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Hereditary Mucoepithelial Dysplasia: A Disease Apparently of Desmosome and Gap Junction Formation

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SUMMARY

A previously unrecognized autosomal dominant syndrome affecting oral, nasal, vaginal, urethral, anal, bladder, and conjunctival mucosa with cataracts, follicular keratosis, nonscarring alopecia, and terminal lung disease is described in a four-generation kindred of German extraction. Severe photophobia, tearing, and nystagmus in infancy heralds the development of keratitis, corneal vascularization, and lens cataracts. Repeated corneal transplants have failed. Red, periorificial mucosal lesions involving the above structures are noted by 1 year of age and may persist throughout life. Chronic rhinorrhea and repeated upper respiratory infections frequently progress to bilateral pneumonia accompanied by loss of hair, diarrhea, occasional melena, enuresis, pyuria, and hematuria. Spontaneous pneumothorax is frequent, terminating in fibrocystic-type lung disease and cor pulmonale. Women have had repeated abnormal vaginal PAP smears. Histologically the mucosal epithelium shows dyshesion, thinning of the epithelial layer, and dyskeratosis. Mucosal PAP smears show lack of epithelial maturation, cytoplasmic vacuoles and inclusions, and individual cell dyskeratosis. Histochemically there is a lack of cornification and keratinization. Ultrastructural studies show lack of keratohyalin granules, a paucity of desmosomes, intercellular accumulations, cytoplasmic vacuolization, and formation of bands and aggregates of filamentous fibers and

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structures in the cytoplasm resembling desmosomes and gap junctions. The condition is probably a panepithelial cell defect of desmosomal and gap junction structure most prominently affecting mucosal epithelia associated with an increased susceptibility to a variety of adventitious organisms.

INTRODUCTION

Hereditary dyskeratoses affecting mucosa include both those with a high frequency of malignant transformation [1–3] as well as a number of benign conditions [4–10]. In none of these conditions are all the orifical mucosae affected as well as skin, hair, eyes, and lung. We describe a unique syndrome characterized by lesions involving all of the above structures with a high risk for premature death from cor pulmonale. Characteristic histologic and cytologic alterations distinguish this syndrome from other hereditary dyskeratotic disorders. Massive cytoplasmic accumulations of lamellar bands and stranded material and a paucity of desmosomes on cell surfaces suggest a disease of desmosomal and gap junctional organization.

PATIENTS AND MATERIALS

The 24-year-old propositus (IV-16, fig. 1) was referred because of red gingiva and palate. Papanicolaou (PAP) and periodic acid Schiff (PAS) stained smears of the palate had unique features incompatible with any known oral disease. She had had cataracts removed, had coarse scanty hair, a right esotropia, nystagmus, fine follicular papules of the skin, and gave a family history of similarly affected relatives. A kindred (fig. 1) was constructed from interviews with family members and from medical records which showed admissions to eleven different specialty services. The findings are presented in the case histories and summarized in table 1.

Patients IV-15, IV-16, and V-18 (fig. 1) were admitted for physical examination and testing. The latter included routine and special laboratory tests on blood, urine, and feces; studies of thyroid, parathyroid, adrenal, liver, kidney, and pulmonary function; radiographs of the

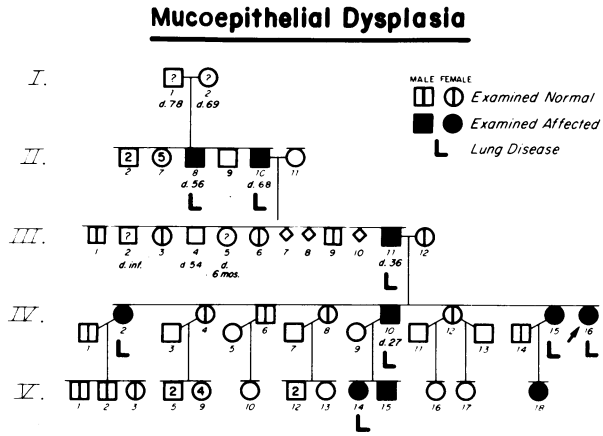


FIG. 1.—Five generation pedigree of kindred studied.

