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HEREDITARY TRICHODYSPLASIA: MARIE UNNA'S HYPOTRICHOSIS*

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ABSTRACT

This is a study of eight members of one family with Marie Unna hypotrichosis occurring in five generations. All affected individuals were born with widespread facial "milia", sparse scalp hair and decreased body hair. Laboratory studies including urinary amino acids and plasma testosterone were normal. On histologic examination the hair follicles of the scalp showed proliferation of the internal root sheath and horn pearl formation in the lower third of the follicle. Abnormal hairs were flat and ribbon-like and twisted at irregular intervals. Extensive peeling of the cuticle was demonstrated by scanning electron microscopy. Electron microscopy of the hair shafts revealed intracellular fractures of the cuticular cells, increased interfibrillar matrix and fractures of the cortical cell fibrils and fractures of the medullary cells. X-ray diffraction studies were normal. On amino acid analysis of affected hairs a small decrease in cysteine-cystine and an increase in methionine content was noted. Since the hair shafts are clearly abnormal in this disorder, the name hereditary trichodysplasia is suggested. The condition is inherited as an autosomal dominant trait.

Abnormalities of hair are commonly observed in a variety of hereditary syndromes which include associated anomalous defects of ectodermal or mesodermal origin (1, 2). Diffuse hereditary hair defects as isolated phenomena are rare, but hereditary hypotrichosis is an example of such a disorder. This syndrome was first extensively studied by Marie Unna (3) in a large German kindred. In 1953 and 1954, respectively, Ludwig (4) and Borrelli (5) described the findings in descendants of the original family, and Kemeny and Csontos (6) added several new cases. Stevanovic (7) reviewed the literature and studied 4 cases, one of which was thoroughly documented. Many of the earlier and subsequent cases (7, 8) of congenital baldness have been incompletely described so it is impossible to determine whether they had the same disorder. Recently, Parrish, Goldsmith and Baden (9) reported a family with normal hair shaft structure, decreased scalp hair density, milia and hypomelanosis. Since the most striking feature of Marie-Unna's hypotrichosis is the bristly hair, the cases reported by these authors may represent a different entity.

We have recently had the opportunity to study eight members of a family with Marie Unna hypotrichosis occurring in 5 generations and feel it would be of interest to report and further define this unusual abnormality.

Case reports. The family of the proband consisted of four generations with 15 living members, all of whom were examined in this study. Additional history of a fifth affected generation was available. There were 9 members with the abnormality to be described and eight of these were examined by the authors. The family pedigree may be seen in Figure 1. After completion of the pedigree individuals IV-I and IV-2 gave birth to a third affected child, an infant male, who is not represented in the pedigree as illustrated.

The family members examined were the great-grandfather of the proband, his daughter, three grandchildren and 7 great grandchildren. All affected individuals were born with widespread facial "milia", "frizzy", sparse, coarse scalp hair and decreased body hair. The eyebrows also were sparse in three of the subjects. With increasing age, but particularly during adolescence, the hair became more sparse on the scalp and formed a

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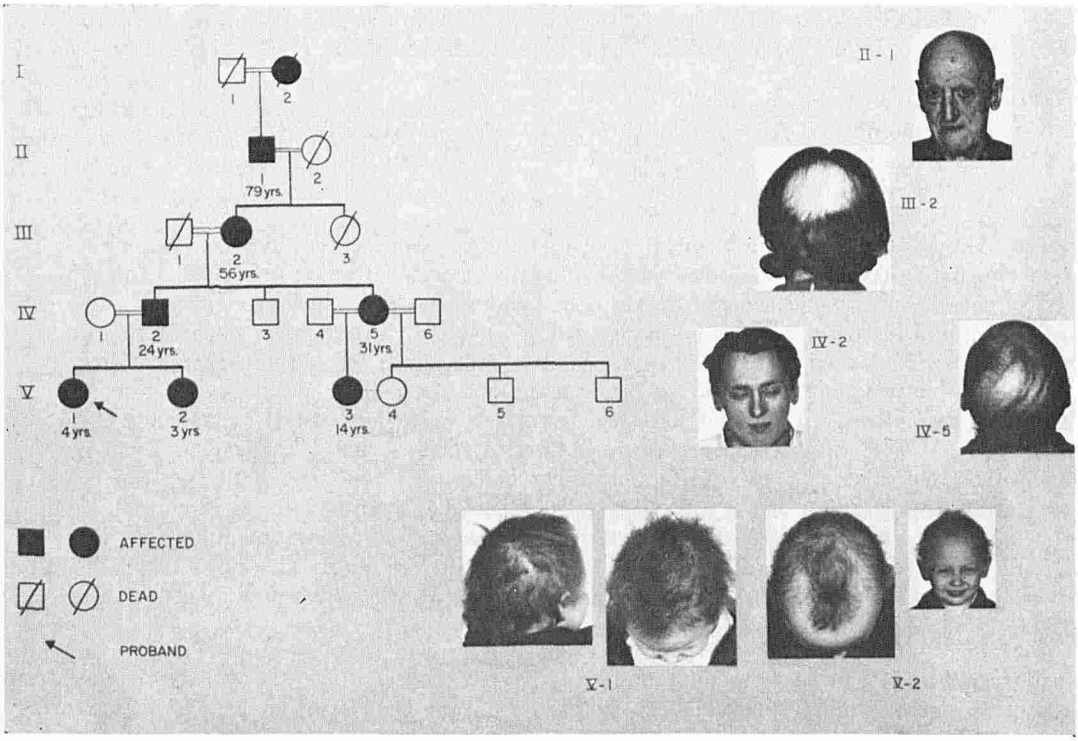

FIG. 1. The inheritance pattern of Marie Unna's hypertrichosis in the family studied is illustrated. A third infant, V-3, born January 1971, is not included.

peculiar pattern resembling that of male-pattern alopecia on the crown and frontal areas, but the perimeter of the scalp was also bald. The resulting picture in the severely affected individual was that of a monk's scalp.

