HOMOLOGOUS DISEASE IN THE ADULT RAT, A MODEL FOR AUTOIMMUNE DISEASE

I. General Features and Cutaneous Lesions*, ‡

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(Received for publication, April 30, 1963)

An autoimmune mechanism has been invoked in a number of disease states, such as the connective tissue diseases (1, 2), chronic thyroiditis (3, 4), hemolytic anemia (5), and other conditions (6). It has been suggested that the lesions of autoimmune disease result from an immunological reaction between abnormal lymphoid cells and host tissues (1). Regardless of the mechanism whereby such abnormally reactive cells may arise, it is possible to study the consequences of their presence by providing the experimental animal with immunologically competent cells capable of reacting with antigens of the new host. This experimental situation is achieved in the animal with homologous disease, in which there is immunologic interaction between homologous lymphoid cells and host antigens. Homologous disease is, in fact, known to be characterized by changes which resemble certain features of human connective disease. Oliner, Schwartz, and Dameshek (7) have called attention to the similarity of the hematological abnormalities of homologous disease to those of human disease.

A large literature describes the development of homologous disease following the injection of immunologically competent cells into newborn animals (8–10), F_1 hybrids (11, 12), irradiated animals (13), and adult animals rendered tolerant by neonatal injection of lymphoid cells (14) as well as after repeated injection of large numbers of lymphoid cells into adults (15).

* This work has been supported by Research Grant No. CRMS-165 from the National Foundation and Grants No. 2A-5154 and AM 02071 from the National Institute of Arthritis and Metabolic Diseases, Bethesda.

‡ Results of this study were presented in part at the 5th Homotransplantation Conference, New York, February 8, 1962; the annual meeting of the Federation of American Societies for Experimental Biology, Atlantic City, April 15, 1962; and the Interim Session of the American Rheumatism Association, Richmond, December 7, 1962.

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Homologous disease in the adult rat, produced by administration of homologous lymphoid cells to tolerant adult recipients, has been studied intensively in this laboratory as a possible model for autoimmune disease in man. Striking changes have been observed in the skin, hematopoietic system, joints, and heart. In the present paper, the production and clinical features of homologous disease in the adult rat are described, and the histological and immunological reactions occurring in the skin are presented in detail. In a subsequent paper (16), changes in the joints, heart, and other organs will be presented.

The characteristics of the cutaneous lesions observed suggest that they are the result of an immunologic reaction. Aside from the clinical and histologic data to be presented which favor this conclusion, the behavior of autografts in these animals suggests that the skin functions as a target organ for immunologic attack by the grafted lymphoid cells. It has also been observed that the spontaneous skin lesions of homologous disease resemble autografts undergoing rejection both in the gross and histologically. Finally, the histologic appearance of the cutaneous lesions has shown a resemblance to certain of the skin lesions of human connective tissue disease.

Preliminary reports have been presented by the authors (17–19). Brief descriptions of autograft rejection have recently also been given by Doak and Koller (20) and by Billingham and Silvers (21) in reports dealing with the behavior of isografts in homologous chimeras.

Materials and Methods

Induction of Tolerance.—Recipients were Sprague-Dawley rats (George Holtzman and Sons, Houston). Donors were inbred rats of the Fischer strain (from a colony developed in this laboratory from breeding stock supplied by Dr. C. W. McPherson, National Institutes of Health, Bethesda) or Lewis strain (Microbiological Associates, Bethesda). Litters were rendered tolerant within 48 hours after birth by intraperitoneal injection of 10 to 20 million lymphoid cells. From 50 to 80 per cent of injected animals accepted donor strain skin grafts, when tested at 2 months of age. These tolerant rats, which were otherwise normal, constituted the recipients in these experiments. Animals which did not accept homografts were discarded.

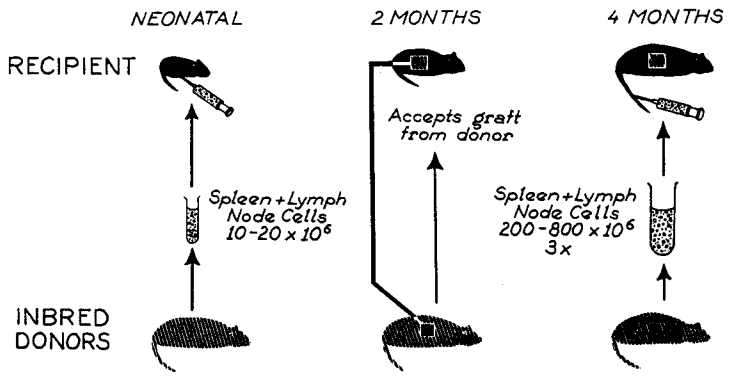
Homologous Disease.—This was produced by injection of tolerant recipients at approximately 4 months of age with 200 to 800 million donor lymphoid cells intravenously three times at weekly intervals (Text-fig. 1). Controls consisted of tolerant rats injected with frozen and thawed cells, tolerant rats which received no further injections, and non-tolerant animals injected with similar numbers of live lymphoid cells. In many experiments, the donors had been preimmunized by a graft of recipient-type skin.

Lymphoid Cell Suspensions.—Under sterile conditions, cervical, axillary, and mesenteric lymph nodes were pooled from a group of donors, minced, and teased in a small volume of Tyrode solution containing 2 per cent normal isologous serum. Spleens were similarly pooled and treated. Following addition of approximately 20 ml of Tyrode solution per donor, large particles were allowed to sediment. The suspended cells were then transferred to another container and aspirated through a 26 gauge needle to remove remaining particles. The combined pool of lymph node and spleen cells were centrifuged at 1200 RPM and resuspended in an appropriate volume of the Tyrode solution. This was adjusted, following cell count, so that each

recipient received 1.0 to 1.5 ml of suspension. Determination of viability was made by the dye exclusion method (22) using either eosin Y or trypan blue (23) and cell counts corrected for non-viable cells.

Skin grafts were 2 × 2 cm full thickness, suprapannicular grafts which were turned 180° before application and held in place by silk sutures. Vaseline gauze dressings were applied. Grafts were examined at 2-day intervals beginning on the 6th day. Biopsies were obtained at varying intervals on approximately half of the grafts.

Ultraviolet Exposure.—Sprague-Dawley rats were exposed to ultraviolet irradiation of a 2 × 2 cm area on the lower back for 30 minutes. The rest of the animal was shielded by an aluminum foil. The ultraviolet light source was a Hanovia lamp, model S-2303A, Hanovia Chemical and Manufacturing Company, Newark, New Jersey, which was placed at a distance of 12 inches above the skin.



TEXT-FIG. 1. Method of production of homologous disease in the adult rat.

RESULTS

Clinical Observations.—Following injection of lymphoid cells into tolerant recipients, approximately 7^ per cent developed clinical evidence of homologous disease (Table I). As will be reported in a subsequent paper (16), however, histologic evidence of disease has been obtained in practically 100 per cent of the recipients.

Clinically, homologous disease in the adult rat was manifested first by erythema and edema of the skin, appearing around the time of the third injection. In the following week, listlessness, weight loss, pallor, dermatitis, purpura, and arthritis appeared. The incidence of these symptoms was variable. In most cases, the course was downhill over a period of 3 to 4 weeks, usually ending in death, but a small percentage of animals recovered, often with loss of tolerance as evidenced by the rejection of a newly applied donor homograft. The disease began earlier and pursued a more rapidly progressive course when the donor animals had been preimmunized by application of a skin homograft from the recipient strain.