TABLE 1

SUMMARY OF FINDINGS FROM MEDICAL HISTORIES AND EXAMINATIONS OF AFFECTED KINDRED MEMBERS

	II-8	II-10	III-11	IV-2	IV-10	IV-15	IV-16	V-14	V-15	V-18	Total
Photophobia	+	···	+	+	+	+	+	+	+	+	9
Tearing & photic sneezing	···	···	···	+	+	−	+	+	+	+	6
Nystagmus	+	···	···	+	+	+	+	−	−	+	6
Esotropia	···	···	···	+	+	−	+	−	−	−	3
Corneal vascularization	···	···	···	+	+	+	+	+	+	+	7
Cataracts	+	+	+	+	+	+	+	+	+	−	9
Otitis	···	···	···	+	+	−	+	+	−	+	5
Follicular keratosis	+	+	+	+	+	+	+	+	+	+	10
Red oral mucosa	+	+	+	+	+	+	+	+	+	+	10
Red nasal mucosa	+	···	···	+	+	+	+	+	+	+	8
Red anal mucosa	···	···	···	+	+	−	+	+	−	+	5
Red vaginal mucosa	···	···	···	+	···	+	+	+	···	+	5
Abnormal oral PAP	N	N	N	+	N	+	+	N	N	+	4
Abnormal vaginal PAP	N	N	N	+	N	+	+	N	···	N	3
Abnormal bladder PAP	N	N	N	+	N	+	+	N	N	N	3
Repeated pneumonia	+	+	+	+	+	+	+	X	−	−	8
Pneumothorax	···	···	+	+	+	+	−	−	−	−	4
Deceased, lung disease	56 yr	68 yr	36 yr	L	27 yr	L	L	L	L	L	4
Coarse scanty hair	+	+	+	+	+	+	+	+	+	+	10
Eosinophila	+	+	···	+	+	+	+	+	+	+	9
Chronic rhinitis	···	···	···	+	+	+	+	+	+	+	7
Clubbing fingers	+	+	+	+	+	−	−	+	−	−	5

NOTE.—N = not done; L = living; X = fibrotic changes on X-ray.

skeleton, chest, and gastrointestinal tract; aggregation of platelets; chemotaxis and killing of leukocytes; quantitative immunoglobulin levels; radioallergoabsorbent tests (RAST) of immune activity; skin test of cellular immune response; lymphocyte function; mycotic cultures of oral and vaginal mucosa and quantitative determinations of urinary amino acids.

Biopsies of gingiva, palate, skin, and cervix were fixed in 10% formalin for hematoxylin and eosin (H&E), PAP [11], PAS [12], and Dane's keratin stain [13] and frozen sections for Sudan black [14], Baker's phospholipid stain [15], and immunofluorescence [16]. Cytologic smears were obtained from oral [17], nasal, cervical, vaginal [18], and midstream urinary sediment [19] and fixed in 95% ethanol for PAP and PAS stains or air dried for lipid and phospholipid stains. Urinary cytologic specimens for electron microscopy were obtained from 150 cc midstream urine voided directly into 30 cc of 3.7% gluteraldehyde in phosphate buffer, pH 6.8, on ice. The centrifuged button was refixed in fresh gluteraldehyde followed by osmic acid, dehydrated in alcohols, and embedded in Epon 812 by methods previously described [20]. Gingival, palatal, and cervical biopsies for electron microscopy were immediately minced in 2% cold gluteraldehyde and processed as above [20].

Case Reports

One case report is presented in detail. Where findings on other affected members differ in significant detail, they are noted briefly. Table 1 summarizes the historical aspects of the kindred.

IV-10 was born in 1947 of a full-term pregnancy, weighed 4280 gm, and was 22 inches long. He refused to open his eyes in bright light and had a severely crossed left eye. He developed draining ears at 2 weeks, measles at 6 months, and had continuous rhinorrhea in winter which persisted until adulthood. At 1½ years an area of erythema in and below the nostrils and around the anus was noted. At 2½ years he had bilateral keratoconjunctivitis with corneal vascularization, bronchopneumonia, and anemia. At 2 years 10 months he was admitted for in-

