The fine morphology of the human skin in dermographism

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Ultrastructural changes in the skin of the upper arm were studied with the electron microscope in a male patient, aged 50, with dermographism. Wheals were produced by stroking with 400 Gm. of pressure. Skin samples were obtained with a high-speed dermal punch without anesthesia after 35 seconds, 3, 10, 20, 30, and 60 minutes, and after 3 weeks. Controls were taken from undisturbed skin areas of the patient and from a healthy individual. Edema of the corium, increase of specific cell types, and disruption of cells were not observed. Morphological changes occurred in the epidermis, mast cells, and some sensory nerve endings. The keratinocytes of the epidermis either developed large vacuoles or took up fluid in the peripheral cytoplasm and villous processes. Basal epidermal cells extended pseudopodia into the corium through gaps in the basement membrane. Mast cells showed abnormal structure. Their granules were not released from the cells but underwent transformation during the wheal development. The free subepidermal nerve endings possessed membrane-bounded inclusions in the cytoplasm of their Schwann cells. Some mesaxons of these endings were split apart by accumulation of granular material. The findings provide evidence that the epidermis is a very active tissue layer of the skin and that the morphologic observations are compatible with the current hypothesis that release of histamine by mast cells may play a role in wheal formation.

It is generally believed that dermographic and urticarial wheals are characterized morphologically by local fluid accumulation in the superficial layer of the corium and that the cause of the edema formation is an increase in vascular permeability caused by the local action of histamine or some other chemical agent.[1, 2] The fine morphological changes and the exact sequence of events that occur in the tissues during wheal development and regression are not known. Similarly, the question of involvement of the peripheral nerve endings, vasomotor as well as sensory, has not been adequately clarified.

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Unlike spontaneous urticaria, the dermographic wheal can be studied conveniently through progressive stages of its development. The results may serve as a basis for comparison in experiments with wheal-producing agents and may be pertinent to studies of other forms of urticaria and angioneurotic edema.

MATERIALS AND METHODS

The study was carried out in a cooperative Caucasian man, aged 50, who was found to have dermographism when he sought treatment for generalized itching. Wheals were produced by stroking the lateral aspect of the upper arm with the use of 400 Gm. of pressure according to a technique previously described.[3] Skin samples were obtained with a high-speed dermal punch, without anesthesia, after 35 seconds, 3, 10, 20, 30, and 60 minutes, and after 3 weeks. The results were compared with specimens obtained from undisturbed skin of the patient and from the upper arm of a healthy 20-year-old Caucasian woman. In the latter case samples were obtained from undisturbed skin areas and from an area that was stroked with 400 Gm. of pressure 10 minutes prior to the biopsy.

The skin samples were immediately cut into strips oriented perpendicular to the external surface of the epidermis with the use of two stainless steel razor blades mounted parallel at a distance of 0.3 to 0.5 mm. The slices were fixed in one per cent osmic acid solution buffered at pH 7.4 with phosphate buffer for 2 hours at 4° C. During dehydration in the alcohol series the strips were divided into blocks of desired orientation. They were embedded in Epon 812[4] or Epon-Araldite mixture,[5] cut on a Cambridge-Huxley microtome with a diamond knife in serial ribbons and stained with one per cent uranyl acetate solution for 10 minutes[6] and lead citrate solution for one minute.[7] Electron micrographs were made on Philips 200 and 300 microscopes. Particular effort was made to trace structures in serial and semiserial sections.

Sections of one micron thickness were also prepared from each tissue block. They were stained with one per cent toluidine blue solution and used for studies with the optical microscope.

RESULTS

Clinical findings

The biopsies were obtained during a 10 month period while the patient was under treatment with chlorpheniramine, 4 mg., and chlorothiazide, 500 mg., which he took every morning, usually 4 hours prior to the session. The medication produced satisfactory relief of itching and some reduction in the intensity of the whealing response.

When the skin of the patient, under the regular medication, was stroked with 400 Gm. of pressure, a pale line appeared for approximately 20 seconds, followed by an expanding erythema and the wheal. The raised area of the wheal was sharply demarcated from the surrounding skin. When fully developed the wheal appeared pale. The course of the reaction varied to some extent from session to session. It is summarized in Table I.

The patient had no history of spontaneous urticaria. Local cooling of the skin with an ice cube or heating with a test tube containing hot water failed to in-

Table I. *Development and regression of the dermographic wheal induced by 400 Gm. pressure*

Time lapse after stroking	*Erythema width (mm.)*	*Wheal width (mm.)*
30 sec.	2	—
1 min.	2-3	—
2 min.	3	No visible elevation, wheal palpable as a linear condensation
3 min.	4	2
5 min.	4-5	3
10-20 min.	5-6	4
30 min.	3	3
60 min.	—	No visible elevation, wheal palpable as a linear condensation

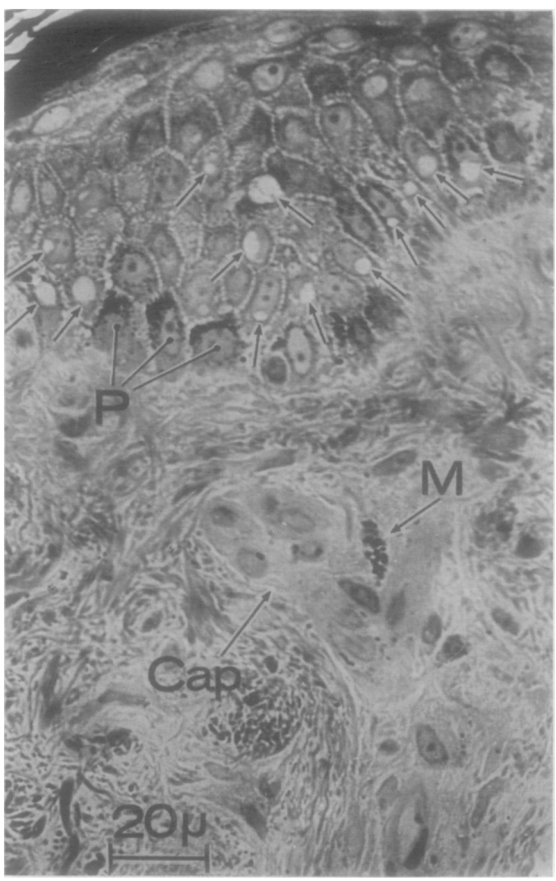


Fig. 1

Section of the skin cut perpendicularly to its surface from a dermographic wheal area 10 minutes after stroking with 400 Gm. of pressure. The corium shows no appreciable interstitial edema or infiltration of any specific cell types. A number of epidermal cells contain vacuoles in their cytoplasm (unlabeled arrows). *P* = pigmented basal epidermal cells, *Cap* = capillary cut obliquely. *M* = adventitial mast cell. Epon-embedded material, 1 μ thick section. (Toluidine blue. ×600.)

duce whealing. A stroke applied over the skin immediately afterwards resulted in a wheal over the untreated and cooled areas only. In the heated, erythematous skin area the reaction appeared to be completely inhibited. When the blood vessels of the arm were occluded with a tourniquet, stroking the skin distal to the occlusion did not produce a wheal. Similarly, no whealing response was obtained in the site of a wheal that had just faded. The length of the refractory period was not determined.

Morphological findings

Thick Epon-embedded sections stained with toluidine blue showed that there was no appreciable interstitial edema of the corium or infiltration of specific cells at any stage of the whealing reaction. This can be seen in Fig. 1, which represents the central area of the wheal 10 minutes after stroking when the reaction is most extensive (compare with Table I). These findings were confirmed electron microscopically in all instances. The principal changes that occurred during the whealing reaction were localized in the cell bodies and occurred both in the epidermis and in the corium.