Skin lesions occurring in the first month of life were seen as tiny, very superficial cyst-like structures which could be removed by gently rubbing the skin. They were concentrated on the upper face and tended to recede in several months leaving no scar. Recurrences of these milial-like lesions were common up to 6 years later.

The teeth, mucous membranes and nails were normal. Body hair was extremely sparse to absent in all affected individuals, and on one of the patients, multiple scattered horny follicular plugs and widely patulous pilosebaceous orifices were seen. The eyebrows were absent in two and extremely sparse in five individuals. The density of scalp hair was greatly reduced. The older members had 0–10 hairs per square cm on the crown and 10–60 hairs per square cm on its periphery. The hair itself was very coarse to the touch, feeling like a horse's tail and was deeply pigmented in the older family members, appearing jet black in color. Hair was sparse to absent in the pubic, axillary, sternal and beard areas in all of the adult patients, although other secondary sexual characteristics were normal as were sexual function in the men and menses in the women. The testes were normal in size.

In addition, typical atopic dermatitis was found in the proband, her sister and mother. Sweating was normal and evidence of functioning sebaceous glands was present in all patients examined. Two patients had mild acne vulgaris. One infant had a nevus flammeus of the fingertip.

The growth, development and intelligence of all of the patients studied were found to be normal. In fact, all the subjects examined were found to be in good health except for the lesions described.

Laboratory studies. All affected individuals were studied. Routine examination of the formed elements of the blood as well as the blood urea

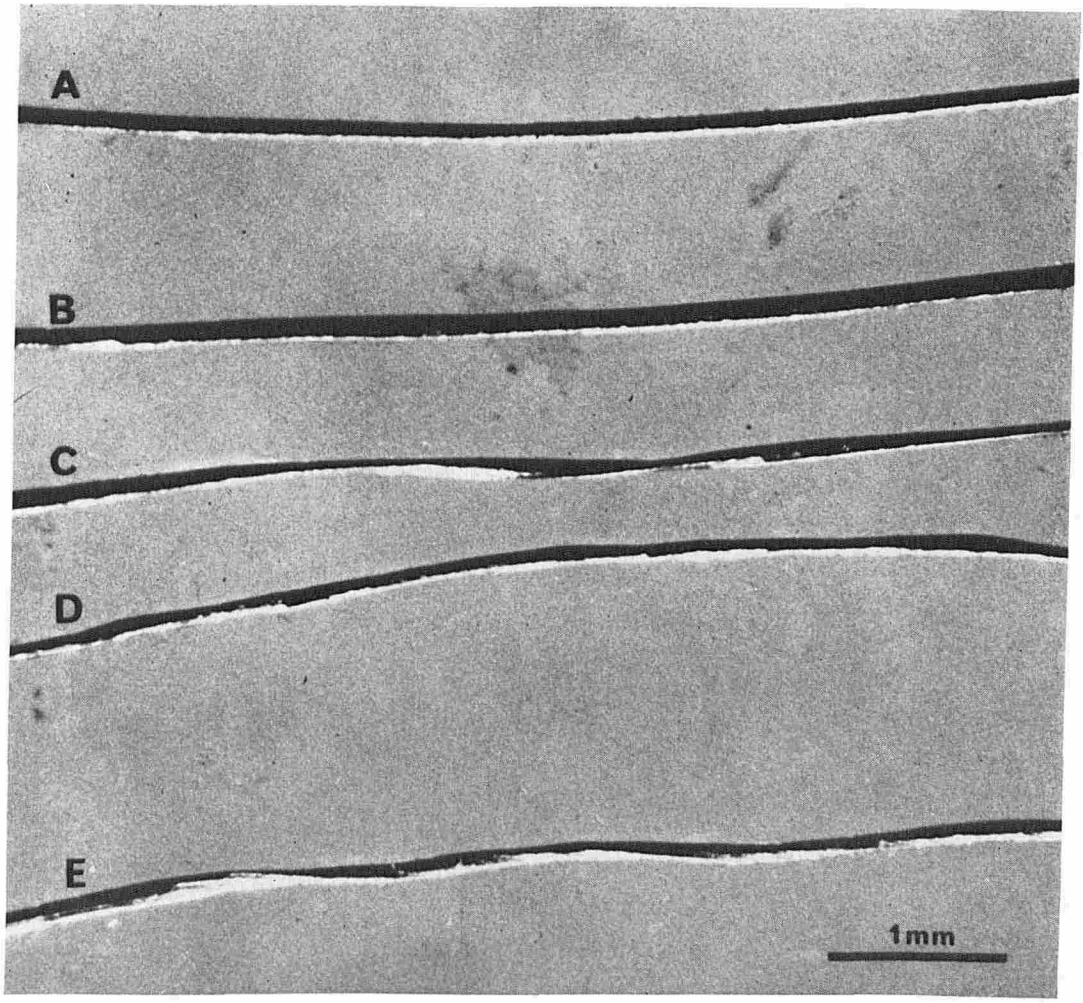

FIG. 2. Normal and dysplastic hairs, as seen by disserting microscopy. (A) Normal. (B) Flat hair from patient IV-2 (See Fig. 1). (C) A wide-angled twist which, over several inches, rotates the hair 360°. (D and E) Multiple severe acute angle twists which result in microscopic fractures.

nitrogen and blood glucose were normal. Serum protein electrophoresis showed a normal distribution of the serum proteins both qualitative and quantitative. Urinalysis revealed no abnormality. Quantitative and qualitative analysis of urinary amino acids were normal in a 24 hour sample. Plasma testosterone levels were also found to be normal.

Genetics (see Fig. 1). The kindred described includes nine affected members, three males and six females, in a family of five generations. Eight of the nine persons with the defect were examined by the authors. Although I-2 was not alive at the time of this study, we feel that the information provided by this family is reliable and valid.