ability to face light, anemia, crossed eyes, and red eruptions of skin around nose and anus. Photophobia was accompanied by lacrimination, nystagmus, erythematous conjunctivae, corneal epithelium heaping at the limbus, corneal vascularization and opacification, and strabismus of the left eye. Cultures of corneal lesions were sterile. Hair was scanty, and ear drums were red, thickened, and retracted. Mucosa of the nose, mouth, lips, gingiva, palate, pharynx, urethra, and anus were bright red. Allergy tests to a large number of foods, Mantoux, and Wasserman tests were negative. He was thought to have avitaminosis A and was treated with 25,000 units of vitamin A daily and oleum percomorph. At 3 years 2 months he broke his right forearm and 2 days later was hospitalized with pneumonia. By 3 years 10 months he had developed a generalized perifolliculitis of the skin with occasional fissuring and multiple filamentous warts on his abdomen. He had repeated colds each winter and with each episode lost large amounts of hair. Cortisone eye drops failed to correct eye lesions. He developed severe lacrimination and a marked sneeze reflex to light. By 5 years he could see fingers at only 3 feet. At 6 years 2 months he was admitted for the complaint that he could neither read nor write. Both lenses were found opaque. A form of ectodermal dysplasia was considered, but a skin biopsy showed normal sweat glands and sweat and temperature tests were normal. His intensely red oral mucosa was attributed to mouth breathing by the dentist. At 8 years 1 month he was admitted for beta radiation of eye lesions without noticeable improvement. During his tenth year he was admitted three times for bronchitis and bronchopneumonia. At 11 years 6 months, when admitted for chest pain and dyspnea, he weighed 62 pounds and was 59 inches tall. His arms and legs were long and thin, finger joints were hypermobile, he had a narrow AP chest diameter, and moderate scoliosis of the thoracic spine. A diagnosis of Marfan syndrome was entertained. Chest films showed a progressive fibrosis of the lungs, bronchial pneumonia, and emphysema. At 16 years 3 months he was admitted for pleuritic pain, melena, diarrhea, and pneumonia. At 16 years 6 months he was admitted for an endocrine evaluation. Blood glucose, blood urea nitrogen, sweat chloride, protein bound iodine, 17-ketosteroids, and FSH were normal. *Pseudomonas aeruginosa* and coagulase positive *Staphylococci* were cultured from his eye. Repeated fungi cultures of eye were negative. At 17 years a right lamellar keratoplasty was performed. The corneal graft became purulent and failed with *Pseudomonas aeruginosa* and coagulase positive *Staphylococci* cultured from the site. Eye cultures for fungi were negative. The excised cornea showed irregular degenerative corneal epithelium, pannus, and stromal edema. At 17 years 6 months a partial lamellar corneal graft was placed, and this also failed. He developed an enophthalmitis. At 17 years 7 months he developed a 35% left pneumothorax. At 17 years 8 months a penetrating corneal graft of his right eye was attempted but failed. Eye cultures were sterile. His final admission to the University Hospitals was at 18 years for cataract extraction on his left eye. A peripheral iridectomy was done, followed by prolapse of his iris, and a sphincterotomy was done to repair the defect. When last seen, his right eye was leukomatous and ectotic. He was admitted to the local hospital on three more occasions for spontaneous pneumothorax, right lung twice and left lung once. Radiographs revealed numerous emphysematous bullae in the upper lobes and a thoracotomy with left upper lobectomy was performed. The surgical report noted numerous pleural inflammatory adhesions, emphysema, and a meaty nonexpansive left upper lobe. The lung surface was covered with small blebs. The pathology report indicated bronchictasis, chronic organizing pneumonitis, and fibrosis of the upper lobe with pulmonary cysts. Throughout his hospitalizations repeated histoplasmin, tuberculin, Mantoux, Frei, VDRL, Klein, and Wasserman tests were negative, but episodes of eosinophilia, ranging from 7% to 29%, were noted. He was lost to follow-up after 22 hospital admissions and 89 outpatient visits.

Subsequent inquiry revealed that the patient married and had two children who were also affected. He had several additional episodes of pneumonia and several spontaneous pneumothoraces. A left thorocotomy with talc insufflation was performed. He developed cyanosis of fingernails and clubbing of fingers. He died at 27 years of cor pulmonale. No autopsy was performed.

II-8. This patient had a history similar to that of IV-10 but did not have a Marfanoid appearance. In addition, he had frequent bouts of diarrhea with melena, enuresis, and hematuria which accompanied frequent upper respiratory infections from childhood onward. He had

repeated bladder and urethral operations for incontinence, hematuria, and pyuria. On his last admission at 56 years, a biopsy revealed an adenocarcinoma of the right main bronchus. He died in less than a year. An autopsy was not performed.

II-10. This patient, in addition to findings similar to other affected family members, developed a left breast mastitis which was surgically removed at 18 years. He also had repeated operations for urethral obstruction. He died at 68 years with atelectasis, pneumonic abscess, parenchymal infiltration, tortuosity of the aorta, cardiac enlargement, decompensated heart disease, and lobar pneumonia.

III-2. This patient had a clinical history similar to other affected family members. At autopsy the final anatomic diagnoses were (1) congenital cystic disease of the lung, (2) chronic interstitial pneumonitis, (3) dilatation of the right atrium and right ventricle, (4) right myocardial hypertrophy, (4) pleural effusion bilaterally, (6) pleural adhesions bilaterally, (7) abnormal shape and location of left pupil, (8) clubbing of fingers and toes, and (9) red cyanotic mucosa.

IV-2. In addition to a history similar to her brother IV-10, she had numerous abnormal vaginal PAP smears, conizations, and treatment for vaginal "fungal" infections. She is presently bald.