The epidermis. The Langerhans' cells and melanocytes appeared to undergo little change except that cisternae of the granular endoplasmic reticulum became moderately distended while the wheal was present. Significant changes were observed in many keratinocytes of the basal and spinous cell layers; though the reaction varied from cell to cell, and a considerable number of keratinocytes remained morphologically unchanged even when the wheal was most extensive.

There were three principal kinds of changes that took place in different epidermal cells.

1. A number of keratinocytes developed single, large membrane-bounded vacuoles adjacent to the cell nuclei. Some vacuoles were already seen in the samples 35 seconds and 3 minutes after stroking (*Vc* in Fig. 2), but they were largest and most numerous 10 minutes after stroking when the wheal was most extensive. At this stage the vacuoles were easily recognized with the optical microscope (unlabeled arrows in Fig. 1). The membrane enclosing the vacuoles appeared smooth. The vacuoles were never found continuous with the cisternae of the endoplasmic reticulum. They invaginated the cell nuclei but did not communicate with or obliterate the perinuclear cisternae. The latter appeared compressed in areas where the walls of the vacuoles abutted the nuclei (*a*, *b*, and *c* in Fig. 3). Elsewhere, the perinuclear cisternae were normal or enlarged (*Cs* in Fig. 3). The vacuoles were filled with fluid and some amorphous material, probably a precipitate resulting from osmium fixation. The intercellular spaces surrounding the vacuolated cells were slightly distended and seemed to contain a similar amorphous material (*Is* in Fig. 3). The mitochondria of the vacuolated cells were not swollen (*M* in Fig. 3). The endoplasmic reticulum was scarce; its cisternae were sometimes slightly distended. Some vacuolated keratinocytes contained pigment granules (*P* in Fig. 3), while others were devoid of them (Fig. 2).

The number of vacuoles started to diminish while the wheal was still noticeable and became scarce 20 minutes after stroking. An occasional vacuolated

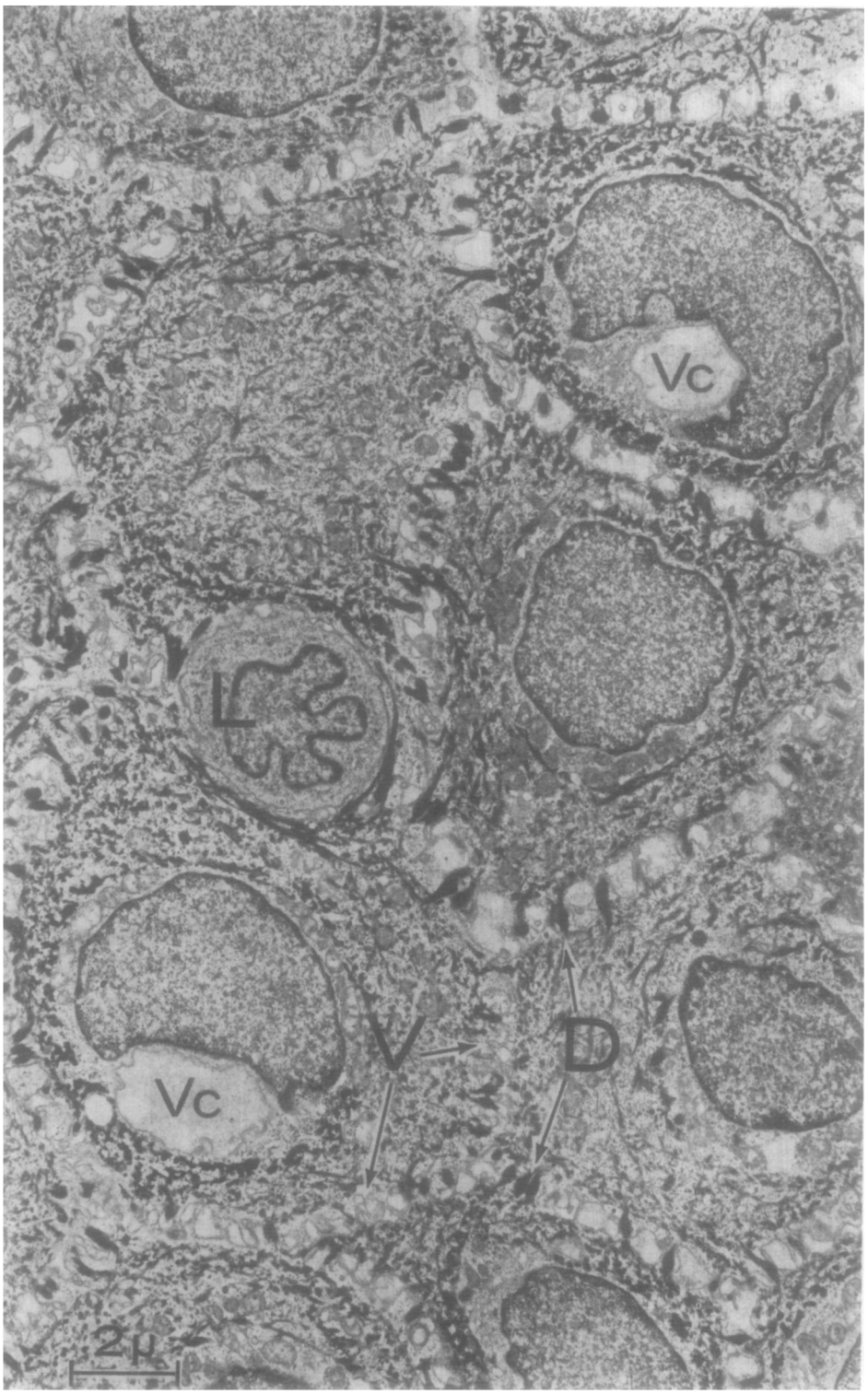


Fig. 2
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keratinocyte was found 60 minutes after stroking. In the latter case, the contents of the vacuole appeared dark and homogeneous. The adjacent intercellular spaces contained a similar dense material.

2. Certain keratinocytes that did not develop vacuoles showed changes in the peripheral cytoplasm. Normally, the cell surfaces of keratinocytes possess fine villous processes that project into the intercellular spaces (*V* in Fig. 4; compare with Fig. 2). During the whealing reaction of the skin, the villous processes and the peripheral cytoplasm of certain keratinocytes were enlarged to a varying degree, obliterating the surrounding intercellular spaces and deforming the adjacent cells (Fig. 5). Some keratinocytes were symmetrically enlarged (Fig. 5), while others developed processes that extended for some distance between adjacent epidermal cells. Not infrequently the distal end of a long process was greatly enlarged and exceeded the size of the nuclei of the surrounding cells (*V* in Fig. 6). The expanded processes of keratinocytes contained fine granular material (Figs. 5 and 6). The above changes were observed during all stages of wheal development and regression. They were even seen in the undisturbed skin, but infrequently.

3. Some basal epidermal cells developed cytoplasmic projections or pseudopodia which extended into the corium through gaps in the basement membrane (*P* in Figs. 7, 8, and 9). In the early stages of whealing, they contained the regular cytoplasmic components (*P* in Fig. 7). In later stages, the pseudopodia were pale and contained some amorphous or fine granular material along with occasional thin-walled vesicles (*P* in Figs. 8 and 9). Most of the epidermal cells that developed pseudopodia appeared to be regular basal keratinocytes connected to their neighbors by desmosomes and anchored to the corium by hemidesmosomes (*D* in Fig. 9 and *HD* in Fig. 7). Occasionally part of a Langerhans' cell was seen extending into the corium through a gap in the basement membrane. At times a cell containing Langerhans' corpuscles was encountered in the corium, separated from the epidermis by the basement membrane. The corial cells in contact with the pseudopodia of keratinocytes had the typical appearance of fibrocytes (*F* in Fig. 8). Exceptionally, the contiguous cell was recognizable as a monocyte.[8] Pseudopodia were observed during all stages of wheal development and regression and occasionally in the undisturbed skin of the patient.