This trichodysplasia appears to be inherited as a simple autosomal dominant trait. Since both males and females are affected and one instance of male to male transmission has occurred (IV-2 to the infant son not depicted in the pedigree), the possibility of an X-linked dominant type of inheritance can be excluded. The gene appears to be fully penetrant since no skipped generations have been noted and more than half of the family members (9/14) were affected. The information available on the ancestors of I-2 suggest that the gene was trans-

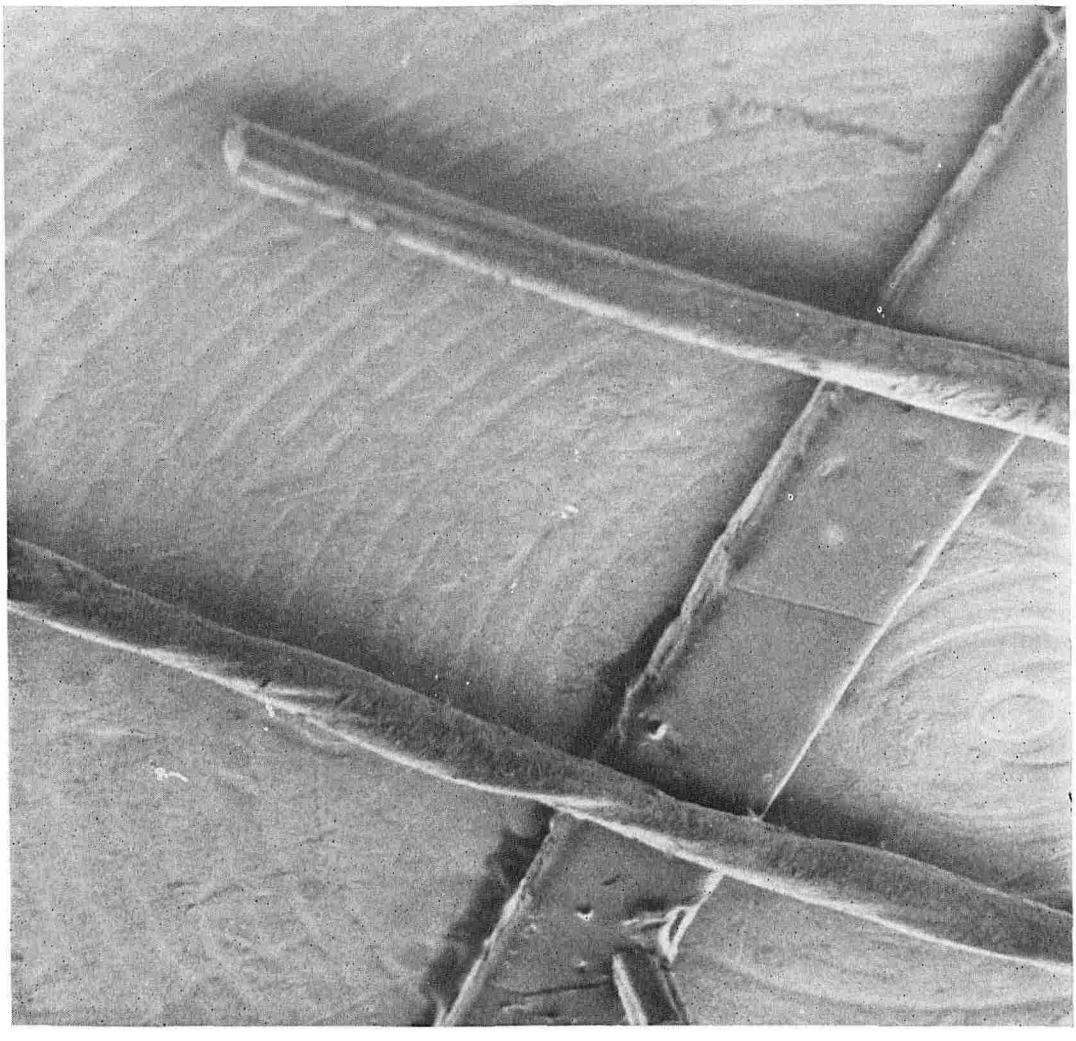

FIG. 3. Scanning electron microscopy of affected hair shown in Figures 2, D & E.

mitted from her mother, but this impression cannot be confirmed.

Histology. Patient V-1. A 4 mm punch biopsy was taken from the scalp and stained with hematoxylin-eosin. Examination of a histological section showed irregular epidermal acanthosis. The hair follicles were fewer in number than that seen in a normal scalp. Some of the follicles were of normal size but others were short, small and contained a vellus hair. Some follicles showed a proliferation of the internal root sheath which constricted the follicle in the upper portion of its lower third. Arrector pili muscles were seen adjacent to many follicles. The dermis showed no inflammatory component.

Patient IV-2. Histologically this case showed a more advanced stage of the process. The epidermis was acanthotic. In general the hair follicles were smaller than those found in the younger subject. The internal root sheath showed kinking and epithelial proliferations which impinged on the hair itself at the superior portion of the keratogenous zone. Some of these proliferations showed horn pearls. Many follicular ostia were dilated and filled with a keratinous mass. Edema, a lymphocytic infiltrate and an increased number of fibroblasts were seen adjacent to the abnormal follicles. A moderate number of lymphocytes were present around blood vessels and sweat glands. Sebaceous glands