Present Investigation of Patients

IV-15 was a 175 cm tall, slim (62 kg) 26-year-old woman, employed as an assistant to a field geologist. She had a narrow AP chest diameter, a mild pectus deformity, and long toes and fingers. She had cataracts removed at ages 8 and 19 years, pneumonia at 20 years, spontaneous pneumothorax at 22 years, and over six episodes of pleuresy and bronchitis, repeated vaginal infections, abnormal vaginal PAP smears, and repeated cervical cryosurgery for post partum metaplasia. She lost all scalp hair in her third trimester of pregnancy. Skin colored or slightly violaceous hyperkeratotic pinhead-sized follicular papules were present on the untanned skin of the trunk and legs. The palms, soles, face, and tanned skin areas were spared. There was diffuse nonscarring alopecia of the scalp. Light hair pull test was normal. The hair had a coarse texture. She had moderate photophobia, irregular pupils, red palpebral conjunctivae, clouding of the right cornea with a rough, irregular surface at the limbus, and a small area of chorioretinitis in the right fundus. Tympanic membranes were opaque and irregularly dense with old scars. She had a chronic serous rhinorrhea and red nasal mucosa. Gingivae, hard and soft palate, tongue, floor of the mouth, buccal mucosa, and pharynx were intensely red. The palate had a micropapillary appearance. She had a large scrotal tongue. Anal mucosa was normal. Vulva, perineum, vaginal walls, and introitus were reddened. An area of metaplasia was present on the cervical os. Slight hyperextensibility of fingers, toes, and elbows was noted, but other joints were not affected.

IV-16 was a 177 cm tall, obese (88.25 kg) 24-year-old laundry worker with long fingers and toes. Her past medical history was similar to patient IV-10 with the exception that she has not had corneal transplants, clubbing of fingers, or spontaneous pneumothorax. Her follicular skin eruption was more extensive than her sister's, attributed to sun shielding by clothes and indoor occupation. Head and pubic hair were coarse, and diffuse nonscarring scalp alopecia was prominent. She had a right esotropia, moderately intense photophobia, and a coarse slow nystagmus with a rotary component. The conjunctivae were red. Pupils were irregular with evidence of previous cataract surgery. The fundi were not visualized because of a pupillary membrane. Tympanic membranes had clear centers with opaque borders. Her left tympanic membrane had a calcified mass from 7 to 10 o'clock and no reflex. Rhinorrhea was not present, but the nasal mucosa was fiery red. Her gingivae and hard palate were red, the latter having a micropapillary appearance. The tongue was red with a scrotal mucosa. Anal mucosa was red. A large (2 cm) area of ectopy was present on the cervix. No metaplasia was noted. Finger, toe, metacarpal, metatarsal, and elbow joints were slightly hyperextensible.

V-18 was a severely photophobic 17-month-old daughter of IV-15, weighing 10.5 kg, 81 cm tall, with slight frontal bossing. Her fingers and toes were normal. She had about twenty, 3 to 5 mm diameter erythematous papules on her trunk and below her left axilla. Her head hair was fine but scanty. Nystagmus, tearing, and severe photophobia were present. Her lid and bulbar conjunctivae were injected. A pannus was present at the edge of the right cornea. Lipoid-like cysts were present on the palpebral conjunctiva bilaterally. Fundi were normal, and lenses clear.

Her tympanic membranes were clear. She had a beefy red scrotal tongue, red gingivae and hard palate, and a 0.5 cm diameter red nodule on her left lower lip. The oral commissures and anal mucosa were red. Her fingers and other joints were normal.

Laboratory Results.* Laboratory values for IV-15, IV-16, and V-18 were all within normal limits except for a mild eosinophilia of 6%–9%. Oral and vaginal PAS smears and cultures were negative for Candida, as were monthly oral smears and cultures from the propositus over a 12-month period. All immune tests were normal. No deposits of IgA, IgM, IgG, fibrin, albumin, C_3 and C_4 complement fractions were present in mucosa or skin. Skin epithelium-bound antiepithelial antibody in serum from patients with pemphigus demonstrated the presence of normal antigen on the cell surface. Chest and heart films and pulmonary function studies showed no significant changes. However, 5 months after this admission, IV-15 had another bout of pneumonia.

Histologic Findings. The gingival, palatal, corneal, and cervical epithelia shared certain features in common: a decrease in the number of epithelial cells, a lack of maturation of epithelia, a dyshesion of squamous cells, and individual cell dyskeratosis. The epithelial layer was thin. This was particularly apparent in the palatal gingiva biopsies, where the normally deep rete pegs were not filled with epithelial cells between projections, accounting for the micropapillary appearance seen clinically (fig. 2*a*). The lack of normal cornification and keratinization of gingiva and palate, respectively, was striking, especially in the PAP and Dane's keratin stains. The typical cell surface was precornified or had a two to three cell layer of cornified cells. The intercellular spaces were prominent between prickle cells, particularly in oral and cervical specimens, but no frank lacunae were seen. Parabasal and basal cells contained vacuoles and had densely staining (H&E, PAP) large pleotrophic folded nuclei. The basement membrane was intact, and a moderate inflammatory infiltrate of plasma cells and lymphocytes was seen with moderately dilated capillaries in the lamina propria. Throughout the middle and upper prickle cell layers were scattered a number of small round eosinophilic (H&E) or orangeophilic (PAP), waxy, rigid-appearing dyskeratotic cells. While all tissues examined contained these cells, they were most numerous in the palatal (fig. 2*b*) and corneal biopsies (fig. 3). Skin biopsies showed hyperkeratotic plugging of hair follicles and a moderate perifollicular inflammatory infiltrate. A review of the postmortem tissue sections of III-11 showed fibrosis of the lungs with numerous cysts up to 1.5 cm in diameter throughout the parenchyma. The lung tissue had thickened fibrotic septa; many cystic alveoli; sloughing, vacuolation, and cuboidal metaplasia of alveolar lining cells; and moderate infiltrates of lymphocytes and heavy infiltrates of mononuclear macrophages.