There was no obvious difference in the clinical findings when different strain

combinations were used (Table I). It should be mentioned, however, that Billingham and coworkers (24), utilizing neonatal rats, and in a different strain combination, observed a more rapid onset of disease and a more severe course than noted in the present investigation.

It is of interest that the presence of only partial tolerance as in groups 4 and

TABLE I

Homologous Disease in Adult Rats

Clinical Findings

Group	Recipient strain	Tolerant of	No. of recipients	Donor lymphoid cells			Listlessness	Weight loss	Pallor	Dermatitis	Purpura	Arthritis
				Strain	No. × 10^{-6}	Imm.*						
1	SD*	F*	5	F	800	0	2	4	1	X‡	X	X
2	SD	L*	7	L	1900–2100	0	3	7	5	4	X	X
3	SD	L	29	L	1200–2225	+	14	18	8	21	5	16
4	SD§	L	6	L	700	+	3	4	2	4	2	2
5	F	L	8	L	1200	+	4	5	3	4	1	3
6	L‖	F	9	F	1000	+	6	7	1	6	2	4
					Controls							
7	SD	Not tol.	7	L	1900–2100	0	0	1	0	0	0	0
8	SD	Not tol.	4	L	1350	+	0	0	0	0	0	0
9	F	L	4	L	1200 (F&T)*	+	0	0	0	0	0	0
10	F	L	4		Not injected		0	0	0	0	0	0
11	SD	F	4		Not injected		0	0	0	0	0	0

* Abbreviations are as follows: Imm., Immunized by previous skin homograft from recipient strain; SD, Sprague-Dawley; F, Fischer; L, Lewis; F&T, frozen and thawed.

‡ X = information not available.

§ Recipients in this group considered partially tolerant because donor homografts demonstrated "chronic" rejection (absence of hair, fibrosis).

‖ Four animals of this group were partially tolerant.

9 (Table I), was no obstacle to the development of homologous disease. Presumably, as pointed out by Billingham and coworkers, this may indicate the persistence of the chimeric state even at a time when the tolerance of skin homografts has been partially lost.

Significant changes were not observed in a group of 23 control rats (Table I) subjected to various parts of the experimental procedure involved in the production of homologous disease; *i. e.*, the injection of normal or immune lymphoid cells into non-tolerant animals (groups 7 and 8), the injection of frozen and

thawed cells into tolerant animals (group 9), or the production of tolerance without further injection of lymphoid cells (groups 10 and 11).

Spontaneous Skin Lesions.—Following the injection of homologous lymphoid cells into 59 recipients who had previously accepted skin homografts, a variety of skin changes were observed (Table II). Twenty-six rats developed erythema of the feet, tail, and ears (Fig. 1), and frequently of the whole body. This was usually observed at the time of the third injection or within several days thereafter. The skin blanched on pressure, and markedly dilated vessels, principally capillaries and venules, were visible on histologic examination. Numerous mast cells were observed in the region of the dilated vessels. In addition, cutaneous edema, noted in 28 animals, occasionally present in the absence of erythema, appeared at about the same time (Fig. 7).

Two types of dermatitis were observed. Clinically, one appeared to be

TABLE II

Skin Lesions in Tolerant Sprague-Dawley Rats Injected with Homologous Lymphoid Cells

No. of recipients	Erythema	Cutaneous edema	Acute dermatitis	Chronic dermatitis	Purpura	No lesions
59	26	28	16	18	11	14

relatively acute and the other a more chronic type of lesion. The acute form, observed in 16 animals, usually appeared at 2 to 3 weeks after the last injection of lymphoid cells, tending to occur in animals with the more severe disease. It was noted most often on the abdomen and inner aspect of the legs, but in some instances was generalized. Pruritus was a prominent feature, and the affected skin was often erythematous and weeping (Fig. 2). The epidermis presented hydropic degeneration of the epithelial cells, fraying and disruption of the basement membrane, alternating acanthosis and epidermal atrophy, hyperkeratosis with follicular plugging, and the presence of aggregates of mixed inflammatory cells, especially about follicles (Fig. 8). Ulceration was frequent (Fig. 9). The dermis demonstrated a chronic inflammatory infiltrate with degeneration of edematous collagen. On occasion, there was complete necrosis of the epidermis and superficial dermis, resembling changes to be described below in the spontaneous rejection of autografts. The inflammatory infiltrate of the dermis was composed of histiocytes, plasma cells, and lymphocytes. In addition, vascular dilatation and edema, and occasional petechiae were present, and fibrinoid necrosis was sometimes observed (Fig. 10). In some areas, there was an inflammatory reaction around skin appendages and portions of hair and sebaceous material could be demonstrated within foreign body giant cells. In the non-ulcerated areas, the changes were less intense. Here, the hydropic degeneration tended to be limited to the basal epithelial layer, but was

of sufficient intensity to produce focal epithelial separation. Atrophy of the epidermal skin appendages was prominent. The collagen bundles were thickened and increased in amount (Fig. 11).

The more chronic type of dermatitis, which was observed in 18 recipients, was characterized by thickening of the skin, scaling, and alopecia. Microscopically, there was increased collagenization of the dermis with atrophy of both the epidermis and skin appendages. The chronic inflammatory infiltrate in the dermis was less prominent (Fig. 11). These changes ultimately progressed to extreme atrophy of the epidermis with marked hyperkeratosis, and thickening of the dermis due mainly to a large increase in collagen content. On occasion, the atrophic epidermis was ulcerated, and the skin appendages appeared so atrophic as to be virtually absent. Remnants of the degenerating appendages could be found within the sclerotic dermis. The dermal infiltrate was minimal (Fig. 12).

Purpura, noted in 11 animals (Fig. 3), was symmetrically distributed, usually on the hind feet, ears, or scrotum. The dermis showed aggregates of extravasated erythrocytes, especially in regions of erythema and edema. The platelet counts were uniformly low in this group.

Abnormalities of the skin were not encountered in the 23 control animals (Table I). Dermatitis was observed, however, in 7 of 13 animals with homologous disease who were treated with tetracycline. These animals received a daily dosage of either 25 mg in the diet or 12.5 mg intramuscularly.

Ultraviolet Irradiation and Trauma.—Seven tolerant Sprague-Dawley rats were injected with live donor lymphocytes from Fischer or Lewis donors, and exposed to ultraviolet irradiation 2 days after the last of three injections. Each animal received a total of 1.3 to 2.1 billion cells. Three days after irradiation, the resulting burns had a deep red appearance; at 8 to 10 days the burn sites were red, indurated, and in some cases ulcerated (Fig. 13 *b*). Ultimately a fibrous scar developed. Controls were 4 non-tolerant rats injected with live cells and 3 tolerant rats not futher injected. In contrast to the experimental group, 5 of the 7 control rats showed only a yellowish discoloration of the burn site, with some crust formation, during the 1st week. Two rats, of the group which received live cells, developed mild erythema during the same period. At 10 days, all lesions in the control animals had healed almost completely (Fig. 13 *a*). Sections of experimental burn sites showed vesicle formation and subepidermal edema while control sections showed only a mild chronic inflammatory reaction.

