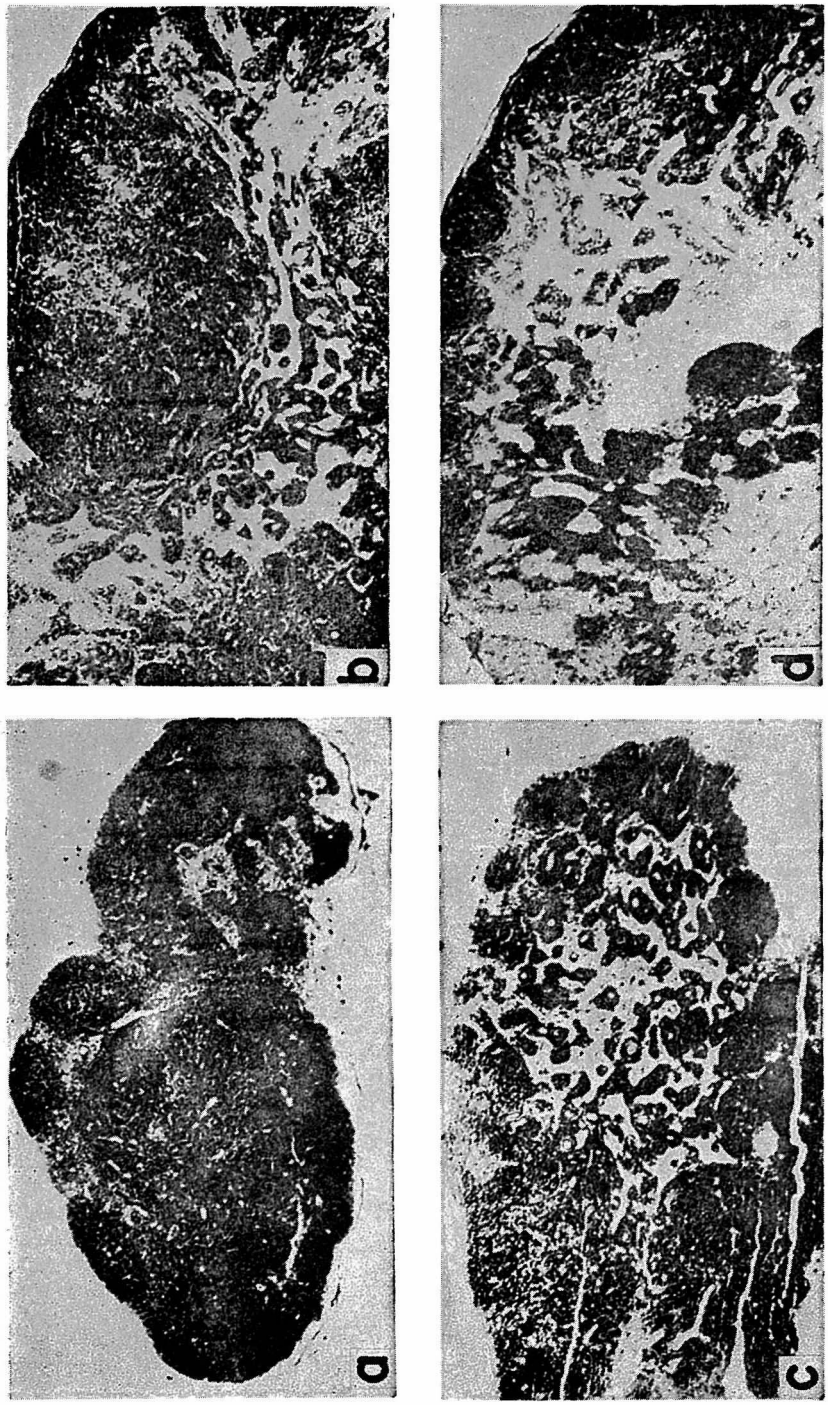


Fig. 1.