The control specimens obtained from the healthy volunteer with clinically normal skin showed normal fine morphology before and after stroking with 400 Gm. of pressure.

The corium. The blood vessels of the corium were usually found empty both in the patient and in the healthy volunteer, possibly as a result of the pressure exerted by the dermal punch when the skin samples were taken. In the specimens

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Fig. 2

Section of the epidermis cut parallel to the skin surface through the germinal cell layer from a dermographic wheal area 3 minutes after stroking. Two keratinocytes contain vacuoles *(Vc)* that invaginate the cell nuclei. *L* = Langerhans' or white dendritic cell. *D* = areas containing desmosomes (black). *V* = villous processes of keratinocytes that project into the intercellular spaces. (×7,000.)

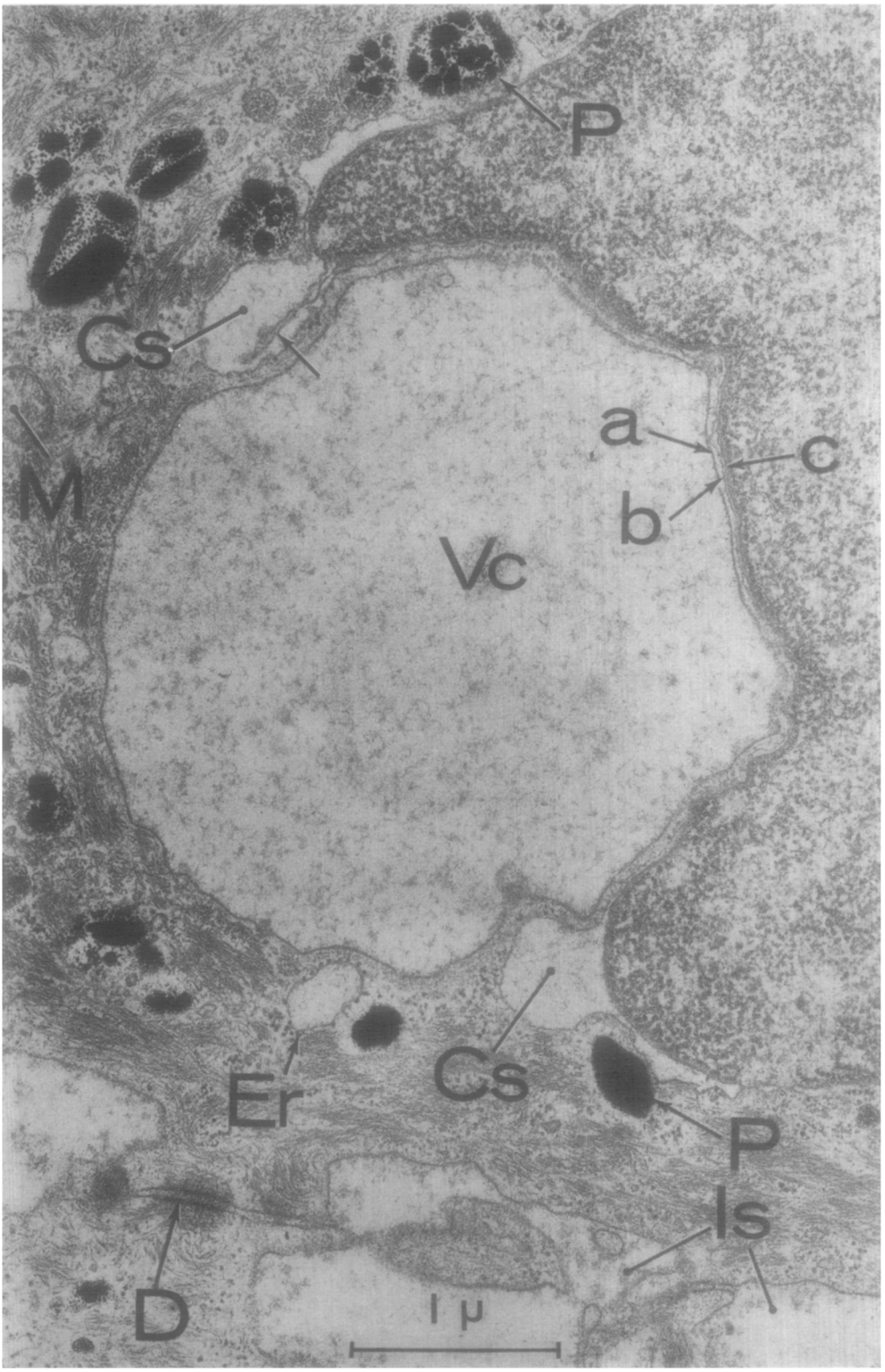


Fig. 3
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Fig. 3

Section of a keratinocyte of the stratum spinosum from a dermographic wheal area 10 minutes after stroking. *Vc* = membrane-bounded vacuole. It invaginates the cell nucleus but does not fuse with or obliterate the perinuclear cisterna: *a* = boundary membrane of the vacuole, *b* = external nuclear membrane, *c* = internal nuclear membrane. *Cs*, = enlarged parts of the perinuclear cisterna. Note the villous projection of the internal nuclear membrane in the cavity of the dilated cisterna (unlabeled arrow). *M* = mitochondrion. *Er* = granular endoplasmic reticulum. *P* = pigment granules. *D* = desmosome. *Is* = intercellular space. (×30,000.)

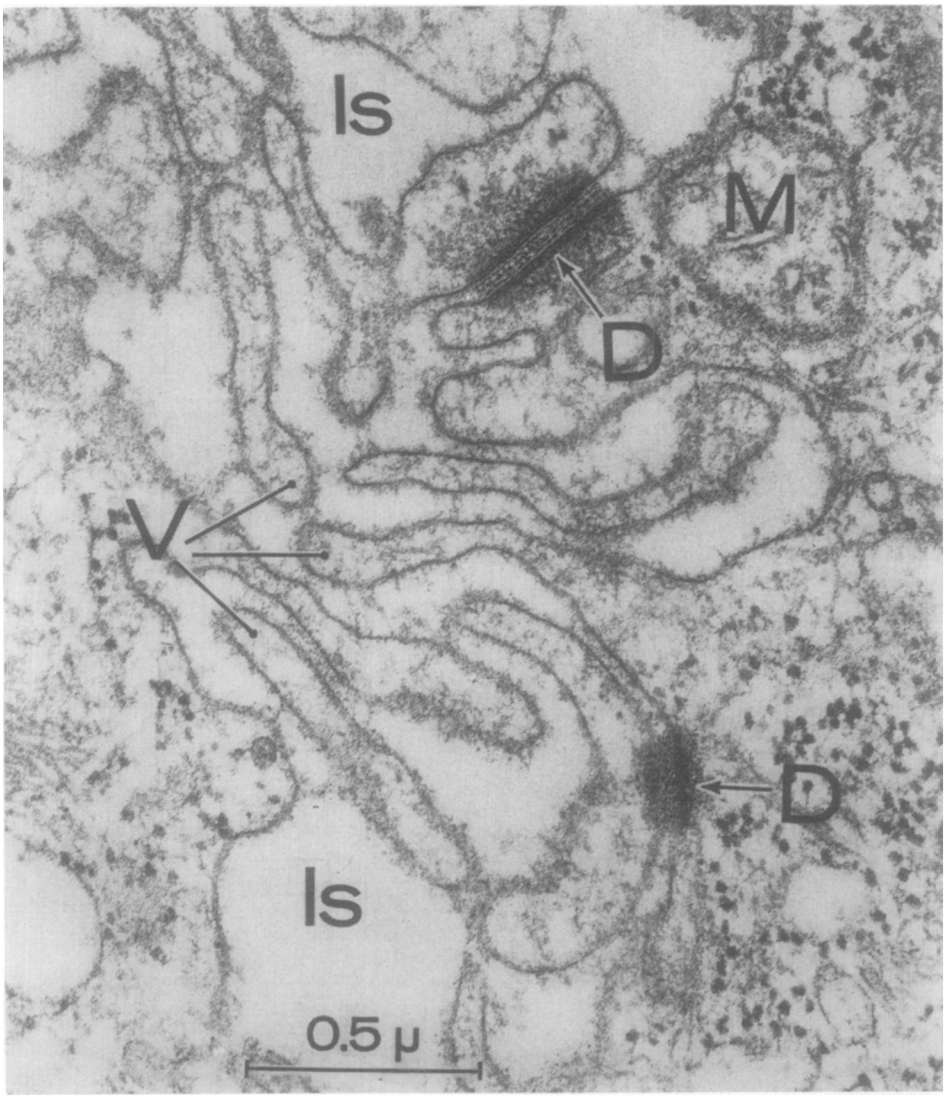


Fig. 4

Section of a junctional area between two basal keratinocytes of the epidermis showing the intercellular spaces *(Is)*, desmosomes *(D)*, and villous process *(V)* of the epidermal cells. *M* = mitochondrion. (×60,000.)