Necrosis of the skin of the tail was observed in 11 rats with homologous disease (Fig. 4). This appeared to be related mainly to the immersion of the tail in warm water, approximately 45–50°C, in preparation for venipuncture, but it is possible that the needle trauma may also have played a role. This change was not observed in any of the control animals.

Skin Lesions in Relation to Donor Homografts.—In 3 rats, an active dermatitis occurred in the skin contiguous to a well accepted and healthy donor homograft which had been present on the back for periods of 70 to 100 days. In all 3 cases the dermatitis was limited to the host skin surrounding the homograft, and spared the homograft itself (Fig. 5).

Behavior of Autografts.—Autografts were applied 1 day after the last injection of homologous lymphoid cells. All of 14 recipients who continued to be tolerant at the time of grafting, as evidenced by acceptance of a donor homograft within the preceding 6 week period, rejected the autografts (Table III). In all of eight animals of this group, in which the donor strain homografts were

TABLE III

Simultaneous Skin Autografts and Homografts in Sprague-Dawley Rats

Experimental group	Rejection of grafts	
	Homografts	Autografts
Homologous disease	0/8*	14/14
Controls		
Non-tolerant‡	4/4	0/16
Tolerant§	0/3	

* Homografts were applied simultaneously with autografts.

‡ Injected with live cells from donor strain before grafting, but did not receive cells neonatally.

§ Received cells neonatally but not subsequently; rejected homografts from an indifferent strain.

simultaneously applied with the autografts, the homografts were accepted at the same time that the autografts underwent rejection.

In comparison with a group of control animals, in which homografts were uniformly rejected in 8 to 14 days, autograft rejection in animals with homologous disease pursued a more prolonged course. Though rejection began at approximately 8 to 10 days, it extended over a period of at least 8 weeks in most cases. Localized ulceration and partial sloughing of the graft occurred early (Fig. 6), but in the non-ulcerated areas, the rejection was characterized by atrophy, alopecia, induration, and fibrosis. In 4 of the 14 animals, ulceration was not noted at all.

Microscopically, rejection of autografts was characterized by alterations in both the epidermis and dermis of the graft. These resembled in a striking manner the changes observed in the spontaneous dermatitis described above. Within the epidermis, there was hydropic degeneration of both the basal epithelial layer and the stratum malpighium, which on occasion reached

sufficient magnitude to form small vesicles (Fig. 14). The basement membrane was sometimes frayed and disrupted, especially when adjacent edema and inflammation were present. These changes progressed to focal necrosis, ulceration, and exudation with sloughing (Fig. 15) which, in some cases, spread to involve the entire graft.

As a result of the epidermal ulceration, secondary acute inflammation of the dermis was often present. The principal dermal changes, however, were located deep in the dermis, and consisted of vascular dilatation, edema, occasionally with petechiae, and a mononuclear inflammatory reaction (Fig. 16). With time, fibrocollagenous tissue assumed an increased prominence as a result both of edema and increase in the substance of the fibers. The skin appendages, especially the hair apparatus, demonstrated an acute inflammatory reaction, which appeared ultimately to result in their disappearance. A granulomatous, foreign body reaction surrounded the degenerating skin appendages. On occasion, this appeared also to be the result of the operative procedure.

Where rejection was especially slow (Fig. 17), and visible changes appeared to take place over a period of 40 days or more, there was gross whitening, scaling, and sometimes ulceration of the epidermis. Occasionally, firm nodules, which were sometimes erythematous, could be palpated, and some of these were ulcerated. Absence of hair and some degree of contraction of the graft were usually present. Microscopically, this more chronic form of graft rejection was characterized by prominence of the dermis, often sufficient to produce a distinct nodulation. Marked collagenization and atrophy of the secondary skin appendages, particularly the hair follicles, were frequently present in the dermis.

In some autografts undergoing this type of chronic rejection, examined after 25 to 60 days, atrophy had progressed to such an extent that the epidermis was only one to three cells in thickness (Fig. 18). Marked hyperkeratosis and intense collagenization of the dermis were present, and the atrophic skin appendages were represented only by small clusters of epithelial cells or erector piloris muscles. The chronic inflammatory infiltrate was minimal.

In the eight tolerant animals in which homografts were simultaneously applied with autografts, acceptance of the homografts appeared to follow the usual course observed with autografts in normal animals (Table III). Healing appeared in the gross to be complete by the end of the 2nd week. Ultimately, a full pelt of hair growing in opposite direction to the surrounding hair, developed. Microscopically, as with autografts in normal animals, the initial acute inflammatory reaction incident to the grafting procedure subsided, leaving an essentially normal structure. Though homografts were accepted in the tolerant animals, they were rejected in the non-tolerant group (Table III).

DISCUSSION

Immune reactivity directed against the skin of the host is demonstrated in the animal with homologous disease by the rejection of autografts. This

appears to be a true graft rejection, which is specific for host skin, since homografts were simultaneously accepted. The acceptance of homografts indicates that the rejection of autografts was not due to some abnormality of healing or non-specific deficiency on the part of the host, resulting from homologous disease. The histologic appearance of the rejection resembled that of homograft rejection. It appeared in particular, to follow the course of "chronic homograft rejection" (25) as described in instances of weak histoincompatibility. Examples of this type of rejection have been described in hamsters (25), in mice that differ at the H-3 locus (26), and in mouse strains which reject skin grafts on the basis of sex-specific antigen (27). Especially characteristic of this form of rejection were the slow course, which extended over a period of many weeks, and the histologic appearance. The relatively acute changes seen in some of the rejected autografts suggest the presence of a gradation in intensity of response in chronic graft rejection.

The reasons why the rejection of autografts pursued a "chronic" course are not immediately evident. At least three possibilities exist: (*a*) a reduced number of reactive donor cells is available at any given site because of dilution by host cells; (*b*) the reactive cells are paralyzed in the presence of excess antigens from the host; and (*c*) the reaction involves weak antigens of the host (26, 27). With regard to the second possibility, it is known that there is a delay in the rejection of skin grafts when very large homografts are applied, due presumably, to the liberation of large amounts of antigen (28).

The specific immunologic reactivity directed at host skin, as manifested by autograft rejection, appears to be responsible for the pathologic changes observed in this tissue; *i.e.*, acute and chronic dermatitis and increased susceptibility to trauma and burns. The histologic appearance of the spontaneous dermatitis, in fact, resembled that of the autograft rejection. Striking, moreover, was the localization of the dermatitis to the host skin surrounding homografts, without involvement of the donor skin, thus emphasizing the specificity of the reaction. In describing the skin changes of homologous disease in the newborn rat, Billingham and coworkers have made a similar observation (24).

The earliest spontaneous skin lesions, consisting of erythema and edema, usually noted about the time of the third injection of lymphoid cells, were associated with the presence of numerous mast cells surrounding engorged blood vessels. This would suggest that this early change is a histamine-mediated effect. A similar phenomenon has been described in rats following intraarterial injection of a histamine releaser (29). Large number of mast cells have also been observed in the course of chronic graft rejection in hamsters (25).