Cytologic Findings. The cytologic features of nasal, gingival, palatal (fig. 4*a*), vaginal (fig. 4*b*), and urinary sediment (fig. 4*c*) epithelium also shared common features. There was a lack of epithelial cell maturation. The smears contained numerous parabasal and precornified cell types. The cells had sharply demarcated round borders and seldom occurred in sheets showing cell-to-cell attachments. There was anisocytosis, poikilocytosis, large paranuclear cytoplasmic vacuoles (figs. 4 and 5), and transcytoplasmic strands and aggregates of material, cytoplasmic polychromatophilia, large nuclear cytoplasmic ratios, densely staining nuclear chromatin, irregularly-shaped and folded nuclei, and pseudopodia of the cytoplasmic membrane. The cytoplasmic changes most closely resembled the ballooning degeneration and polychromatophilia seen in erythema multiforme. Among these cells were small, orangeophilic, waxy, dyskeratotic cells or prematurely keratinized cells (figs. 4*a* and *b*). Except for these latter cells, the PAP and Dane's keratin stains did not stain either the vacuoles or the cytoplasmic inclusions. Further, the inclusions did not stain with Sudan black of Baker's phospholipid stain. Many cells stained intensely with PAS; this reaction, however, was reduced with diastase digestion.

Electron Microscopic Findings. Thin sections of tissue biopsies from the palate, gingiva, and cervix and cells from the urine sediment fixed for electron microscopy revealed striking abnormalities not observed in samples of similar material from normal individuals. Fibroblasts in the lamina propria of the gingiva were filled with dilated endoplasmic reticulum. Amorphous mate-

* Values may be obtained upon request.