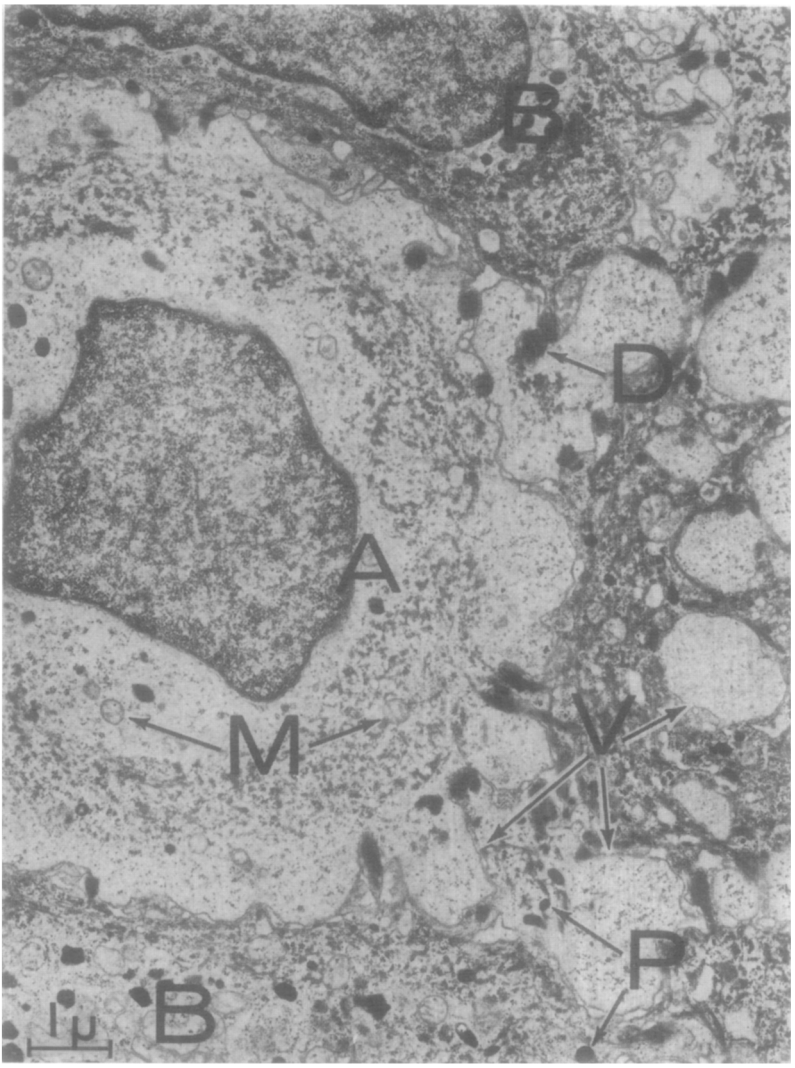


Fig. 5

Section of the epidermis through the germinal cell layer from a dermographic wheal area 3 minutes after stroking. *A* = swollen keratinocyte. *B* = apparently normal keratinocytes. *V* = expanded villous processes (compare with *V* in Fig. 4). *M* = mitochondria of the swollen cell that have normal appearance. *D* = desmosomes. *P* = pigment granules. (×10,000.)

Fig. 6

Section of the epidermis through the germinal cell layer from a dermographic wheal area 30 minutes after stroking. *A* = keratinocytes of normal appearance. *B* = keratinocyte with slightly swollen marginal cytoplasm. *V* = enlarged villous processes of keratinocytes. L = Langerhans' cell deformed by the greatly enlarged adjacent villous process. *Is* = intercellular space containing villous processes of normal appearance. *D* = desmosomes. *P* = pigment granules. (×10,000.)