The subsequent histologic changes both of the more acute and chronic forms of dermatitis closely resembled the changes seen during the rejection of autografts. This is well demonstrated by a comparison of Figs. 8 to 12, illustrating the spontaneous dermatitis, with Figs. 14 to 18, illustrating autograft rejection. Ulceration, sloughing, and serous exudation were seen both in the more acute

examples of dermatitis as well as in the more active instances of autograft rejection. In less intense reactions, both phenomena had in common subepidermal edema, periappendigeal inflammation, hyperkeratosis with follicular plugging, alternating atrophy and acanthosis, and dermal infiltration. In more chronic reactions, atrophy of the epidermis, disappearance of appendages, and increase in thickness and number of collagen bundles were present in both. Similarity between the skin lesions of homologous disease and homograft reactions has been previously pointed out by DeVries and coworkers (30) in the monkey with homologous disease following administration of bone marrow.

The purpura observed was in all likelihood a manifestation of the thrombocytopenia of homologous disease, although other factors may have been involved. Bleeding was not restricted to the skin, however, since in several instances, internal as well as external hemorrhage appeared to have been the cause of profound anemia and death.

The production of skin lesions in the tail by the trauma incident to application of heat with venipuncture may have something in common with the poor healing of wounds (31) and deficient regeneration of bowel epithelium after x-irradiation (32) which have been noted in mice with homologous disease. It is likely the observed sloughing of the tail skin, as well as the delayed healing of the ultraviolet burns in our experiments, are based on the factors operative in autograft rejection. It is suggested that the necrosis of epithelium incident to trauma resulted in local liberation of antigen with subsequent influx of sensitized cells. No doubt, non-specific factors associated with trauma also play a role.

The skin lesions observed in the present experiments showed no overt evidence of infection, either clinically or histologically; and their occurrence was not prevented by administration of tetracycline, suggesting that PPLO (mycoplasmataceae) or other tetracycline-sensitive organisms were not causative agents. Also against the likelihood of infection was the fact that dermatitis was not observed in control animals injected with either living or dead cell suspensions.

The possibility that these lesions were a result of malnutrition was considered since dermatitis has been reported in rats with a variety of nutritional deficiencies (33). The evidence is against this possibility. Earliest skin changes began to appear at about the time of the third injection of lymphoid cells, and definite dermatitis was seen as early as 10 days later, that is, at a time when most of the animals appeared healthy and were eating well. The lesions showed a different pattern of distribution and differed in gross and histologic appearance, as well as clinical course, from that observed in a variety of deficiency states (33). Finally, the associated clinical manifestations and visceral lesions of specific nutritional deficiencies were not observed, including the changes in the liver commonly seen with inanition. Also against the possible role of malnu-

trition in the development of the dermatitis was the sparing of homografts in the presence of involvement of the neighboring skin. Billingham and coworkers (24) have also concluded that the dermatitis of rats with homologous disease, in their case newborn animals, was not a result of metabolic deficiency.

The evidence appears convincing that the spontaneous skin lesions of homologous disease are the result of an immunologic process. In favor of this conclusion are: (*a*) the impressive similarity in morphologic appearance between skin lesions and autografts undergoing rejection; (*b*) the latent period between injection of lymphoid cells and onset of dermatitis; (*c*) the earlier development of inflammation when cells from preimmunized donors were transferred; and (*d*) the specificity of the dermatitis for host skin alone and not for the skin of neighboring homografts.

The observed skin lesions, in which hyperkeratosis, epidermal atrophy alternating with acanthosis, follicular plugging, and intraepithelial edema were prominent, bear a morphologic resemblance to the changes described in human discoid and systemic lupus erythematosus. This similarity was also present in the pattern of histologic changes observed in the more active examples of autograft rejection. Also noteworthy was the resemblance of the chronic spontaneous lesions, characterized by marked atrophy of the epidermis, increased collagen content of the dermis, and disappearance of the skin appendages, to the histologic changes seen in the skin of patients with scleroderma. In this case too, similar histologic alterations in autografts were noted in instances where autograft rejection was very slow. Although morphologic similarity cannot be considered as conclusive, the resemblance of the lesions of lupus erythematosus and scleroderma to the apparently immunologically based cutaneous lesions of the rat with homologous disease suggests that the skin lesions of the human diseases mentioned may also have an immunologic basis.

The animal with homologous disease contains immunologically competent cells which are capable of reacting with host antigens. Irrespective of the underlying mechanism for the development of such cells, a similar situation must prevail in the patient for whom an autoimmune process is postulated. For this reason, the occurrence of abnormalities in the skin of the rat with homologous disease, which resemble those seen in human connective tissue disease, may be of significance.

SUMMARY

The cutaneous lesions of adult rats with homologous disease are described, and evidence is presented to indicate that they have an immunologic basis. The skin changes included erythema, purpura, edema, and a variety of inflammatory lesions. In the more active lesions, dermal infiltration, hydropic degeneration, acanthosis, and atrophy of the epidermis with hyperkeratosis and follicular plugging were present. In some cases, ulceration and sloughing were

also observed. More chronic lesions were characterized by atrophy of the epidermis and collagenization of the dermis with disappearance of the skin appendages.

Rejection of autografts was observed simultaneously with acceptance of homografts. The histologic appearance of autografts undergoing rejection was similar to that of the spontaneous skin lesions, suggesting that the latter, too, had an immunologic basis. In favor of this, also, was the specificity of the dermatitis for the skin of the host, with sparing of neighboring homograft tissue.

There was a histologic similarity between the spontaneous skin lesions of homologous disease and those of lupus erythematosus on the one hand, and scleroderma on the other, thus supporting the possibility that the cutaneous lesions of these connective tissue diseases of man may also have an immunologic basis.

It was concluded that the adult rat with homologous disease may furnish a model for human autoimmune disease.

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EXPLANATION OF PLATES

PLATE 63

FIG. 1. Foot of adult rat with homologous disease demonstrating erythema and edema.

