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THE HISTOLOGY OF ICHTHYOSIS*

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Descriptions of histological characteristics in ichthyosis differ on the significance of certain features. Nevertheless, in the textbooks of Blum (1), Degos (2), Lever (3) and Percival, Montgomery and Dodds (4) there is agreement on the following: the stratum corneum is thickened and there is no parakeratosis; the stratum granulosum is thinned or absent; the stratum mucosum is thinner than normal; the stratum germinativum is normal; the rete ridges are thinned and reduced in number; the hair follicles may show follicular plugging and both the sebaceous and sweat glands are reduced in number. The two French authors concluded that there was usually a perivascular infiltrate in the dermis. Degos agreed with the observation of Unna and Tomassoli (5) that this infiltrate contained mast cells. Degos summarized the changes by stating that the only constant feature was hyperkeratosis, while Lever emphasized that hyperkeratosis was associated with diminution or even complete absence of the granular layer.

Blum (1) and Laymon and Murphy (6) tabulated the histological differences between ichthyosis and ichthyosiform erythrodermia. The histological features of the latter were better defined and consisted of very marked hyperkeratosis, hypertrophy of the granular layer, greatly increased thickness of the stratum mucosum, elongation and irregularity of the rete ridges, well-developed sebaceous glands and a definite perivascular infiltrate. Similar changes were present in the bullous form of ichthyosiform erythrodermia, but Nikolsky (7) was the first to report additional features which have since been confirmed by Barker and Sachs (8), Lapière (9) and Simpson (10). In their patients the upper part of the stratum mucosum showed intracellular edema with the formation of small cavities of irregular shape and size. Some of the prickle cell boundaries had disappeared, and the nuclei and protoplasm had become granular. Cell boundaries that had survived adjacent to the granular layer formed multiloculated cavities some of which were empty, while others contained a much modified nucleus which resembled a "corps rond" or "grain" and some contained granules of varying size. Cavity formation extended into the granular layer and to a lesser extent into the horny layer.

The purpose of the present report is to describe characteristic features of some types of ichthyosis classified on a clinico-genetic basis (11).

MATERIAL AND METHODS

Among the patients with ichthyosis who were examined during a survey in five English counties there were 89 affected men from families whose pattern of inheritance was that of a sex-linked recessive gene. An additional 180 persons of either sex came from families in which the condition was attributed to an autosomal dominant gene. Skin biopsy specimens were obtained from 27 persons, of whom 15 (all men) had sex-linked ichthyosis, and 12 (8 men and 4 women) had the dominant variety. As judged by the extent of body-surface involvement all the sex-linked patients were classified as severely affected, and of the dominant group, 8 were regarded as severely affected, 3 as moderately and 1 as mildly affected. Four men with dominant ichythosis had one or more manifestation of atopy, and one woman suffered from atopic eczema. In addition, five clinically normal women, established on genetic evidence as heterozygous for sex-linked ichthyosis, were examined.

Biopsy specimens were obtained from the posterior aspect of the upper arm, an area commonly and often markedly involved by ichthyosis. None of those with atopic lesions had eczema in this area.

Hibitane was used to clean the skin and remove loose scales. The procedure was undertaken with a Martin's biopsy punch handle and 5 mm drill under local anesthetic. The sections were stained with hematoxylin and eosin. Two sections from each ichthyotic group and from controls were stained with Azur A in order to examine mast cells.

For comparison, sections were taken from two patients with the characteristic features of ichthyosiform erythrodermia and stained with hematoxylin and eosin. No patient was encountered with bullous ichthyosiform erythrodermia. Control biopsy material was obtained from six cadavers with skin of normal appearance using a technic similar

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TABLE I

	Age group in years			
	<20	20-40	40+	Total
Sex-linked ichthyosis				
Affected men	5	5	5	15
Heterozygous women	—	4	1	5
Dominant ichthyosis				
Affected men	3	3	2	8
Affected women	1	1	2	4
Controls				
Men	2	2	1	5
Women	—	1	1	2
Total	11	16	12	39

to that described above, except that no local anesthetic was injected. An additional biopsy specimen was taken from one normal woman. The post-mortem specimens obtained from persons who had been dead for less than eight hours (four had been dead for less than four hours), were as follows, beginning with the youngest: two male children with Fallot's tetralogy, three men who had died respectively from pulmonary hypertension, aplastic anaemia and carcinoma of the bowel, and one woman with a glioma.

Because sections from women heterozygous for sex-linked ichthyosis showed, as predicted, no abnormal features they were included in the control group.

The age group and genetic category of the patients and their controls are given in Table I. Each section was examined independently by two observers, neither aware of its origin.