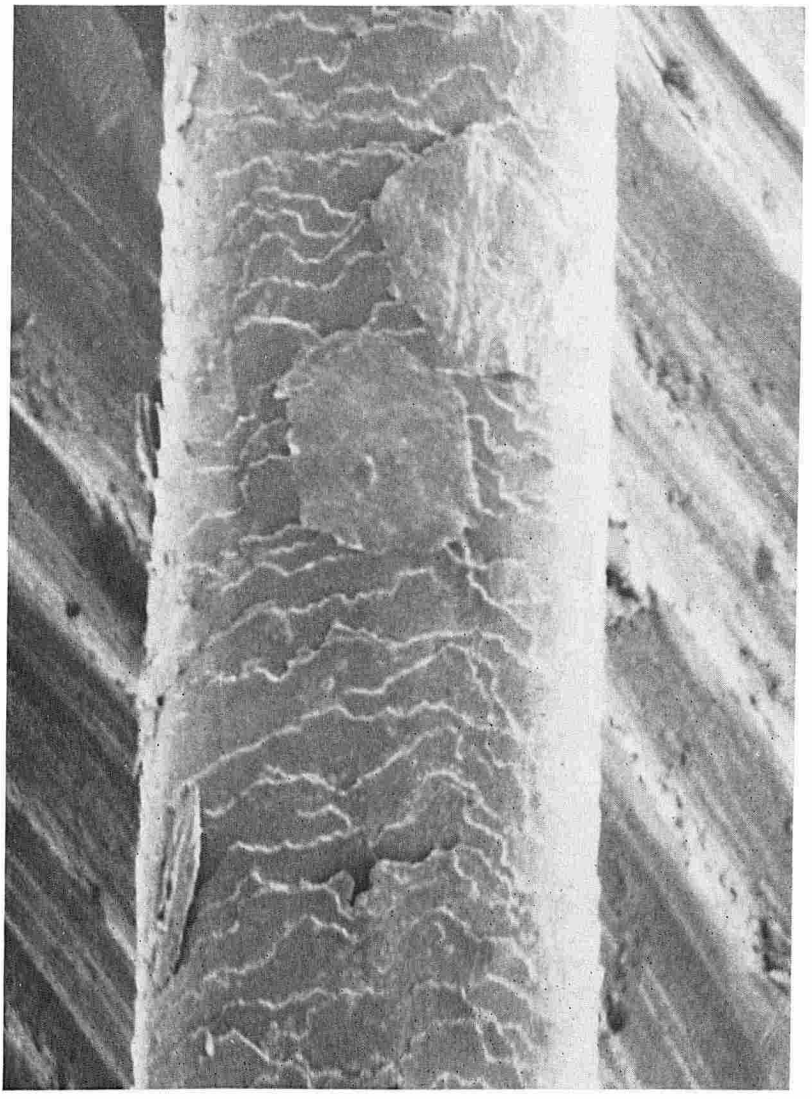

FIG. 4. Scanning electron microscopy of affected hair shows peeling of the cuticle.

were present. Piloerector muscles were evident but their insertion onto the follicle was not observed.

Patient III-2. The histological changes in the epidermis and hair follicles were similar to those seen in the younger patients but the lymphocytic infiltrate was denser, the fibrosis more advanced, and the sebaceous glands more atrophic and fewer in number.

Examination of a milial-like lesion (Patient V-2). Examination of a cross section of the milial-like lesion revealed that it was in fact the result of a keratinous plug occluding a dilated and deformed hair follicle. There was no cyst formation.

Microscopic examination of the hair. The abnormal hair examined under the light and dissecting microscopes showed a periodic disturbance in the morphological structure. The affected hair is oval or flat, ribbon-like and at irregular intervals becomes twisted (see Figure 2). The twisted appearance in the affected areas appeared to be due to torsion of the hair long its widest axis resulting in an axial rotation of 90–180°. Occasional segments were rotated 360°. Some interspaces between the periodic dysplastic

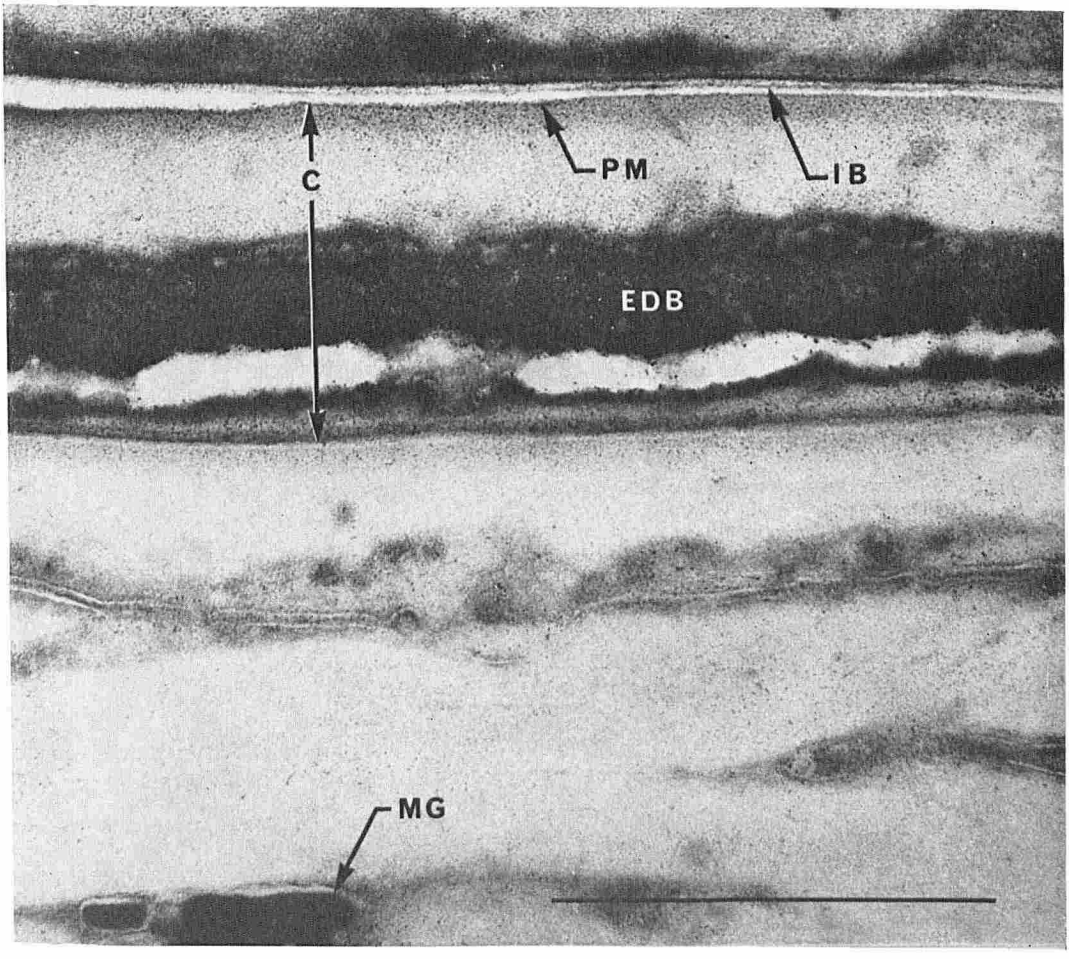

FIG. 5. Electron micrograph shows fracture through the electron dense band of the cuticular cell. The area between the arrows delimits the cuticular cell. E.D.B. = electron dense band. P.M. = plasma membrane. I.B. = intercellar band. M.G. = melanin granule.