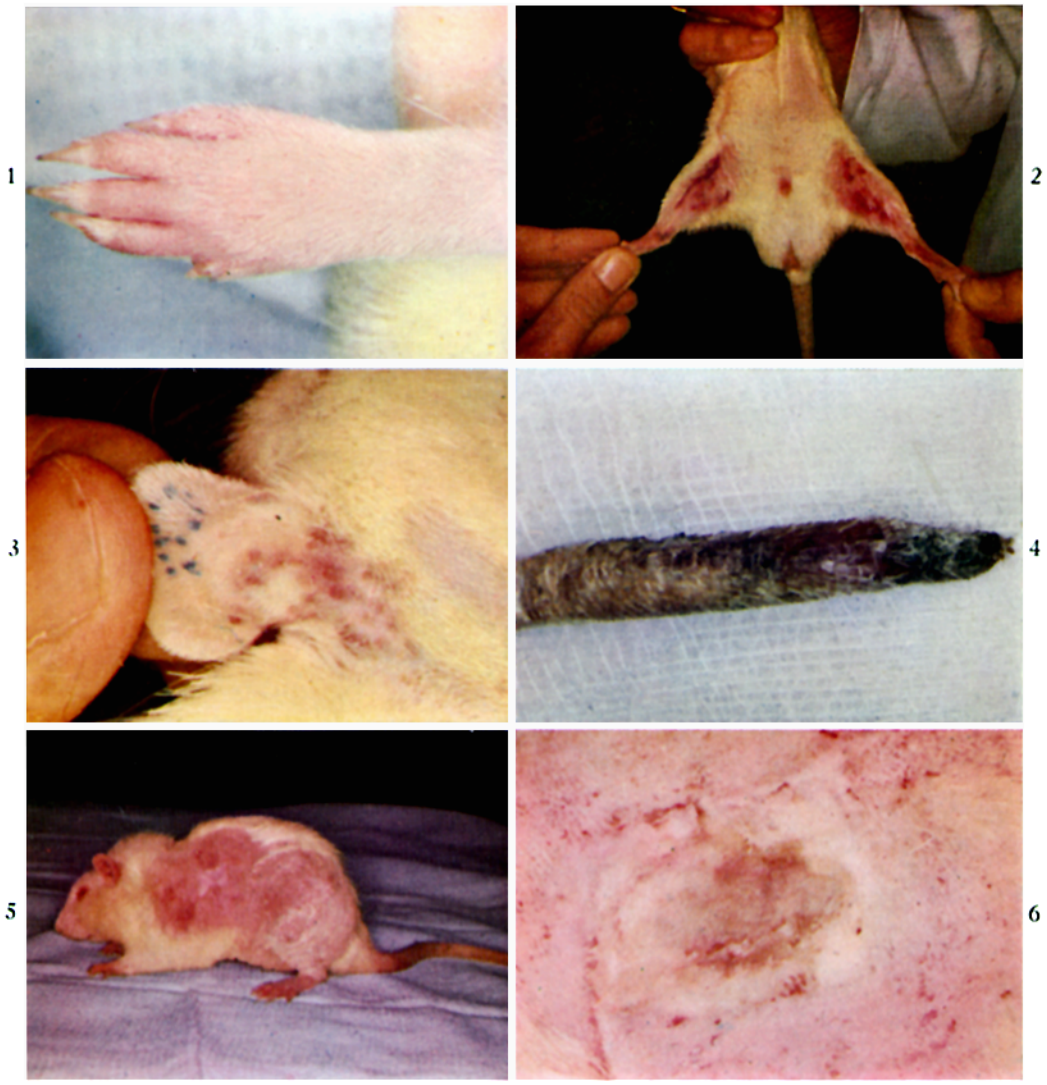
FIG. 2. Acute dermatitis on abdomen and thighs of rat with homologous disease. Lesions are erythematous and weeping.

FIG. 3. Purpura on ear of rat with homologous disease.

FIG. 4. Necrosis of tail in rat with homologous disease.

FIG. 5. Spontaneous dermatitis in host skin surrounding donor strain homograft in adult rat with homologous disease. Note absence of lesions in homograft.

FIG. 6. Acute autograft rejection in adult rat with homologous disease at 8 days. Graft was applied 1 day following last injection of donor lymphoid cells. Note ulceration in graft and surrounding erythema.



(Stastny *et al.*: Homologous disease, model for autoimmune disease)

PLATE 64

FIG. 7. Dermal edema in homologous disease. Marked congestion of capillaries and venules; moderate chronic inflammatory infiltrate characterized principally by lymphocytes and occasional plasma cells; a number of mast cells are seen. × 330.

FIG. 8. Spontaneous dermatitis in homologous disease. Moderate hydropic degeneration of the epidermis principally involving the basal cells with early vesicle formation; moderate hyperkeratosis with follicular plugging; mild chronic inflammatory reaction in the subepithelium. × 150.

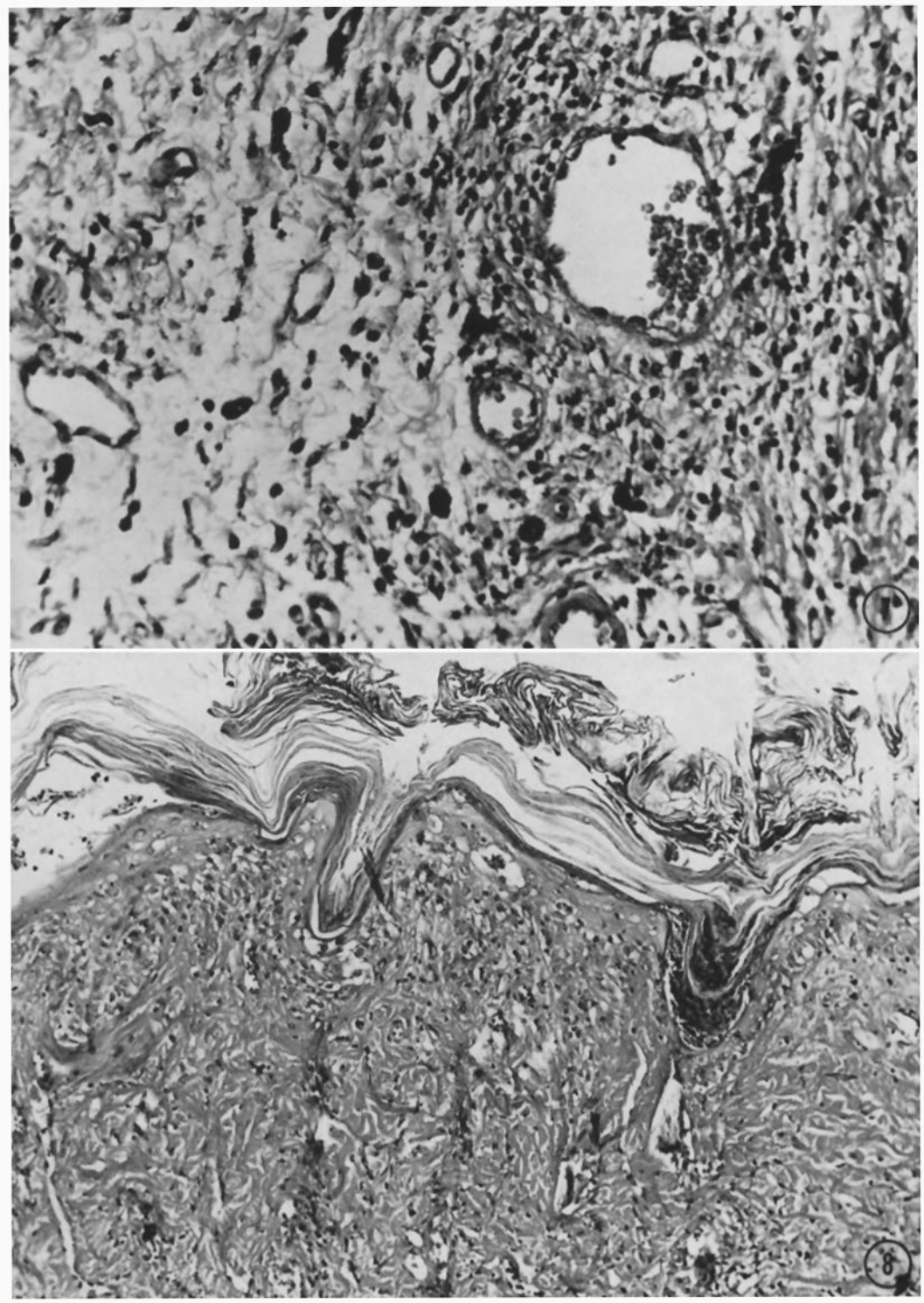


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PLATE 65

FIG. 9. Spontaneous dermatitis in homologous disease. Atrophy and hydropic degeneration of epidermis; exudation of serous fluid beneath epidermis, ulceration with acute inflammation, and degeneration and chronic infiltration of the collagen. × 180.