RESULTS

The results for 12 controls, 12 dominant patients and 12 sex-linked patients are given in Table II. As noted in Table II there was little disagreement between the assessment of each observer. Three of the 12 sex-linked patients had affected brothers whose skin was also examined, and their results are added in the final column.

A. Ichthyosis inherited as an autosomal dominant trait

Hyperkeratosis was not marked in these patients, and by comparison with the controls was increased in only four sections (Fig. 1). Follicular plugging was seen in three sections and parakeratosis in one (Fig. 2). The stratum granulosum was thinned and occasionally absent in 75% of the sections. The stratum mucosum and rete ridges did not show any definite change and in none of the sections appeared more thin than normal. Sweat glands were seen in two ichthyotic sections as compared to four of the controls, and similarly, sebaceous glands in one section and six controls. Definite perivascular infiltrate was noted in eight patients and three controls and in the former there was also some dilation of the sub-epidermal lymphatic plexus. The most mildly affected patient did not show any changes which would distinguish the section from that of normal skin. Mast cells appeared to be slightly more numerous in these sections than in controls or in skin from sex-linked ichthyotics; but with the small amount of material available it was not possible to evaluate this finding.

TABLE II

Analysis of sections of dominant and sex-linked ichthyosis

Histological feature	Controls Total 12	Dominant Total 12	Sex-linked Total 12	Sex-linked Total 15
Epidermis				
Stratum corneum				
a) Hyperkeratosis	—	4*	10	13***
b) Parakeratosis	—	1	1	1
c) Follicular plugging	—	3	—	—
Stratum granulosum				
a) Increased in thickness	—	—	9	12
b) Decreased in thickness	—	9	—	—
Stratum mucosum				
a) Increased in thickness	—	—	9	12**
Rete ridges				
a) More priminent	—	—	5	8***
Dermis				
a) Sweat glands present	4	2	—	—
b) Sebaceous glands present	6	1	5	5
c) Perivascular infiltrate	3	8	12	15

* Different scoring by each independent observer. Scored as abnormal by one observer and normal by the other on one*, two** or three*** sections.