The black bar on the bottom of each electron micrograph represents 1 micron in length.

segments were essentially normal to inspection under low power magnification.

Examination of individual hairs under polarized light revealed no peculiarities of light transmission and no evidence of alternating birefringence in the affected, unaffected or bulb regions.

Examination of the hair by scanning electron microscopy (See Figs. 3 and 4). The instrument used was a Mark 11-A Cambridge "Stereoscan" scanning electron microscope, Kent Cambridge Scientific Instruments Inc., Morton Grove, Illinois.

Unfixed hair specimens were mounted on the specimen holders of the microscope using double adhesive Scotch tape. These holders were placed in the Tilting Omni Rotary Shadowcasting accessory of the Denton DV-502 Laboratory Evaporator. When proper vacuum was attained, the hairs were coated with a moderately heavy layer of carbon followed by a lighter coat of gold and examined.

There was extensive peeling of the cuticle with its separation occurring in large patches. The overall appearance was that of sycamore bark. The twisted areas result in a hair with an erratically helical structure containing curves of varying tightness.

Electron microscopic studies (See Figs. 5–8). For transmission electron microscopy the selected areas of twisted hairs were cut into small pieces approximately 1.0 mm in length and fixed

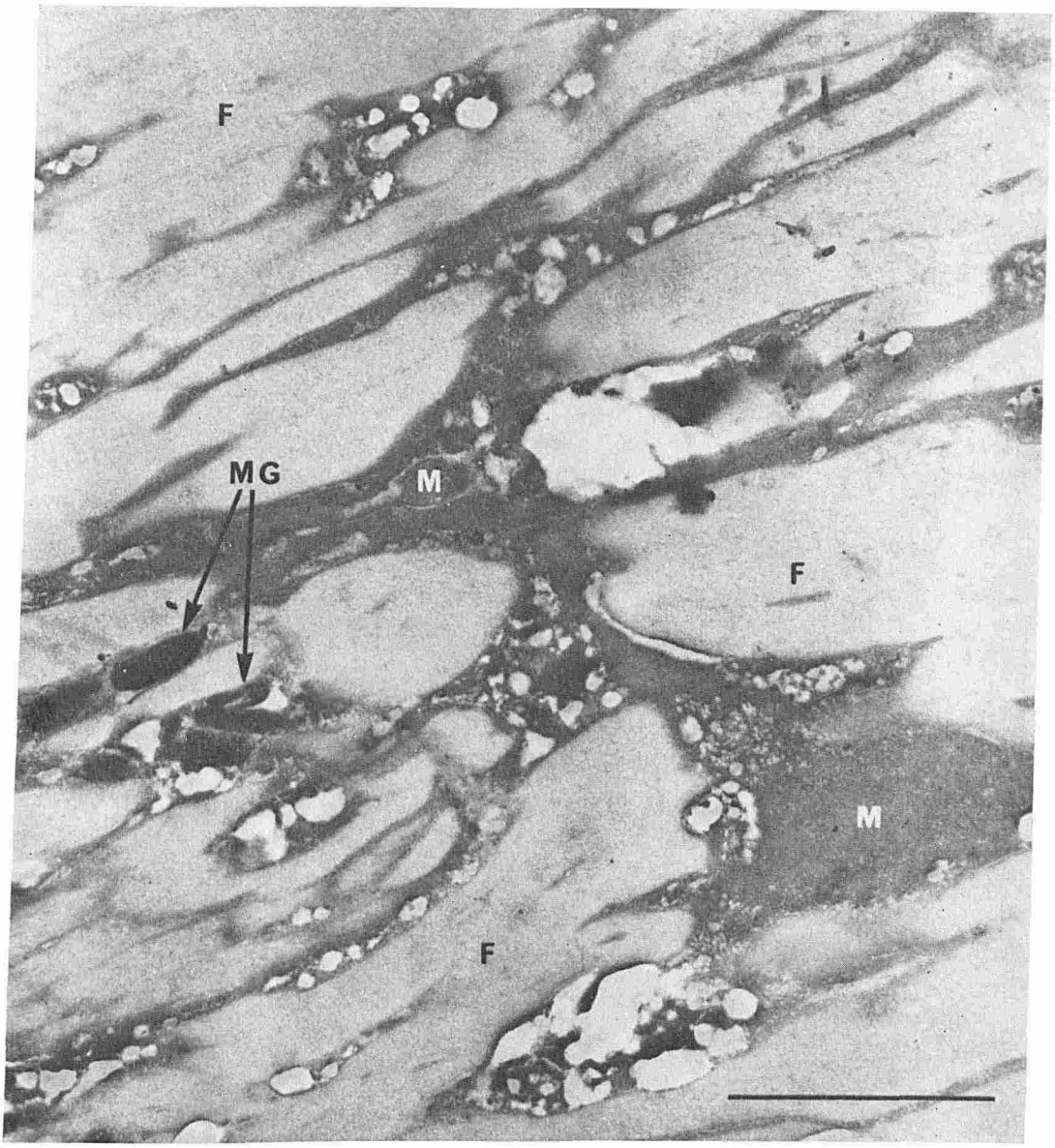

FIG. 6. Electron micrograph of the hair cortex shows increased numbers of small fibrils as well as an increased amount of the matrix substance. M. = matrix. F. = fibril. M.G. = melanin granule. White areas are probably artefact.

overnight in 3% glutaraldehyde buffered with Millonig's buffer pH 7.4 and then post fixed for 1½ hours with 1% osmium tetroxide in Veronal buffer, pH 7.4. These were then dehydrated in ethanol, embedded in araldite, and sectioned on a Porter-Blum ultramicrotome. Sections 600–800 angstroms thick were stained with uranyl acetate and lead citrate and examined with an RCA EMU-3 electron microscope. Sections about 1 micron thick were stained with a mixture of 1% pyronine and 1% toluidine blue in a ratio of 1:4 and viewed with a light microscope.