FIG. 10. Inflammation of dermis with fibrinoid degeneration. Early atrophy of epidermis with subepidermal edema; beginning collagenization of fibrous tissue; intense chronic inflammatory reaction in dermis with associated fibrinoid necrosis (arrow); beginning atrophy of the skin appendages. × 110.

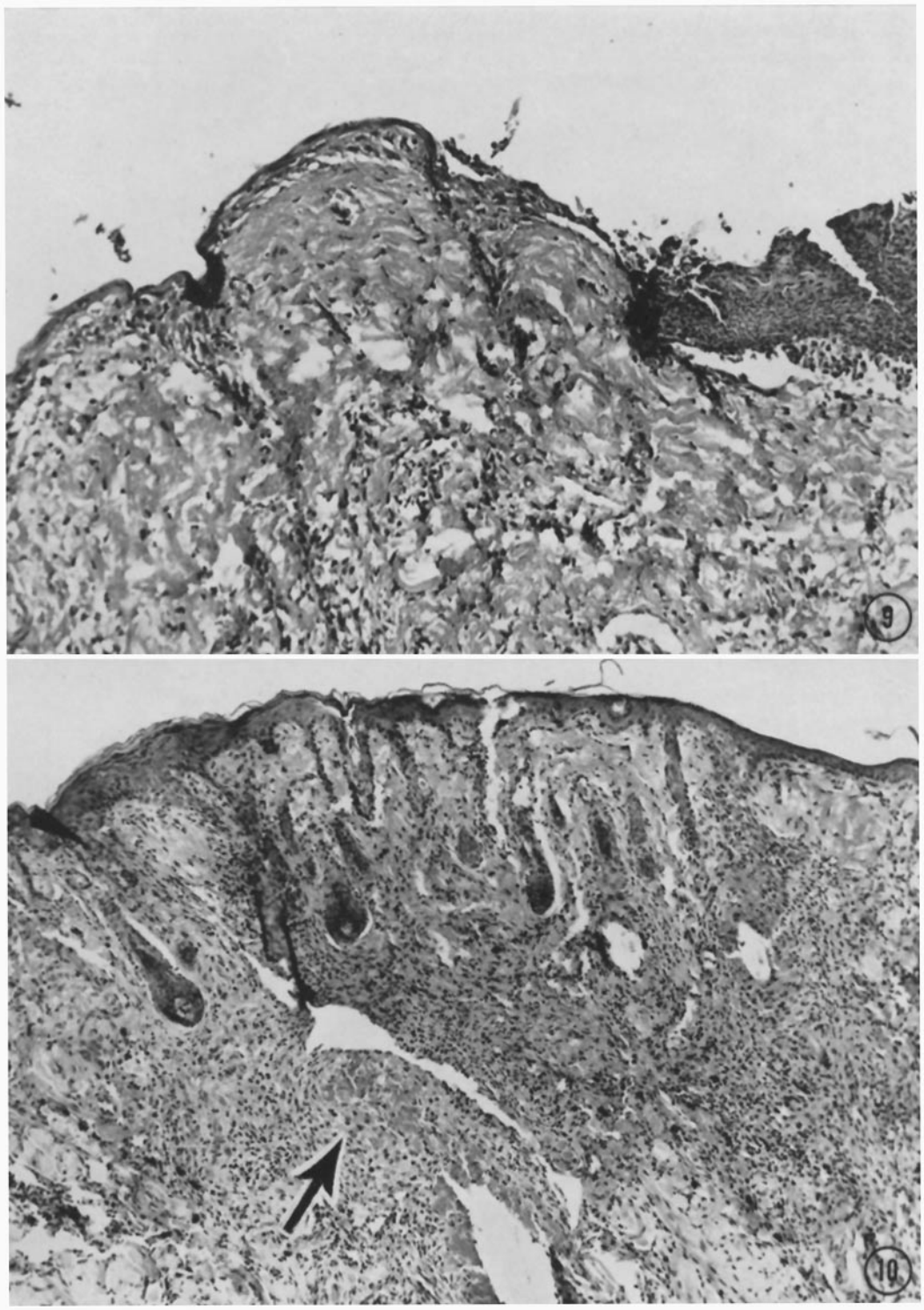

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PLATE 66

FIG. 11. Epidermal separation. Moderate atrophy of the epithelium alternating with focal areas of acanthosis; intense edema of basal epithelial cells producing epidermal separation; increase in collagen of dermis with concomitant atrophy of skin appendages; chronic inflammation in deeper dermis. × 115.

FIG. 12. Chronic dermatitis in homologous disease. Marked atrophy of epidermis with moderate hyperkeratosis; disappearance of skin appendages; marked increase in collagenization of dermis. × 115.