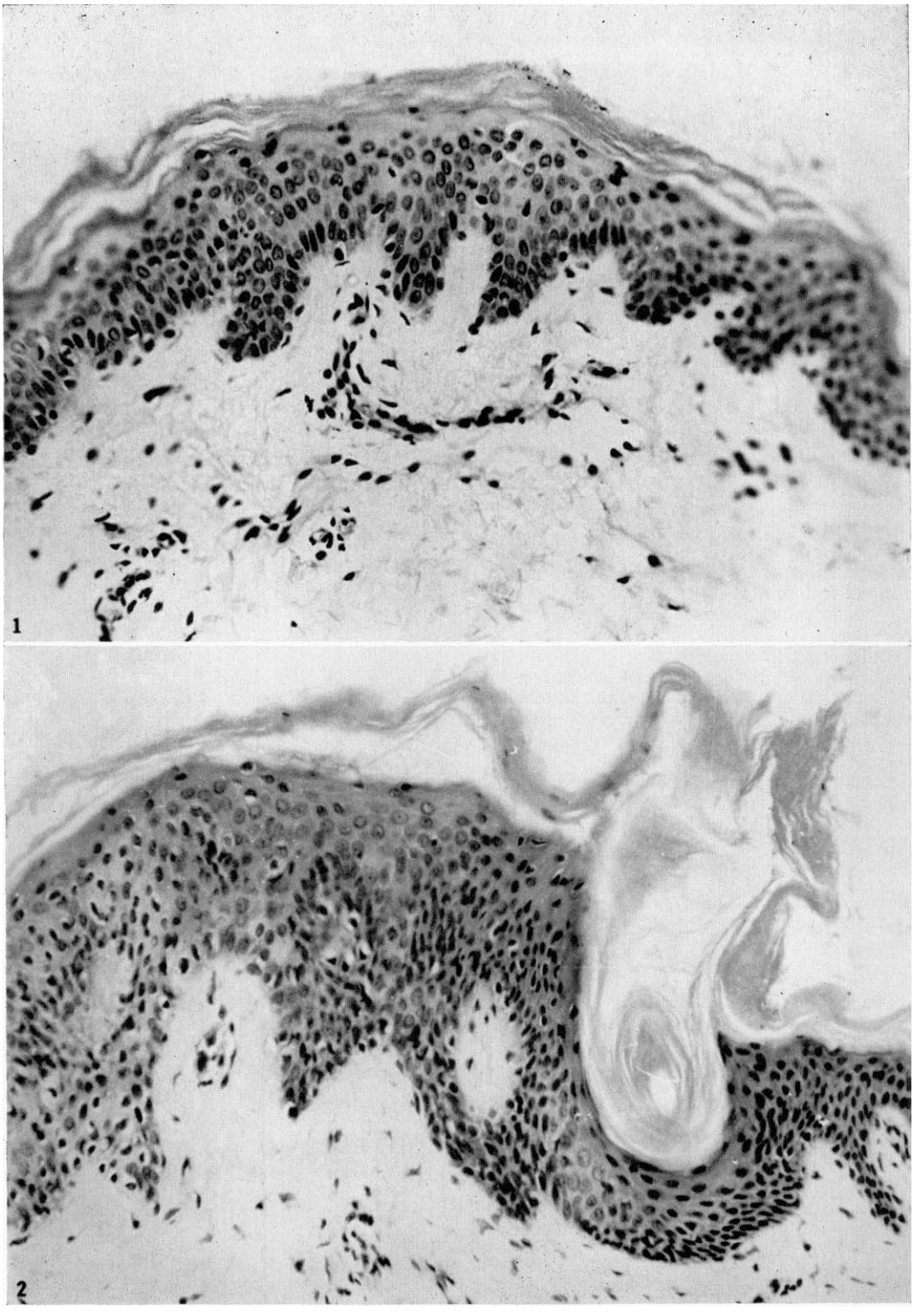

FIG. 1. Dominant ichthyosis. Hyperkeratosis. Absent or thinned granular layer. Moderate perivascular infiltrate.

FIG. 2. Dominant ichthyosis. Hyperkeratosis with some parakeratosis. Follicular plugging. Absent or thinned granular layer. Moderate perivascular infiltrate.