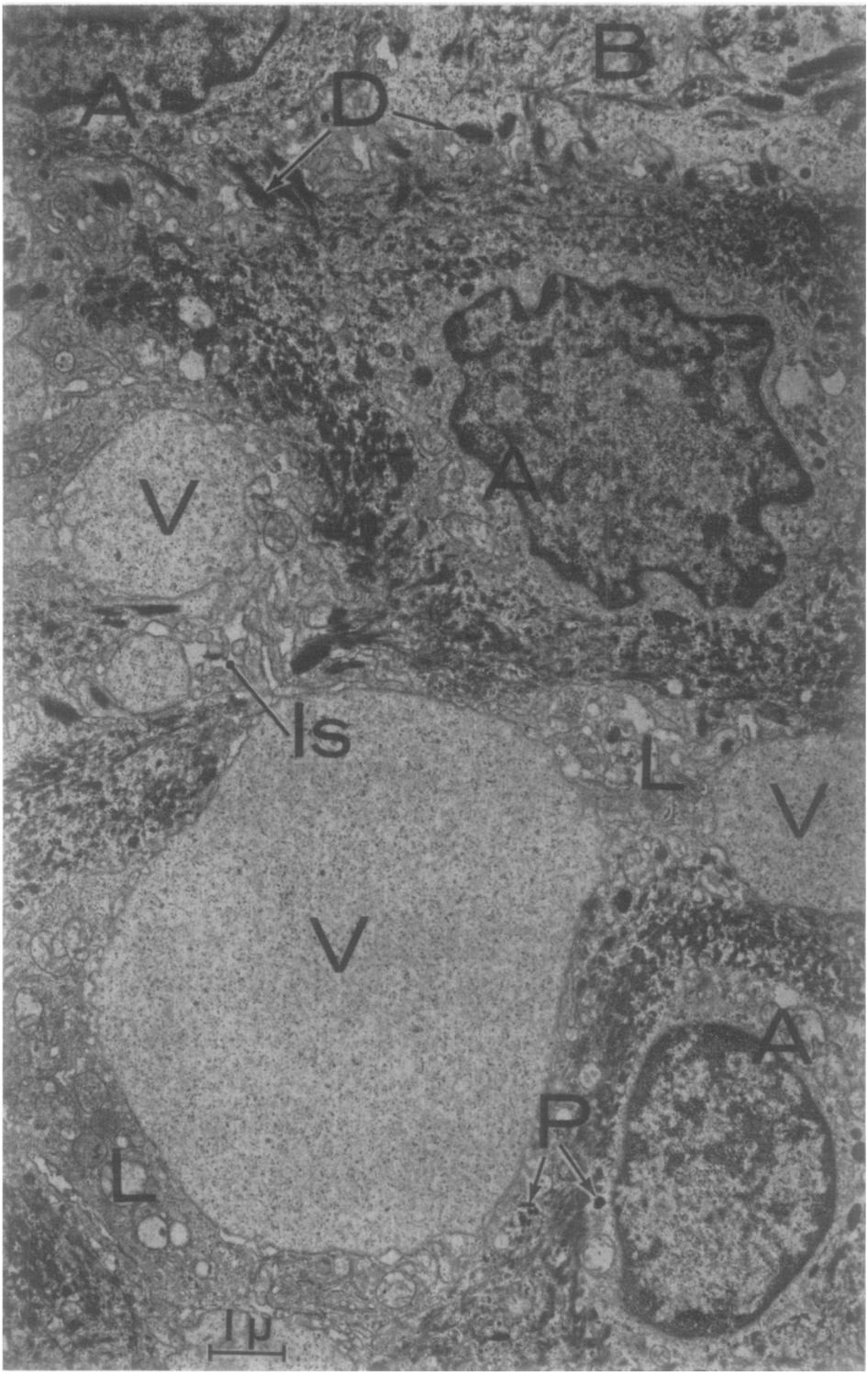


Fig. 6
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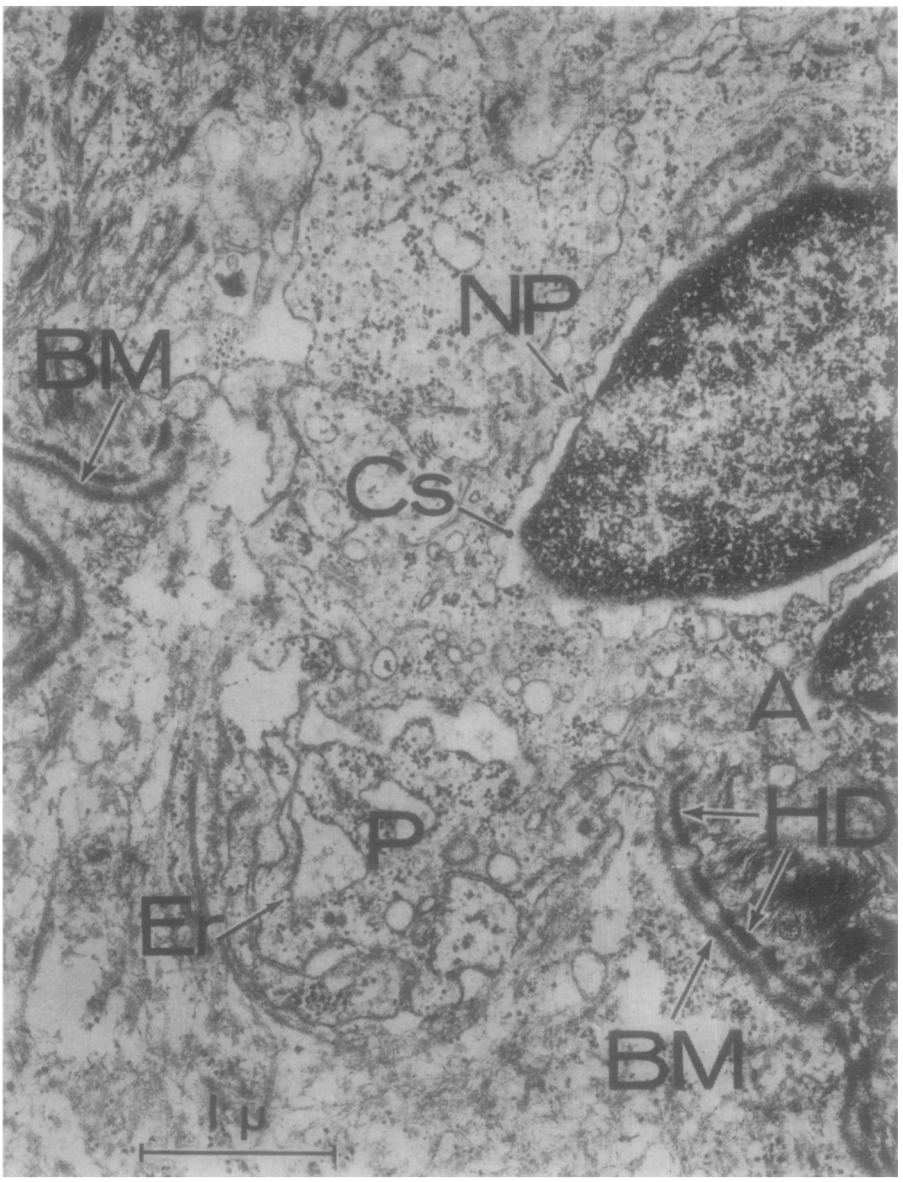


Fig. 7

Section of the skin through the junctional area between the epidermis and the corium from a demographic wheal area 3 minutes after stroking. *BM* = basement membrane of the epidermis. *A* = basal epidermal cell sending a cytoplasmic process or pseudopodium *(P)* into the corium through a gap in the basement membrane. *HD* = hemidesmosomes. *Cs* = slightly enlarged perinuclear cisterna. *NP* = nuclear pore. *Er* = granular endoplasmic reticulum, dilated. (×25,000.)