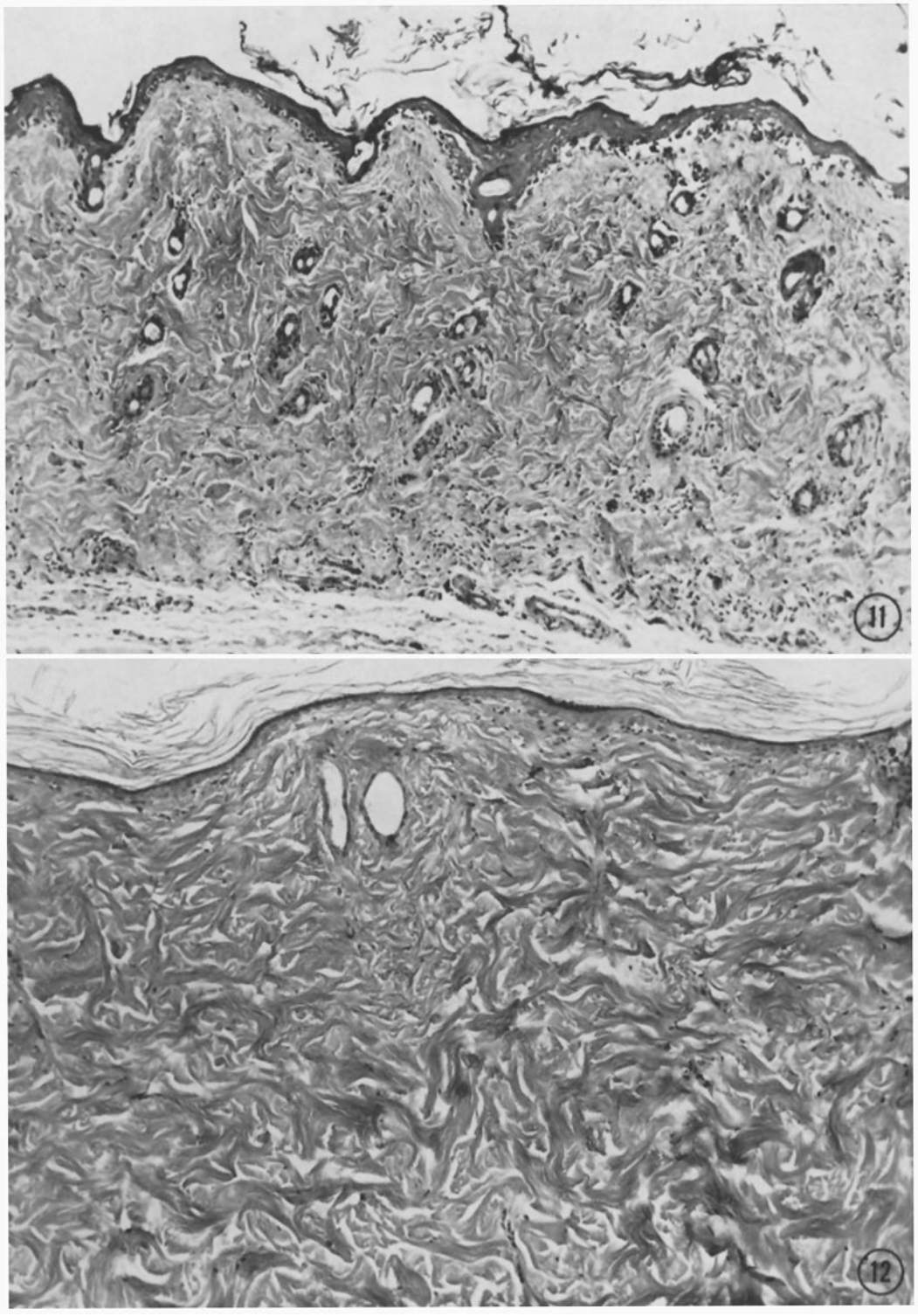

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PLATE 67

FIGS. 13 *a* and 13 *b*. Ultraviolet irradiation in homologous disease.

FIG. 13 *a*. Appearance of skin 10 days after irradiation of normal rat.

FIG. 13 *b*. Appearance of skin 10 days after ultraviolet irradiation of experimental rat.

FIG. 14. Autograft rejection in adult rat with homologous disease at 10 days. Hydropic degeneration of basal cells with subepidermal edema and separation of the epidermis from dermis; minimal hemorrhage and modest chronic inflammatory reaction. × 160.

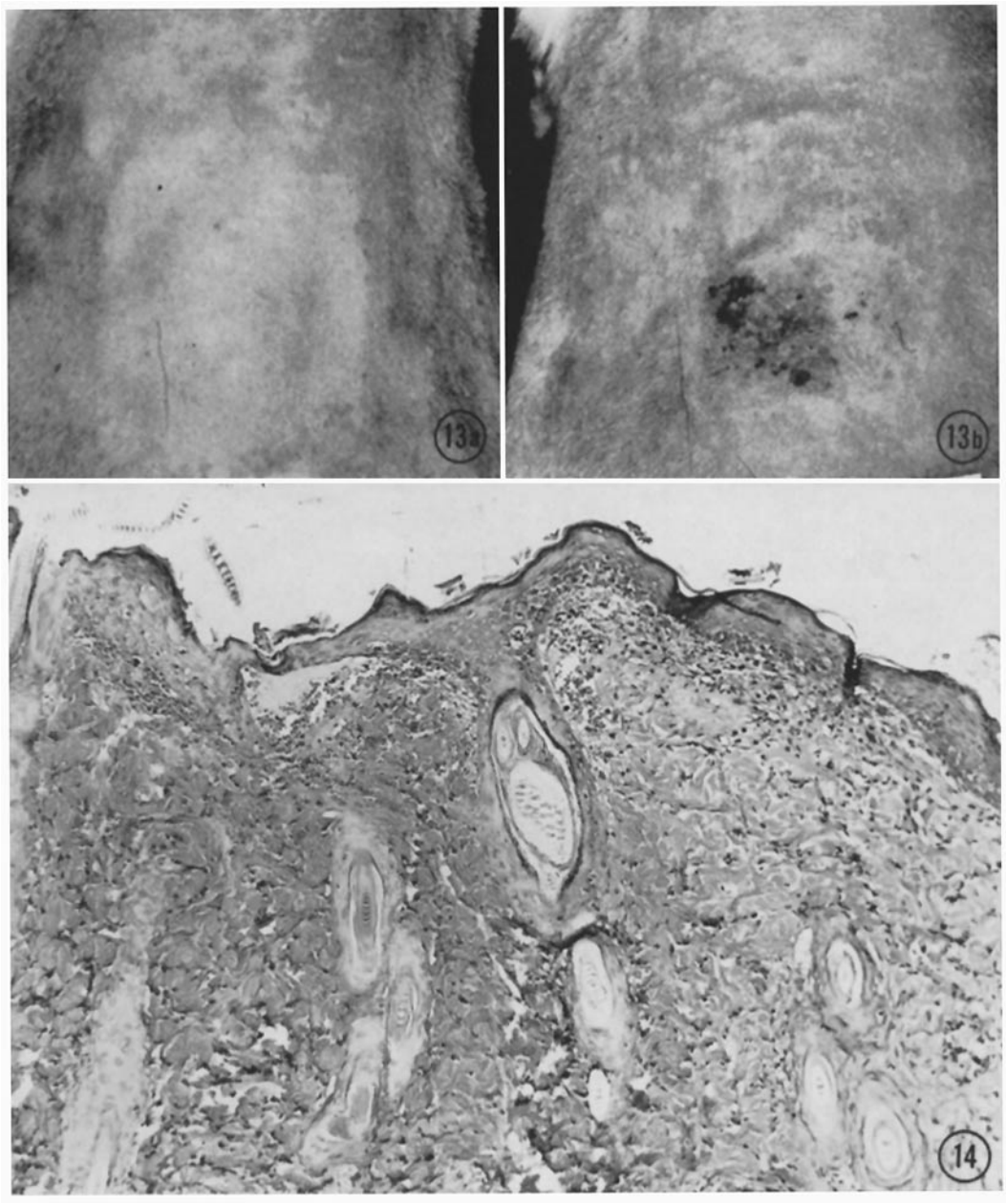

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PLATE 68

FIG. 15. Acute autograft rejection. Hydropic degeneration of epidermis with vesicle formation, progressing to ulceration with acute inflammation and exudation; moderate collagenization and edema of upper portion of dermis in association with moderate chronic inflammatory response. × 115.

FIG. 16. Dermal changes in autograft rejection at 15 days. Intense chronic inflammation in deep dermis; subepidermal edema with epidermal separation with subepithelial zone of collagenization. × 150.