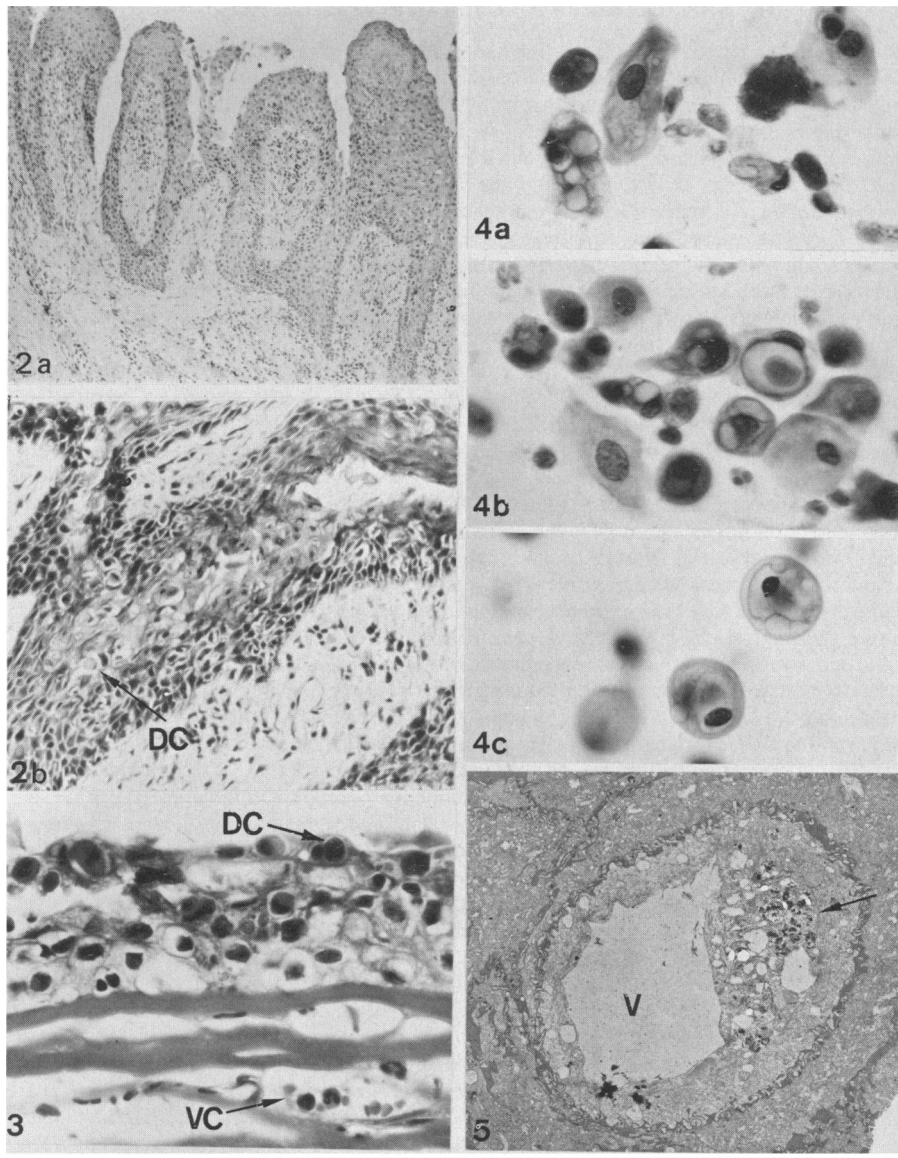


FIG. 2*a*—Section of palatal gingiva from an erythrematous area which had a micropapillary appearance clinically. Epithelial cell layer is thin, and cells do not fill areas between normally deep rete pegs (H&E stain × 75).

FIG. 2*b*—A rete peg from hard palate showing dyshesive nature of squamous cells, cytoplasmic vacuolations, small round dyskeratotic cells (*DC*), and dark-staining pleomorphic nuclei (PAP stain × 192).

FIG 3.—Recruit of paraffin block of corneal specimen from IV-10. Artifactual separation of Bowman's membrane has occurred, but vessels within the stroma (*VC*), loss of nuclear polarity of basal epithelial cells, vacuolations, and numerous small round dyskeratotic cells (*DC*) are easily discerned (PAP stain × 480).

FIG. 4.—Exfoliated cell smears from (*a*) hard palate, (*b*) vagina, and (*c*) urine sediment show similar cytologic features of numerous immature epithelial cells, perinuclear vacuoles, and strand-shaped inclusions. Small dark cells are dyskeratotic cells which stain orangeophilic (PAP stain × 480).

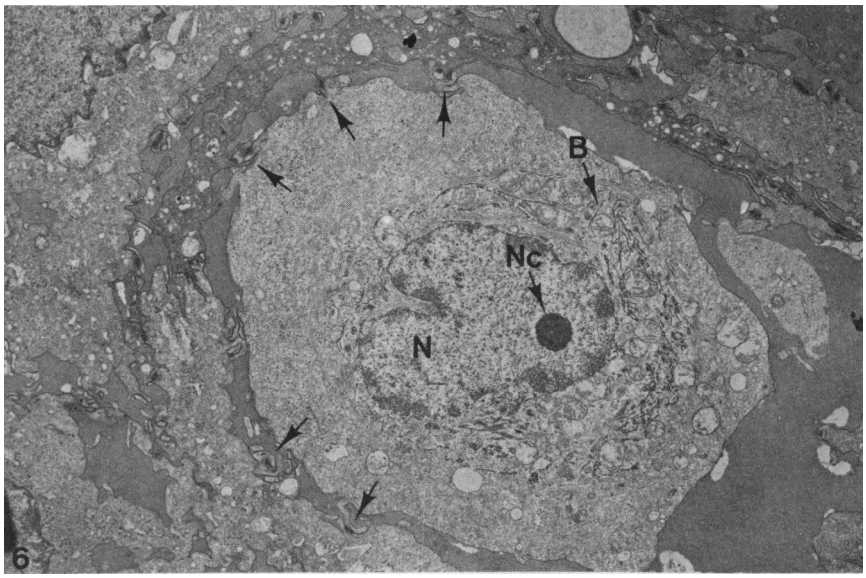
FIG. 5.—Keratinocyte from gingival biopsy. Although not evident at this low magnification, this cell and others in this layer of gingival epithelium reveal a decreased no. of desmosomes and an increased amount of amorphous material between cells compared to the cell-to-cell associations in normal biopsies. The cell contains a large vacuole (*V*) and many small ones, some filled with amorphous debris (*arrow*). Magnification × 3,300.