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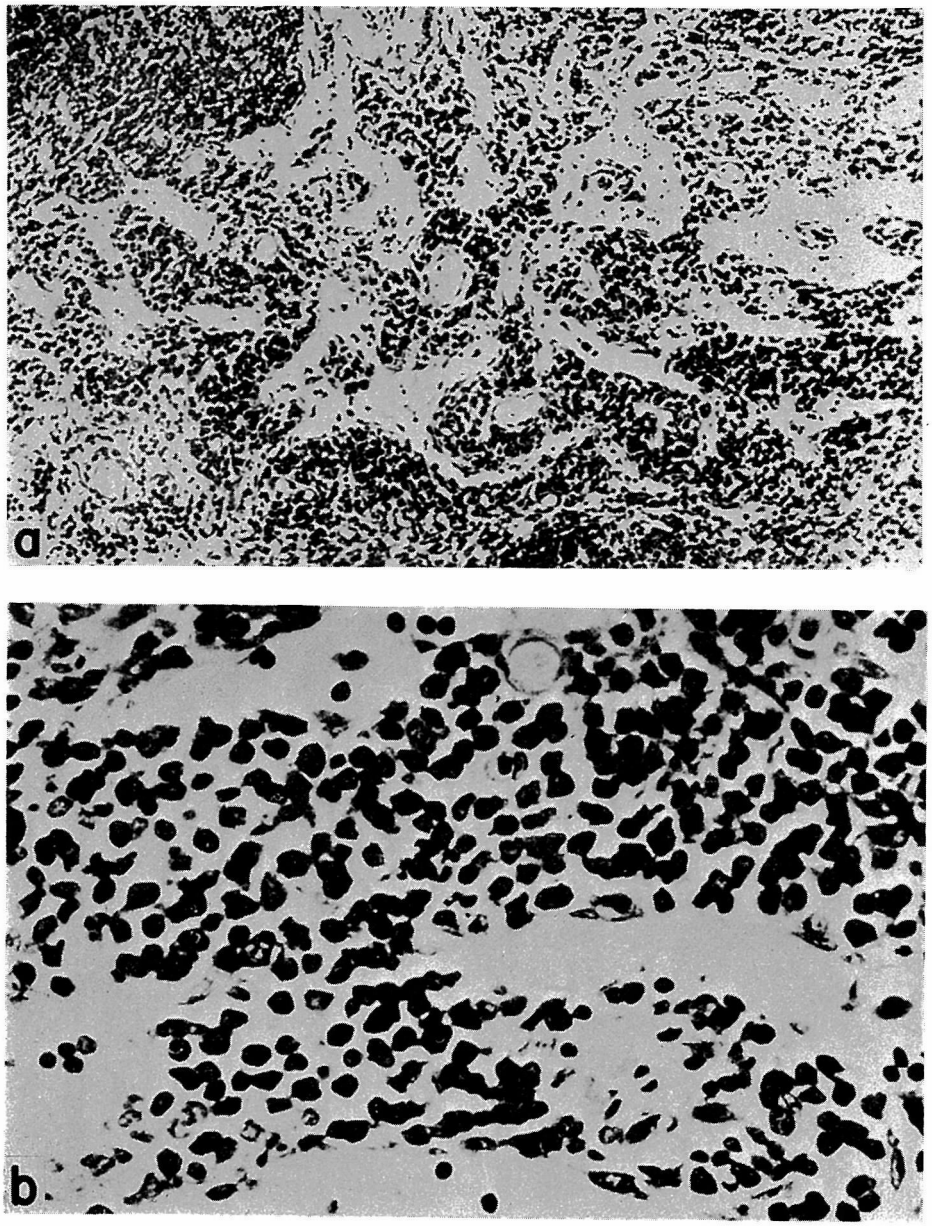

Fig. 3.