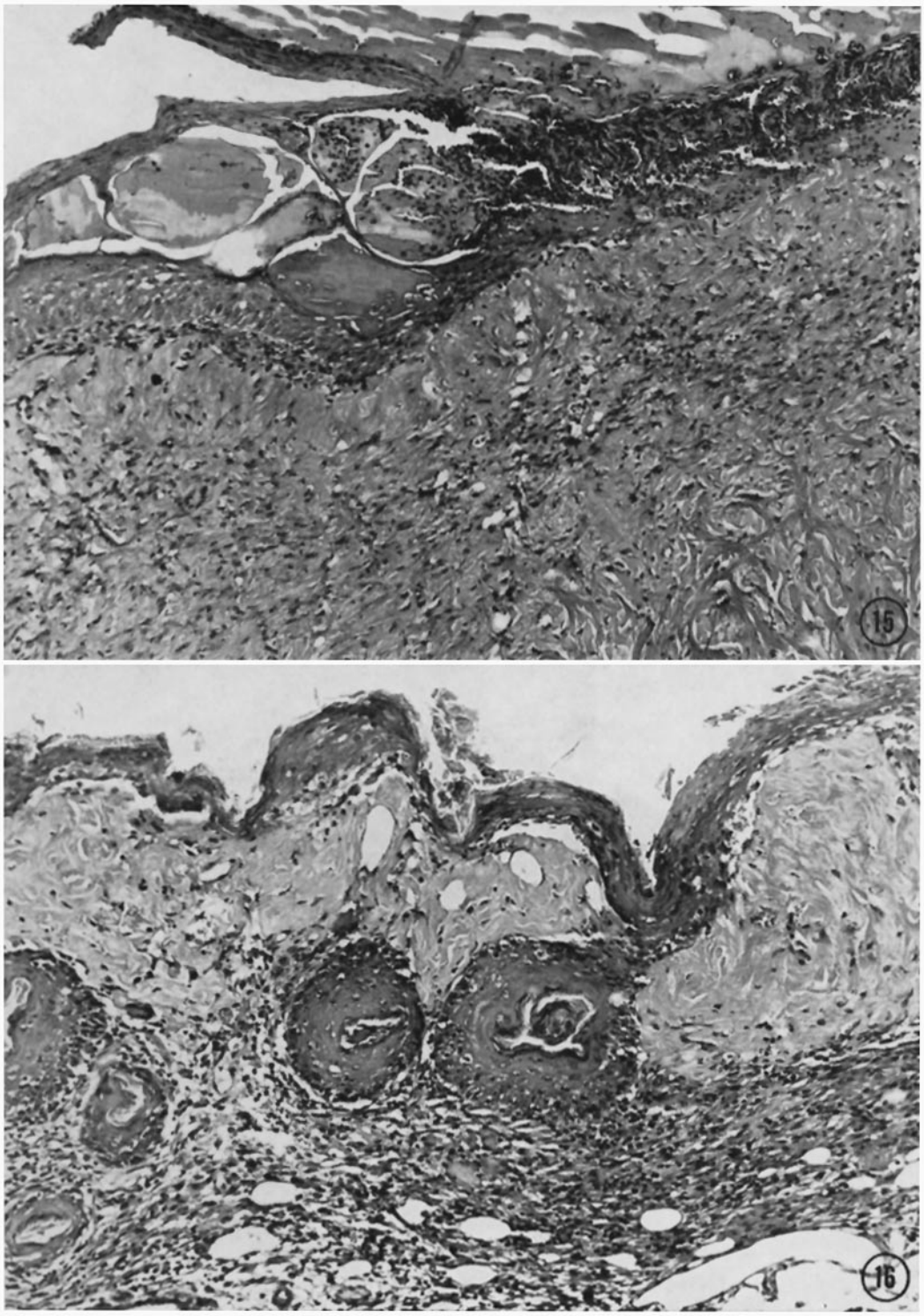

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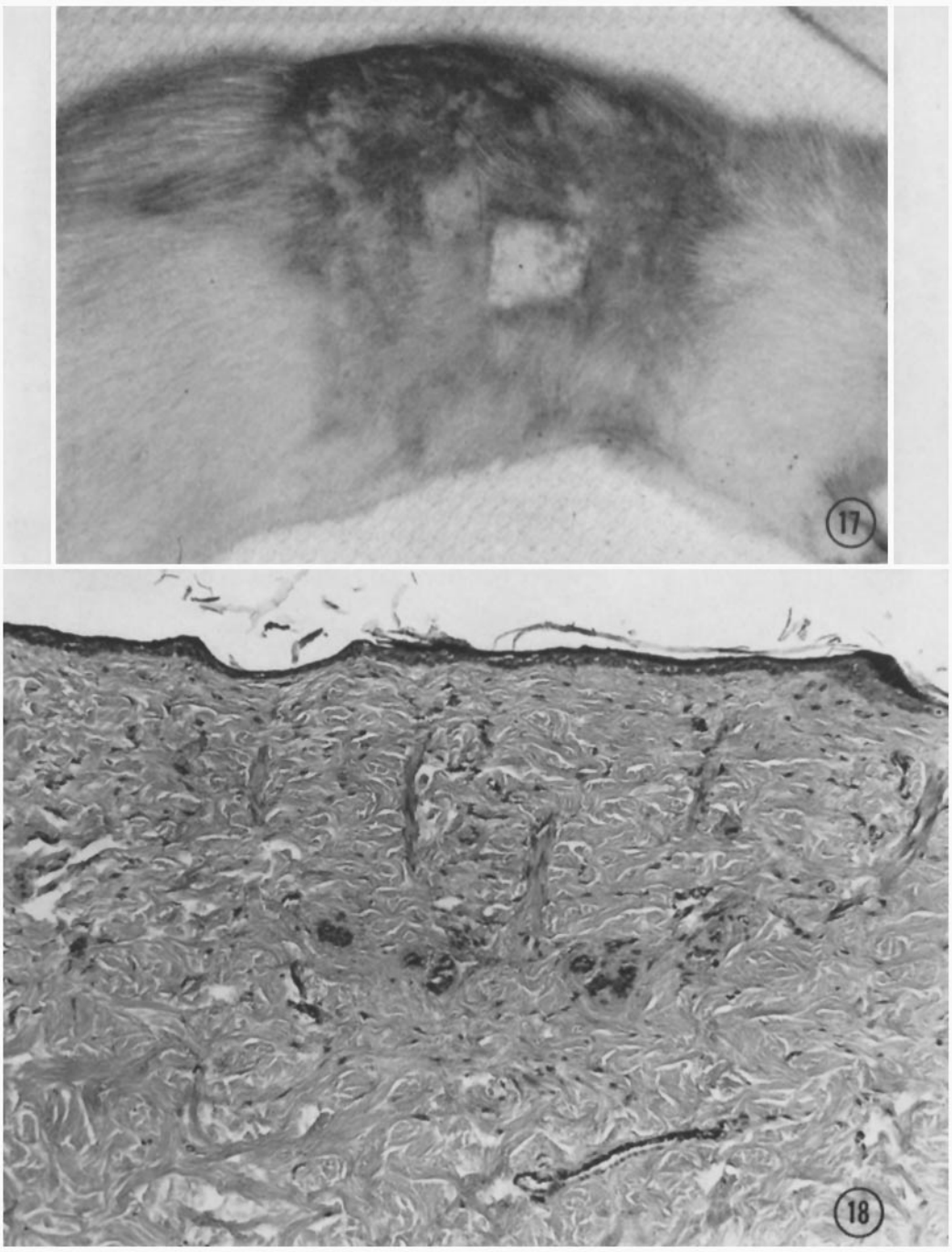
PLATE 69

FIG. 17. Chronic autograft rejection at 45 days. Graft is white, indurated, and leathery in texture. Size is somewhat contracted.

FIG. 18. Chronic autograft rejection at 45 days. Extreme atrophy of overlying epidermis; intense collagenization of dermis with marked atrophy of skin appendages; small clusters of occasional epithelial cells remain. × 115.



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