Skin biopsies of 2 and 3 mm were bisected. One-half was processed for light microscopy. The other half was cut in 3 pieces fixed in collodine buffered osmic acid for 1½ hours. These were then processed exactly as was the hair.

Cuticle. The cuticular defect was found to be

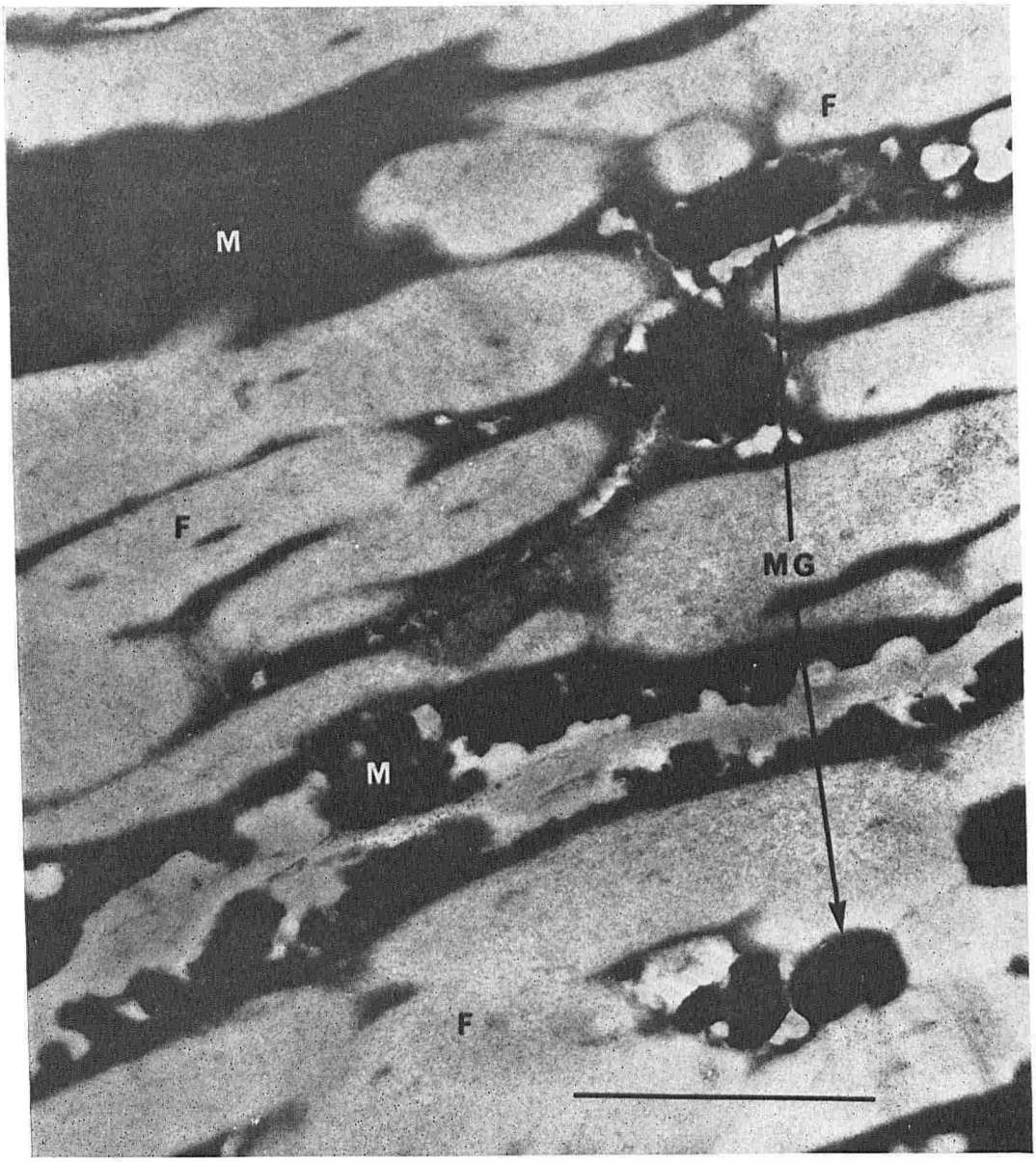

FIG. 7. Electron micrograph through the cortical area of a sharply twisted hair. Fracture is seen extending through the interfibrillar matrix substance. F. = fibril. M. = matrix. M.G. = melanin granule.

intracellular in the areas of the osmiophilic band proximal to the hair cortex. Within this band were seen multiple separations or fractures, at times containing an amorphous debris (Fig. 5). In some areas the longitudinal fractures of the osmiophilic band led to intracellular fractures which separated one or more layers of cuticular cells from the body of the hair. The intercellular substance was normal.

Cortex. In some areas the cortical cells showed a normal pattern. In other areas, there appeared to be an increased number of small fibrils in the cortex, suggesting imperfect interfibrillar cross-linking (Fig. 6). In the hairs that showed multi-