rial was present in the dilated channels. The basement membrane was intact but frequently redundant. The number of desmosomal attachments progressively decreased from basal to squamous layer such that many squamous cells in thin sections had fewer than six identifiable desmosomes (figs. 6 and 7). Many desmosomes had reduced numbers or a virtual absence of attached tonofilaments. Intercellular spaces were wide and filled with amorphous material varying in electron density and containing cellular debris (fig. 6). Keratohyalin granules were not observed in the cells at any stage of transformation. Many cells revealed a striking and unusual cytoplasmic organization. Masses of fine tonofilaments oriented parallel or perpendicular to the surface membrane occupied the peripheral one-third of the cytoplasm (figs. 6–9). Interior to the peripheral band was an area of cytoplasm containing a variety of structural aberrations. Usually this zone was to one side of the eccentric nucleus, but in some cells it formed a perinuclear band. Numerous vacuoles of varying size were present in this zone. Some contained amorphous debris and strongly resembled autophagic vacuoles. Other vacuoles were very large, occupying one-third to one-half of the cytoplasm, and contained little or no sequestered material (fig. 5). Intermingled with the vacuoles, or in cells without vacuoles, were unusual cytoplasmic structures. The most prominent were wheatsheaf-like bundles of filaments (figs. 7 and 9). Individual filaments were often fused into thicker strands which were very straight. Occasionally the strands were single or in bundles. Ribosomes were frequently associated with strands and bands, often lining up at regular intervals on each side (figs. 9 and 10*a*). Other unusual structures were often evident in the inner zone of cytoplasm. Some resembled long bands, were undulating rather than straight, slightly more electron dense than the strands, and revealed an organized substructure (fig. 8). Short segments of this material possessed a pentalaminar structure similar to the organization of gap junctions (fig. 10*b*). These short segments commonly aggregated into thicker, multilaminar bands, up to several microns long (fig. 10*d*). In some areas tonofilaments were attached to the multilaminar bands (fig. 10*b*). In addition to the strands and bands, some cells had masses of amorphous material in the inner zone of cytoplasm. The masses resembled the filamentous strands in wheatsheaf-like bundles and may have derived from them. Although thin sections of cervix and bladder cells revealed morphological differences from gingival cells, the organization of the cytoplasm into zones, vacuolization, wheatsheaf-like bundles of strands, and undulating bands of desmosomal-like and gap junction-like material were observed in cells from all tissues.

DISCUSSION

The disorder described appears to involve a defect in the formation, assembly, or organization of the materials essential for establishing gap junction and desmosomal connections between epithelial cells. Desmosomes were observed between cells, but were reduced in number and often had few attached tonofilaments. The unusual cytoplasmic strands of filament-like material and bands resembling gap junctions and desmosomes in several affected tissues suggests a defect in the process of assembly underlying formation of intercellular connections. Multilaminar bands appear to be aggregates of trilaminar gap junction-like material. Isolated gap junctions in vitro aggregate into similar appearing structures [21]. Structures resembling gap junctions or desmosomes as seen frequently in this study are not previously reported and until now were not known to exist inside cells. The specific relationship between the unusual inclusions observed in patient cells and the dyshesive nature of their epithelial disease remains unclear. Nevertheless, the disorder is an epithelial cell dyshesive disease [22] with a reduced formation of desmosomal attachments rather than a strictly acantholytic process [23].

The ultrastructural abnormalities in the formation of desmosomal attachments could account for the dyshesive features seen in the histologic and cytologic material and the thin red mucosa seen clinically. A defect in the gap junctions may be involved in the development of cataracts, as gap junctions normally are found in remarkable density in



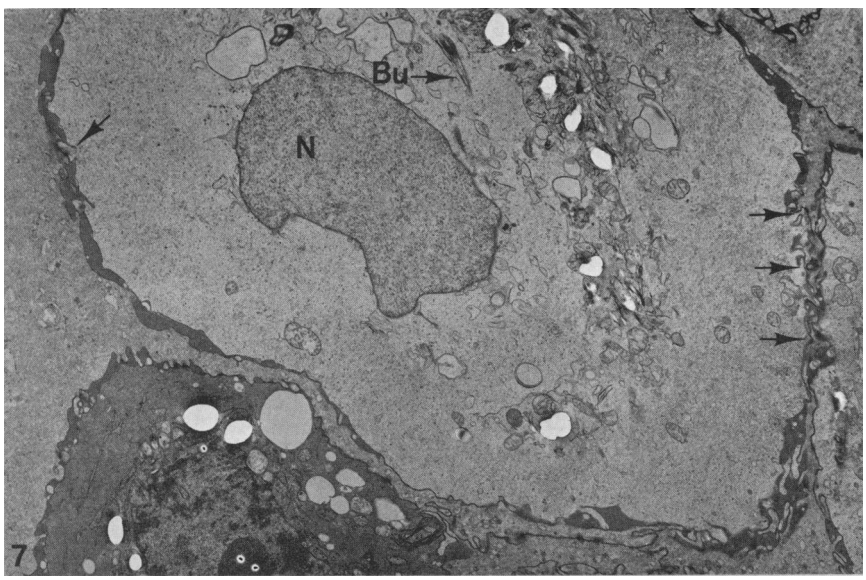
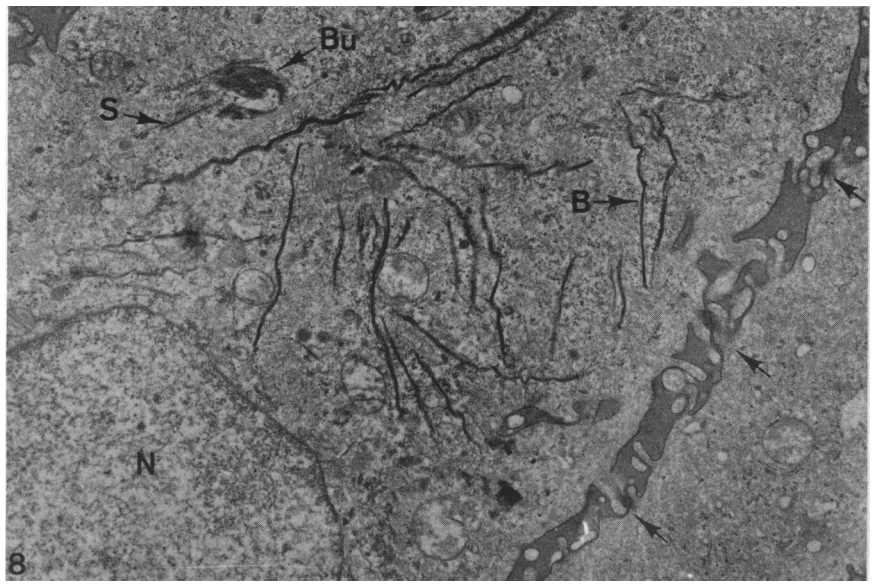