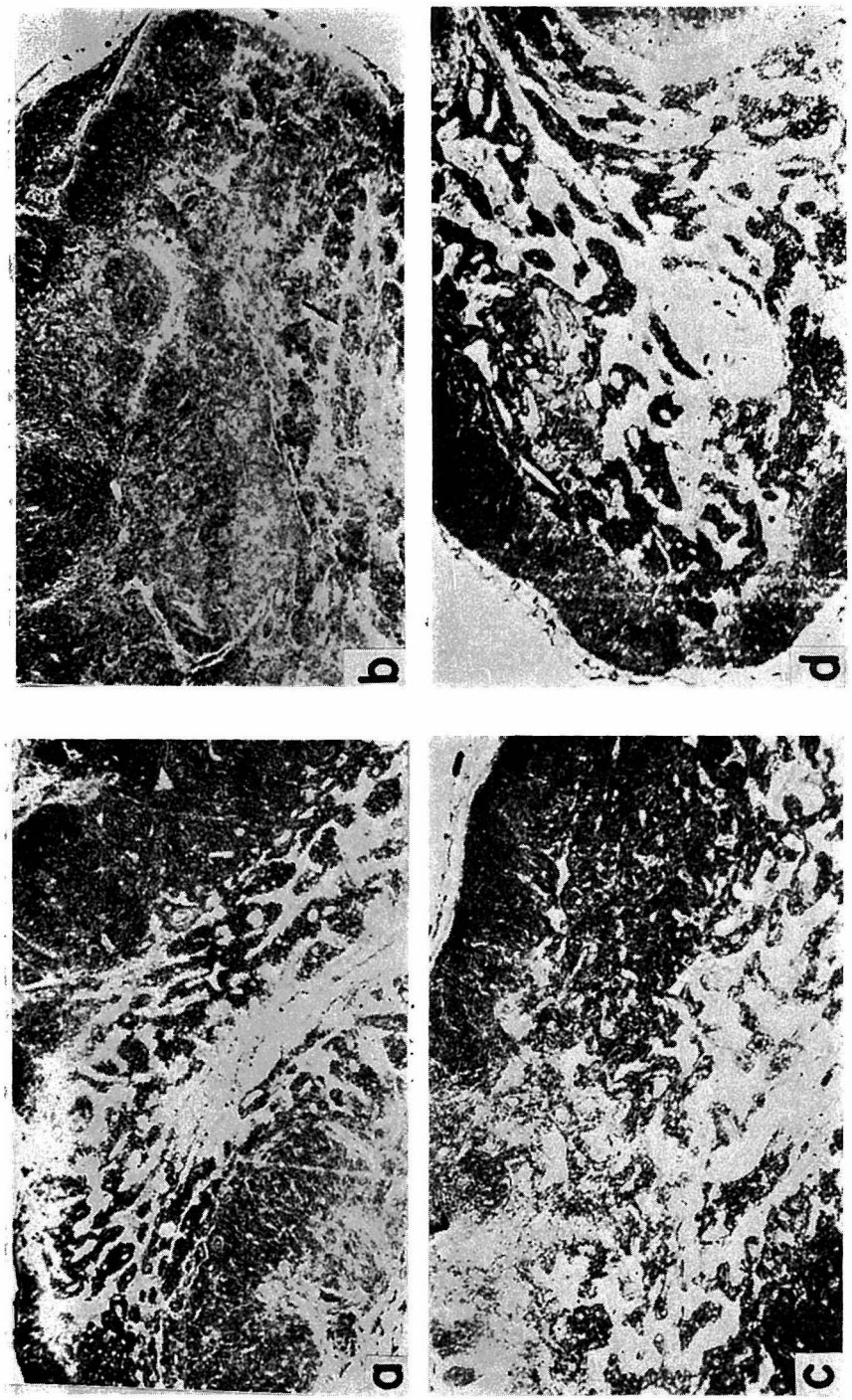

Fig. 4.