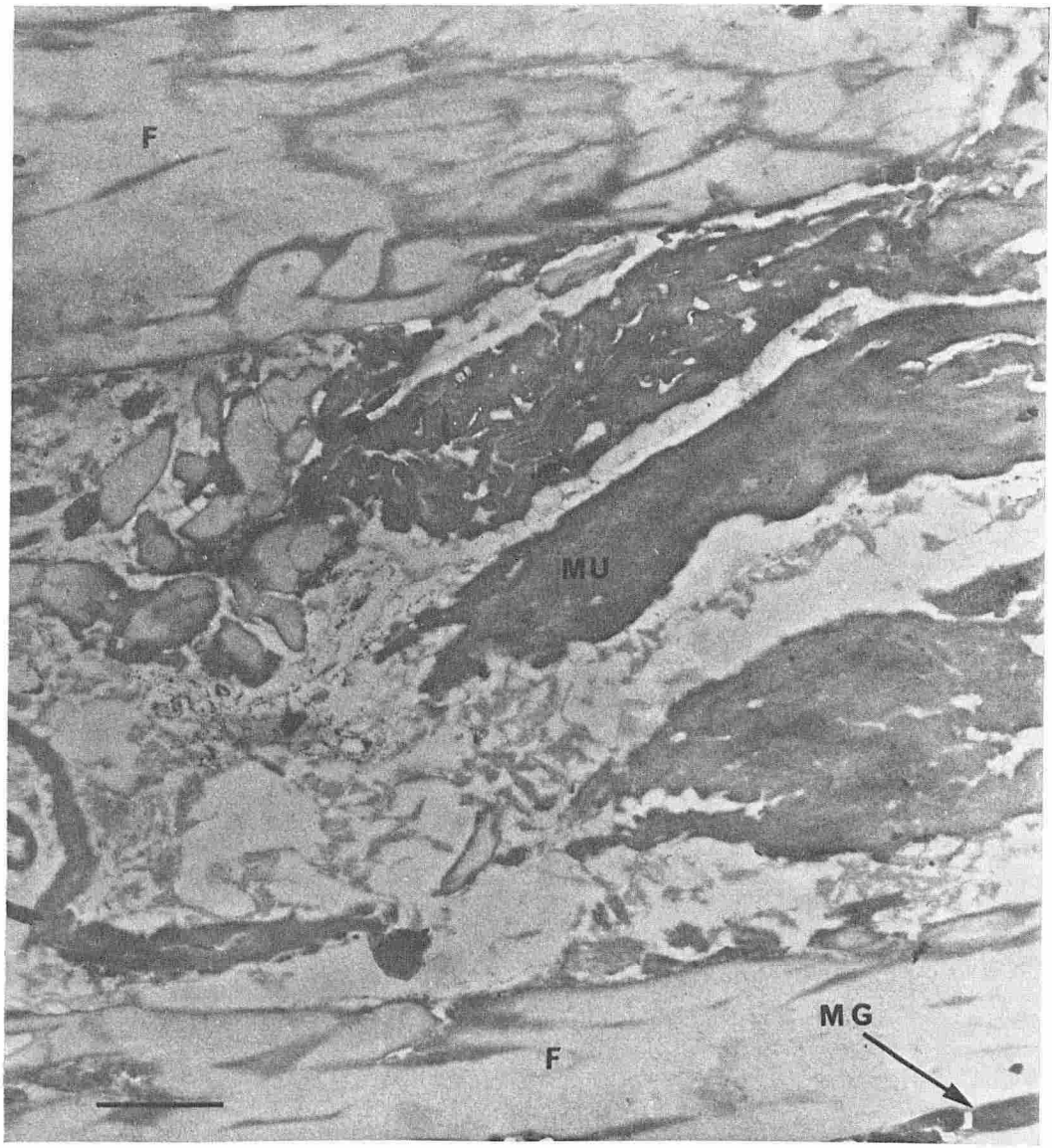

FIG. 8. Section through the medullary region of a sharply twisted hair showing multiple fractures of the medullary cells. F. = fibril. Mu = medullary cell.

ple sharp twists the cortical cells contained many fractures of their fibrils as well as separations within the interfibrillar substance (Fig. 7). There was also an impression that the interfibrillar matrix was increased compared to what is normally seen (10).

Medulla. The medullary region of the severely twisted hair showed multiple fractures of the cells (Fig. 8).

The bulb. The bulbous portion of the hair follicle did not show any abnormality when examined by electron microscopy. The abnormalities seen in the cuticle and cortex seemed to occur at a level just beyond the bulb in the keratogenous zone.

The epidermis. No abnormalities could be discerned within the epidermis.

X-ray diffraction studies. For this study a

TABLE

Amino acid analysis of hair

	Normal controls	Patient IV-2
	Percent	*Percent*
Lysine	3.35	2.62
Histidine	0.67	0.97
Arginine	9.90	8.58
Apartic acid	5.93	6.12
Threonine	6.54	6.71
Serine	10.06	9.38
Glutamic acid	14.27	14.15
Proline	7.66	7.81
Cysteine-cystine	18.71	16.72
Glycine	3.98	3.66
Alanine	3.11	3.03
Valine	4.76	4.56
Methionine	0.81	1.70
Isoleucine	2.43	2.10
Leucine	6.42	6.71
Tyrosine	2.96	2.83
Phenylalanine	2.01	2.06

Phillips electronics instrument x-ray diffractometer with a 2½ KW generator was used. The source of the x-rays was copper. The data was gathered, angles calculated and plotted by a Norelco data control and processing panel. A monolayer of affected hair and normal control hair specimens was mounted on Scotch brand tape. Two sets of x-ray diffraction patterns were obtained for each sample. One set of patterns resulted from orientation of the sample parallel to the x-ray beam and the other perpendicular to the beam. The patterns thus obtained in both the affected and normal hairs showed no significant difference, suggesting that the disease process had not altered the alpha helix structure of the hair protein.

Amino acid analysis (See Table). Matched weighed samples of affected hair and control hair from 6 normal subjects were suspended in 3 ml 6N HCl in closed hydrolysis tubes. After heating for 16 hours at 105° C, the suspensions were diluted to 100 ml and an 0.5 aliquot was run on a Beckman 120C amino acid analyzer. The results are shown in the Table. The findings suggest an increase in methionine and a small decrease in cystine-cysteine.

Stress-strain studies. A sample of 25 hairs was measured for tensile strength, using an Instron-Tensile Testor Model TM, according to the method previously described by Beyak, Meyer, and Kass (11). The affected hair was found to be markedly fragile in areas of severe twisting, so that the hair would fracture at these points when placed on the instrument. Areas of extreme twisting occurred on some hairs at periods of 1–2 inches, permitting study of less severely affected parts of the hair. One-inch sections of hair of more or less uniform diameter were tested in water to determine yield point under 15% strain. Following treatment with 0.5M sodium bisulphite solution for one hour at 25° C, the hair was rinsed in tap water and immersed overnight in distilled water. The next day the yield point was remeasured and compared to control samples of virgin hair (normal human hair previously not treated with bleach or other chemicals). The results of these tests indicate that the less deformed hair reacted as did normal virgin hair.