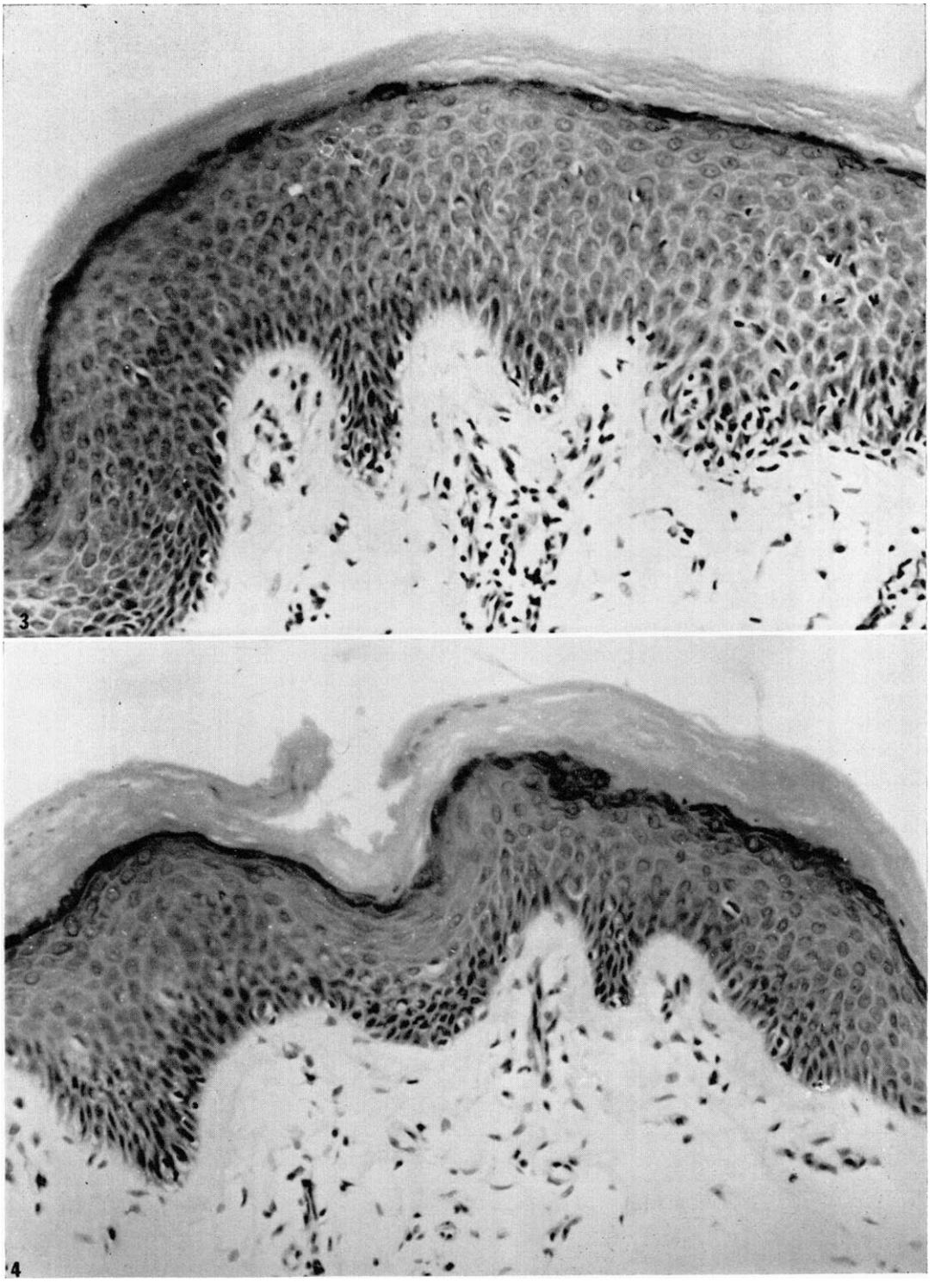

FIG. 3. Sex-linked ichthyosis. Hyperkeratosis. Increased thickness of the granular layer. Acanthosis. Well-marked perivascular infiltrate with dilation of subepidermal lymphatics.
FIG. 4. Sex-linked ichthyosis. Hyperkeratosis with some parakeratosis. Increased thickness of the granular layer. Perivascular infiltrate with dilation of subepidermal lymphatics.

B. Ichthyosis inherited as a sex-linked recessive trait

The stratum corneum showed definite hyperkeratosis in thirteen of fifteen sections (Fig. 3). There was no follicular plugging. Parakeratosis was seen in one section (Fig. 4). The stratum granulosum was increased in thickness in twelve of the fifteen sections; the stratum mucosum showed definite acanthosis and the rete ridges were more prominent and well-developed in the same twelve sections. Sweat glands were not seen in any section, but well-developed sebaceous glands were observed in five. A well-marked perivascular infiltrate was a constant feature in this group, being noted in all sections, and there was some dilation of the subepidermal lymphatic plexus in each case. Mast cells appeared as frequently as in control sections.

C. Ichthyosis inherited as an autosomal recessive trait

Two patients with ichthyosiform erythrodermia showed the same histological features as those with sex-linked ichthyosis, but the changes were more pronounced and, in particular, there was more marked hyperkeratosis and acanthosis.

DISCUSSION

The microscopic features of dominant and sex-linked ichthyosis are summarized in Table III. The distribution of characteristics for each variety permits differentiation histologically.

In the present series, patients with the dominant type of ichthyosis showed a thin stratum granulosum. This supported Lever's (3) observations and it is probable that he was referring to sections from patients in this group, because dominant ichthyosis is the most commonly encountered variety of ichthyosis. However, it was not possible to support claims that the stratum mucosum was significantly diminished in thickness and the rete ridges were less prominent.

By contrast patients with ichthyosis inherited in a sex-linked manner showed an increase in the thickness of the horny layer accompanied by increased thickness of the granular layer. Again, previously recorded descriptions could not be supported because there was also definite acanthosis, and the rete ridges were more obvious and well-developed.

Some sections from controls showed a perivascular infiltrate. Even if quite wide limits are allowed for normal variation, many with

TABLE III

Histological characteristics of dominant and sex-linked ichthyosis

	Dominant	Sex-Linked
Stratum corneum (horny layer)	Mild hyperkeratosis Follicular plugging occasionally Parakeratosis occasionally	Definite hyperkeratosis No follicular plugging Parakeratosis occasionally
Stratum granulosum (granular layer)	Normal or thinned	Increase in thickness
Stratum mucosum (Malpighian layer)	Normal appearance	Increase in thickness
Rete ridges (papillary bodies)	Normal appearance	Prominent rete ridges
Sweat glands	Probably reduced in number	Diminished in number
Sebaceous glands	Reduced in number	Normal number
Perivascular infiltrate	Present in most sections	Well-marked perivascular infiltrate in all sections
Mast cells	As normally present, or slightly increased in number	As normally present

dominant ichthyosis showed a definite increase in perivascular infiltrate, and in sex-linked patients this feature was even more marked. In the latter group the infiltrate was always associated with some dilation of the subepidermal lymphatics.

The posterior aspect of the upper arm has fewer sweat glands than many other areas of the body, and because of the limited number of sections available it was not possible to conclude that the small number of sweat glands present in the sections represented a real diminution in their number. However, the number of sebaceous glands was obviously not reduced in the sex-linked group.

Although only two sections were available from patients with ichthyosiform erythrodermia, histological features were similar, but more pronounced, to those of the sex-linked group.

SUMMARY

Histological features of 12 biopsy specimens from patients with ichthyosis inherited as a dominant trait were compared with 15 specimens from patients with ichthyosis inherited as a sex-linked recessive trait and with 12 control sections from normal skin. Characteristic features that distinguished each inherited variety were described. The histology of sex-linked ichthyosis is very similar to that of non-bullous ichthyosiform erythrodermia.

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