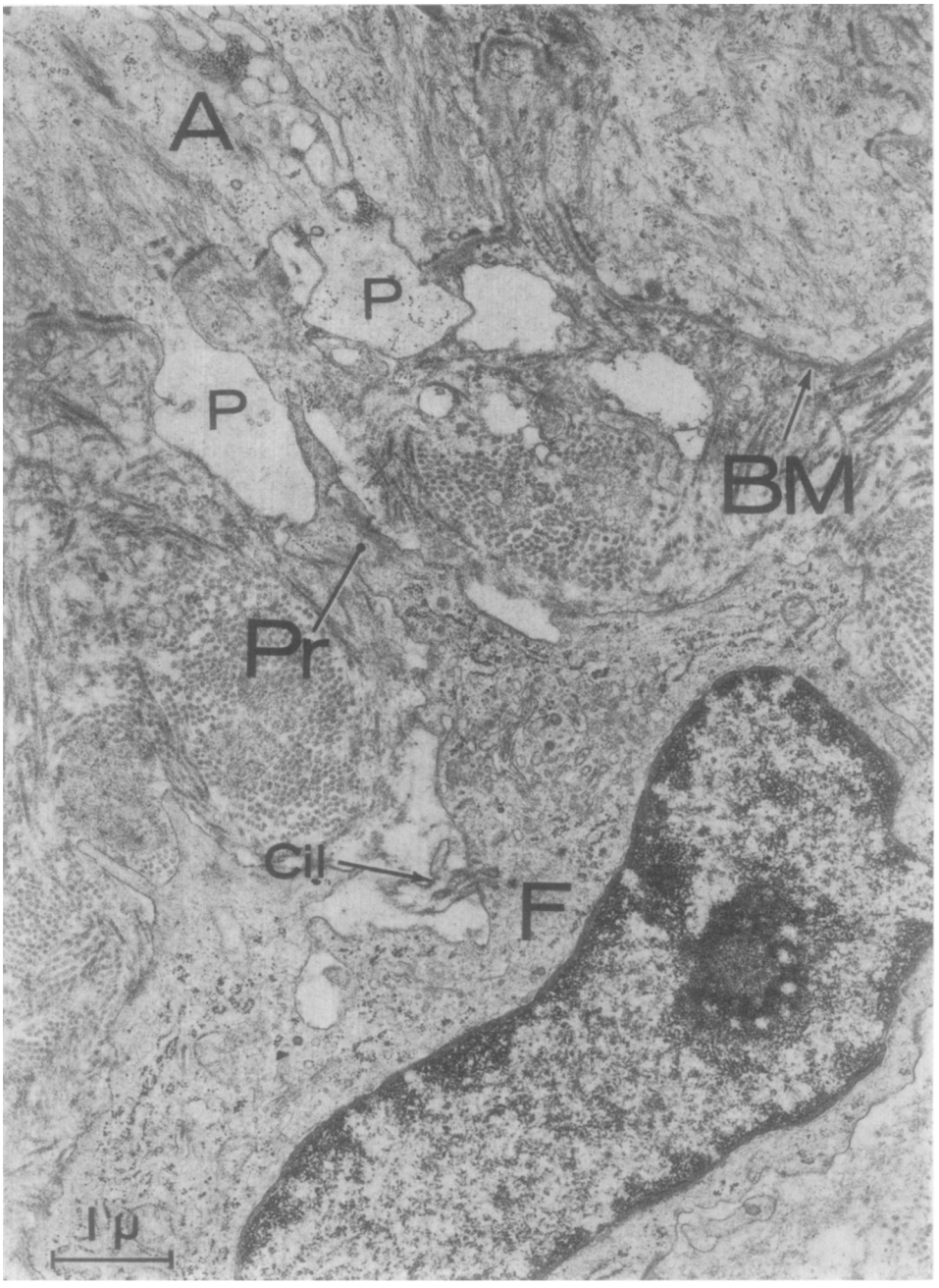


Fig. 8

Section of the skin through the junctional area between the epidermis and the corium from a dermographic wheal 60 minutes after stroking. *BM* = basement membrane of the epidermis. *A* = basal keratinocyte sending pseudopodia *(P)* into the corium through gaps in the basement membrane. *F* = subepidermal fibrocyte sending a process *(Pr)* towards the pseudopodium and enwrapping part of its surface (compare with Fig. 9). *Cil* = cilium of the fibrocyte. (×15,000.)

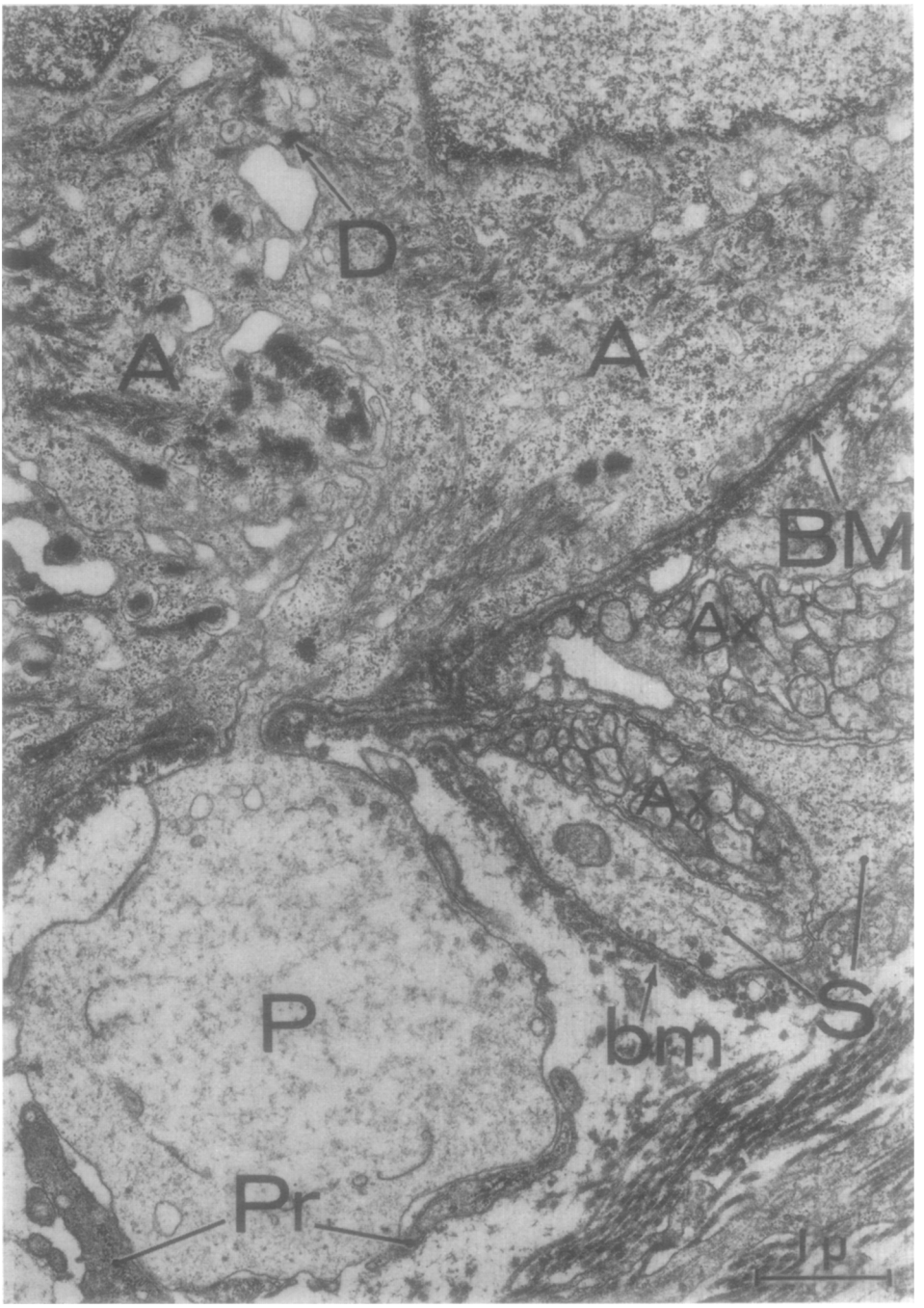


Fig. 9

Section through the junctional area between the epithelial root sheath of a hair and the surrounding corium from a dermographic wheal area 60 minutes after stroking. *BM* = basement membrane of the epithelial root sheath. *A* = basal keratinocytes one of which sends a pseudopodium *(P)* into the corium through a gap in the basement membrane. *D* = desmosome. *Pr* = processes of a corial cell enwrapping the surface of the pseudopodium. *Ax* = axon terminals of a nerve ending cut transversely. Their axoplasm is filled with mitochondria, granules (probably glycogen), and occasional vesicles. *S* = terminal Schwann cell processes of the ending containing granular endoplasmic reticulum, free granules, and some fine vesicles. *bm* = basement membrane of the nerve endings. (×17,000.)