DISCUSSION

The clinical appearance and physical examination of our patients was similar in almost all details to those previously reported by Marie Unna (3) and others (4–7). Our patients were affected by a trichodysplasia with a well defined pattern of inheritance and with structural and biochemical abnormalities in the hair.

Inheritance. The genetic transmission of the cutaneous defect in our patients is clearly due to an autosomal dominant gene. This confirms the findings of the only previoiusly published pedigree extensive enough for genetic analysis. Marie Unna (3) studied a family of 202 individuals with 74 affected members in six generations. Of these, 35 were male, 37 female, and 2 of unspecified sex. The pattern of inheritance was that of an autosomal dominant trait with no skipped generations and 16 instances of male to male transmission. Although the illustrated pedigree contains the maximal information available, it is stated in Unna's paper that the defect was clearly documented only from the fourth generation on (62 affected individuals).

Borelli (5) reported two cases of Marie Unna hypotrichosis (a mother and daughter) among five individuals of three generations. This family was said to be a branch of the large German kindred reported by Unna. In 1970, Stevanovic (7) studied an additional four affected patients (two males and two females) in a family of three generations. Neither of the latter reports contains a pedigree; but an autosomal dominant

type of inheritance seems likely in both of these families as well.

The structural defect. Our light microscopic findings were identical to those described and illustrated by Marie Unna and Stevanovic (3, 7). The disease process appears to produce morphological changes in the hair, resulting in deformity of the root sheath of the follicle and the cuticular layer of the hair. Not all hairs are involved nor is the involvement uniform in each hair. Grossly, the resultant change is one of a brittle, coarse, twisted hair. With time, the hair follicle becomes atrophic; and alopecia results. The follicular opening develops a horny excrescence to mark the resting place of a previously active follicle. The presence of recurrent episodes of "milia" suggested that the epidermis may be undergoing a parallel change; but we could discern no consistent pathologic changes in the epidermis. The "milial" lesions in reality were keratinous plugs in dilated follicular orifices.

The ultrastructure of hair has recently gained increased attention (10, 12, 13). At this level, the defect in our patient group is represented by two changes: (a) there is a sharp separation inside the cuticular cell within an electron dense band occupying the third of the cell proximal to the cortex; (b) numerous cells of the cortex seem to have an increased interfibrillar matrix, and the fibrils are less compact.

The biochemical defect. Three of the findings are particularly pertinent to consideration of the specific defect. (a) The x-ray diffraction patterns were no different from those of normal hair, suggesting that the α helical pattern of the cortical hair protein has maintained its integrity—a finding consistent with those of the electron microscope. (b) The hair tested in the bisulfite stress-strain studies reacted as did normal virgin hair. (This latter finding may be supportive of the studies of Goldsmith and Baden (14) who have recently shown that the elastic modulus of pathologic hair may be minimally affected even when oxidative changes are induced in the disulfide bonds and underlining the difficulty of interpreting the elastic modulus, a physical property, with respect to the various components of a complex non-homogeneous structure such as hair.) (c) In the light of the electron microscopic findings suggestive of cuticular and cortical matrix involvement, it is of interest to look at the sulfur-containing amino acids in the amino acid analysis of the hair. In this regard, there was a small decrease in cystine-cysteine and an increase in methionine in the hair studied. The increase in methionine may have been real or due to an increase in S-methyl cystine which cannot be detected as different from methionine by the amino acid analyzer.

How can one pool the observable data to understand the disease? Disulfide links are found primarily in the matrix of the cortex and the cuticle. Its function is not entirely understood; but the disulfide bond probably plays some role in the integrity of the matrix and, in the cortex, the binding of the keratin fibers to matrix. The abnormality we saw in the cuticle was in the osmiophilic band which is normally rich in disulfide bonds. It is possible that the formation of disulfide bonds is deficient in our patients. Such an abnormality in the osmiophilic band might lead to its fracture and focal separation within the cuticular cells. This of itself could subsequently result in twisting of the hair. An alternative mechanical hypothesis would place the defect in Huxley's layer which, by its deformity, could cause twisting of the hair. A third possible theory is that the fracture of cortical fibrils may be due to an associated defect of cortical interfibrillar substance.

Is it possible that the cuticular involvement is of particular significance? Recent studies have demonstrated a new interest in the cuticular layer (12, 15, 16). A fibrous protein, characterized by the presence of citrulline, has been described by Steinert, Dyer, and Rogers (17) in the inner root sheath cells of the guinea pig hair follicle; and Forslind (18) has recently demonstrated that this area has an affinity (but less than the cortex) for exogenously administered S^{35}. Although more definitive experiments would help to clarify the issue, it is possible that this disorder represents a genetically determined defect in the sulfur-containing interfibrillar substance of the inner root sheath, cuticular cells, and cortex of the hair and which results in deficient bonding of keratin (or other) fibrils into larger fibers. The total effect is that of hair which is vulnerable to torsion damage but not to longitudinal strain unless the former has fractured the keratin fibers.

The biology of the inner root sheath and cuticle. It should be noted that follicles which produce irregularly shaped hairs are found in most mammals, including man. The guard hair of the rabbit has a texture and flat dumbbell shape, not

unlike that seen in our patients, as does the zigzag hair of the rat (15). Since hair growth is the result of the differentiation and flow of cells produced by the matrix, both the cuticle of the hair and the inner root sheath are the product of the cells migrating from the matrix. Straile (16), in a review of the literature, pointed out that hair shape is the result of complementation between hair and its internal root sheath, which in turn is a reflection of dermal papillary and proliferative matrix size. He believes there is a "shunt" determining which cells of the proliferating matrix enter Huxley's layer of the internal root sheath and which enter the cuticular layer of the hair. Since the shape and cuticular structure of our patients' hair is abnormal, the mechanism governing the distribution of cells, as well as the enzyme governing oxidative formation of disulfide bonds in the cuticle and inner root sheath deserve further attention.

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