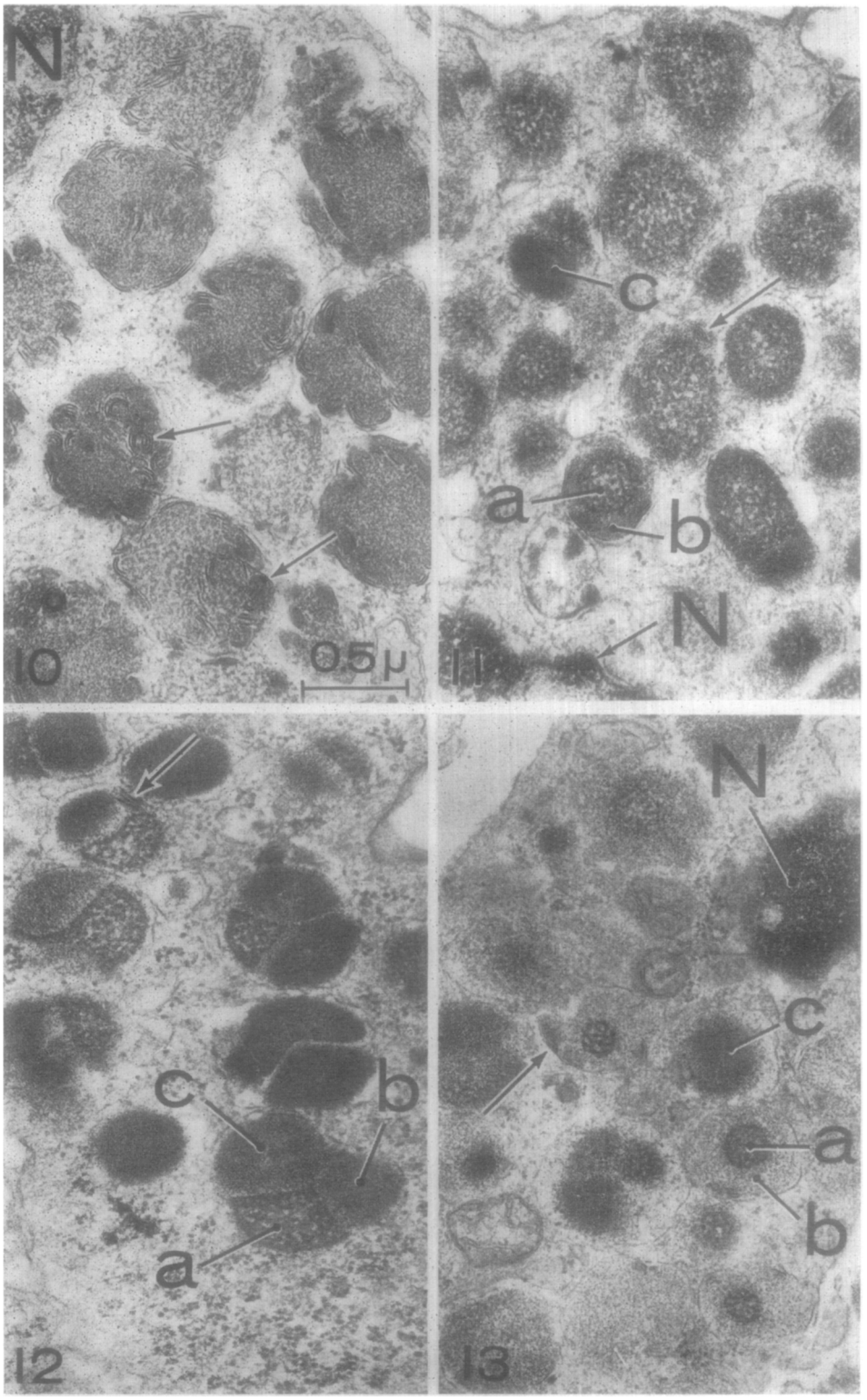
of the dermographic wheal obtained 35 seconds after stroking, the endothelial cells of some capillaries and venules were filled with vacuoles of various sizes. Some venules possessed open endothelial junctions resembling the condition demonstrated by Majno and associates in experiments with histamine and serotonin.[9, 10]

The fibrocytes of the papillary layer, the Schwann cells of the nerve endings, and some smooth muscle cells were characterized by distended cisternae of the granular endoplasmic reticulum. As the wheal regressed, the corial cells became similar to those found in the undisturbed skin.

The tissue mast cells of the patient appeared to be more extensively involved. Although their distribution did not appear to be significantly different from that of the normal skin, their abundant granules differed in appearance from normal human mast cell granules and underwent changes during the wheal development.

The mast cells of the dermographic patient were compared with those obtained from normal skin and also with those obtained from clinically normal nasal respiratory mucosa in 3 patients who underwent corrective surgery of a deviated nasal septum. In the apparently normal cases, the mast cell granules were spherical or nearly spherical and of a rather uniform size, ranging between 0.6 and 0.7 μ in diameter. Their internal structure appeared partly granular, partly lamellar. The lamellar element was arranged in layers which frequently resembled scrolls or myelin figures (unlabeled arrows in Fig. 10). In the skin of the patient suffering from dermographism, the mast cell granules were irregular in shape, size, and internal structure. Mast cell granules typical of the undisturbed skin areas of the dermographic patient are shown in Fig. 11. The diameter of the granules ranged from 0.3 to 0.7 μ; their internal structure varied in texture and density (*a*, *b*, and *c* in Fig. 11). The lamellar element was mostly absent except at the periphery of some granules (unlabeled arrow in Fig. 11). During the wheal development, disruption of mast cell membranes or release of their granules into the interstitial space was never observed, but the granules underwent structural changes inside the cells. Fig. 12 shows part of a mast cell from the skin 3 minutes after stroking. Some granules are large and consist of clearly demarcated segments of varying substructure (*a*, *b*, and *c* in Fig. 12). The lamellar element is scarce (unlabeled arrow in Fig. 12). Fig. 13 shows part of a mast cell from a 10 minute wheal. The number of granules has not decreased, but most granules appear pale except for some central core regions. The different substructural components can be recognized (*a*, *b*, and *c* in Fig. 13), and an occasional lamellar element is also seen (unlabeled arrow in Fig. 13).

The autonomic nerves supplying the blood vessels, arrectores pilorum muscles, and sweat glands showed no conspicuous morphological changes during the wheal development except for occasional dilated cisternae of the granular endoplasmic reticulum in the Schwann cells. The sensory end organs showed additional changes. These were quite marked in the frequently seen subepidermal horizontal endings,[11, 12] which were found between hair orifices, sending fine axonal twigs into the overlying epidermis. The preterminal segments of the horizontal endings were found in the vicinity of the small blood vessels



Figs. 10 to 13
For legends see opposite page.

Fig. 10

Part of a mast cell from histologically normal nasal respiratory mucosa from a male patient, aged 16 years, who does not suffer from dermographism. The mast cell granules are spherical and of uniform size and structure consisting of granular and lamellar elements. The lamellar elements are arranged in layers which frequently show scroll patterns (unlabeled arrows). *N* = mast cell nucleus. (×30,000.)

Figs. 11 to 13

Portions of mast cells from the skin of the patient suffering from dermographism. Fig. 11, from undisturbed (unstroked) skin. Fig. 12, from dermographic wheal area 3 minutes after stroking. Fig. 13, from dermographic wheal area 10 minutes after stroking. The mast cell granules are irregular in shape, size, and internal structure. They contain at least three kinds of granular material: *a* = coarse granules, *b* = fine granules of random orientation, *c* = fine granules showing varying degree of crystalline structure. The lamellar element (unlabeled arrows) is restricted to the periphery of some granules. *N* = mast cell nucleus. (×30,000.)

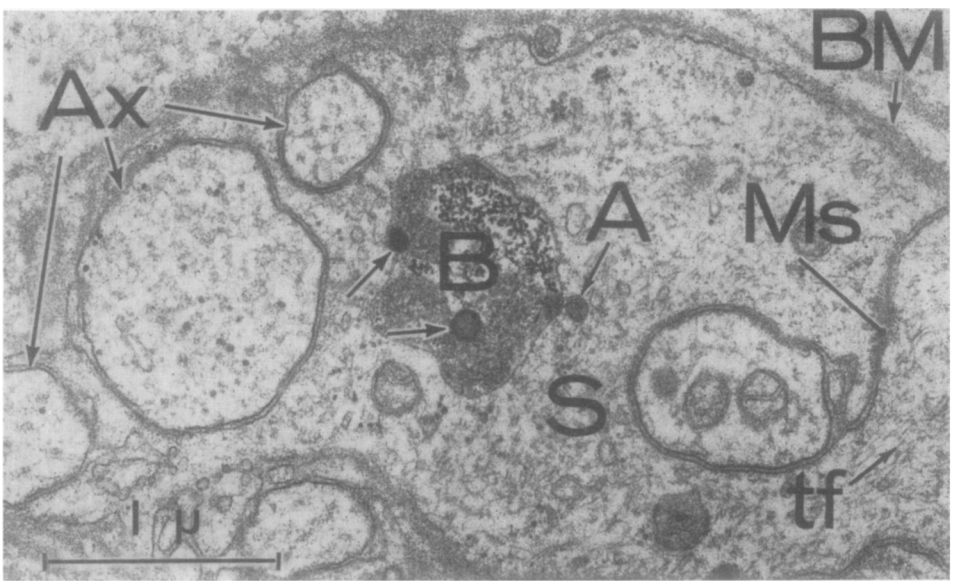


Fig. 14

Part of a horizontal subepidermal nerve ending, cut transversely from a dermographic wheal area 3 minutes after stroking. *S* = Schwann cell of the ending containing mitochondria, fine granules, vesicles, and tubular or filamentous material *(tf)*. *A* = small spherical inclusion. *B* = large irregular inclusion which contains fine and coarse granules and two dense structures (unlabeled arrows). *Ax* = axon terminals. *Ms* = mesaxon. *BM* = basement membrane of the nerve ending. (×30,000.)

and, therefore, are most likely involved in the axon reflexes. A common feature of the Schwann cell cytoplasm of the horizontal endings was a fibrillar or tubular component oriented parallel to the course of the axon terminals (*tf* in Fig. 14). In samples obtained from the wheal areas, many Schwann cells also contained membrane-bounded inclusions of spherical or irregular shape. Their diameter ranged from less than 0.1 μ to over 1 μ (*A* and *B* in Fig. 14). They were packed

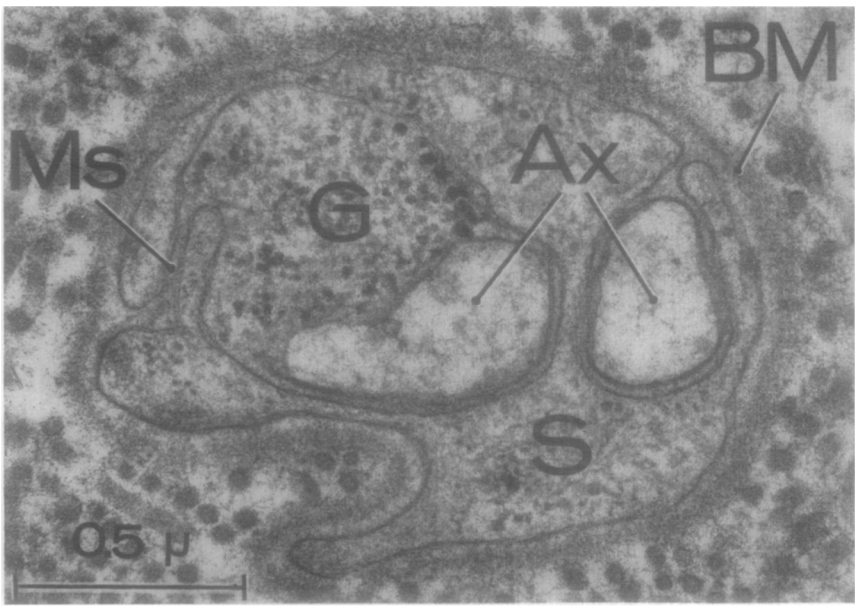


Fig. 15
Part of a horizontal subepidermal nerve ending cut transversely from a dermographic wheal area 3 minutes after stroking. *S* = Schwann cell of the ending. *Ax* = axon terminals. *Ms* = mesaxon. *G* = granular material between the layers of the mesaxon. *BM* = basement membrane of the ending. (×60,000.)

with fine and coarse particles of irregular arrangement and sometimes contained dense spherical structures (unlabeled arrows in Fig. 14).

An unusual feature was observed in some subepidermal horizontal endings 35 seconds and 3 minutes after stroking. In these nerves, the apposed layers of the mesaxons were widely separated by accumulation of irregular granular material (*G* in Fig. 15). The granules were extracellular but were separated from the general extracellular space by the basement membrane of the nerve ending. The axoplasm of these nerve endings appeared relatively pale (*Ax* in Fig. 15).

The papillary nerve endings of the skin and the nerve spindles that encircle the tactile hairs were infrequently encountered in this study. The axon terminals of the tactile hairs were packed with mitochondria. The spaces between these organelles were filled with granules, probably glycogen, and some vesicles (*Ax* in Fig. 9). The Schwann cell processes flanking the axon terminals contained unusually few pinocytotic vesicles for this kind of nerve ending[13] but did contain some granular endoplasmic reticulum, free granules, and fine tubular or fibrillar material (*S* in Fig. 9).

DISCUSSION

Contrary to the generally accepted view, the present findings suggest that whealing of the skin is an active process in which the cells of the epidermis and the corium are involved. Some of the fluid that is released from blood vessels

apparently spreads out in the corium and is reabsorbed without producing an appreciable edema. The rest of it is taken up by the overlying germinal cell layer of the epidermis. The keratinocytes either develop single large membrane-bounded vacuoles (Figs. 1, 2, and 3) or take up fluid in the cytoplasm. In the latter case, they send out cytoplasmic processes which compress and displace the neighboring cells that do not undergo apparent morphological changes (Figs. 5 and 6). At the same time, some basal epidermal cells extend pseudopodia into the corium through gaps in the basement membrane and establish contact with the corial cells (Figs. 7, 8, and 9). As a result of intracellular fluid accumulation in the epidermis, the wheal is sharply demarcated and moves with the epidermis, and the edema does not spread out. Before the swelling becomes elevated at the beginning of the wheal development, its position can be palpated as a condensation. The same happens in reverse when the wheal subsides (Table I).

The present findings provide morphological evidence that the epidermis is a very active tissue layer of the skin and that its cells are capable of several kinds of responses to agents released in the corium. The diversity of the response, or lack of it, by apparently identical keratinocytes is somewhat puzzling, but it could be related in part to variation in age of the cells with respect to their last division and to uneven distribution of the active agent.

The changes observed in the epidermal cells may not be specific to the dermographic wheal. Large intracytoplasmic vacuoles in the epidermal cells have been observed under diverse conditions, including ultraviolet irradiation[14] and epidermolysis bullosa.[15] To the authors' knowledge, pseudopodia of the basal epidermal cells have not been seen traversing the basement membrane in unbroken skin, but they have been found in regenerating epidermis during wound repair.[16] Therefore, the morphological findings in dermographism give some insight into the biological processes that may take place in the epidermis during metabolic disturbances or physical damage.

In the papillary layer of the corium, most cell types undergo some change during wheal development, including increased activity of the granular endoplasmic reticulum. Mast cells of the dermographic patient show abnormal structure even in the undisturbed skin areas (compare Fig. 11 with Fig. 10), and their granules undergo a process of transformation during the development of the wheal (Figs. 12 and 13). Mast cells are the principal source of endogenous histamine,[17] which is stored mainly in their granules.[18] Therefore, the above morphological changes in the mast cell granules during wheal development may be associated with the release of histamine. When released, this agent would act upon the walls of the capillaries and venules causing a permeability change in the endothelium and at the same time would initiate a reaction by the cells of the corium and the epidermis. The refractory period of the skin to repeated stroking could signify the time required by mast cells to reform histamine. The epidermis of the patient contains occasional swollen keratinocytes in all samples taken from undisturbed skin areas and from the site of the wheal 3 weeks after stroking. Considering that the mast cells have an abnormal structure in these areas, the finding may indicate that some histamine is being released from the

mast cells in response to minor irritation of the skin or even to normal friction to which it is constantly subjected.

During wheal development, morphological changes also occur in the sensory nerve endings that supply the epidermis and the papillary layer of the corium. The nerves are closely related to the superficial capillaries and venules that are devoid of autonomic innervation. Therefore, these sensory endings may affect local microcirculation by means of axon reflexes. In particular, they may be responsible for the erythema that precedes and accompanies the wheal. The present findings offer no indication as to what extent the sensory nerve endings are involved in the actual wheal formation mechanism. The changes that occur in the structure of the end organs may be the consequence of the wheal development rather than the cause and may be a morphological reflection of the itching or burning sensation that is associated with the lesion. These findings should be useful in further studies of the normal and abnormal functions of the peripheral receptor organs.

Wheal formation can be elicited by a number of agents other than histamine,[1, 2] and experimental evidence has been offered that other mechanisms may be involved in whealing.[19] Therefore, the present findings may not characterize all forms of dermographism but may rather provide a starting point for systematic and comparative studies.

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