FIG. 6.—Keratinocyte from gingival biopsy. Cytoplasmic constituents are roughly divided into zones. The nucleus (*N*) occupies the central region or is slightly eccentric. This example contains a nucleolus (*Nc*). Perinuclear zone contains a variety of structural aberrations, including many undulating bands (*B*). Peripheral region is dominated by masses of filaments. Intercellular substance separating this keratinocyte from its neighbors is markedly increased, and the no. of desmosomes (*arrows*) decreased. Only 5 desmosomal complexes can be identified along the entire border.

FIG. 7.—Keratinocyte from gingival biopsy. Cytoplasm and nucleus (*N*) are partially extracted, but cell retains its rough division into 3 zones. Wheatsheaf-like bundles of strands (*Bu*) are visible in the perinuclear area. Although the intercellular substance is not increased, the no. of desmosomal junctions (*arrows*) between this cell and its neighbors appears decreased. Only 4 desmosomes can be identified with certainty along the cell border. Magnification × 6,000.



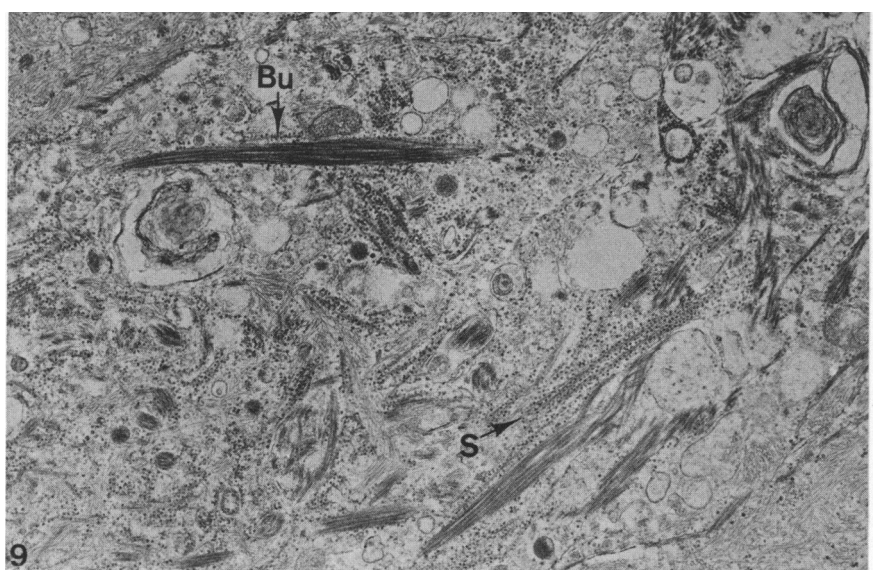


FIG. 8.—Keratinocyte from gingival biopsy. Cytoplasm is dominated by undulating bands (*B*) of various lengths. Occasional fibrous strands (*S*) with associated ribosomal particles and wheatsheaf-like bundles (*Bu*) occur in the same cell. Three desmosomes (*arrows*) are seen along the visible border of this cell and its neighbors. Magnification × 15,000.

FIG. 9.—Keratinocyte from gingival biopsy. Strands (*S*) and bundles (*Bu*) of fibrous strands dominate the perinuclear cytoplasm. Small dark particles are ribosomes which are regularly associated with strands and wheatsheaf-like bundles. Magnification × 16,500.

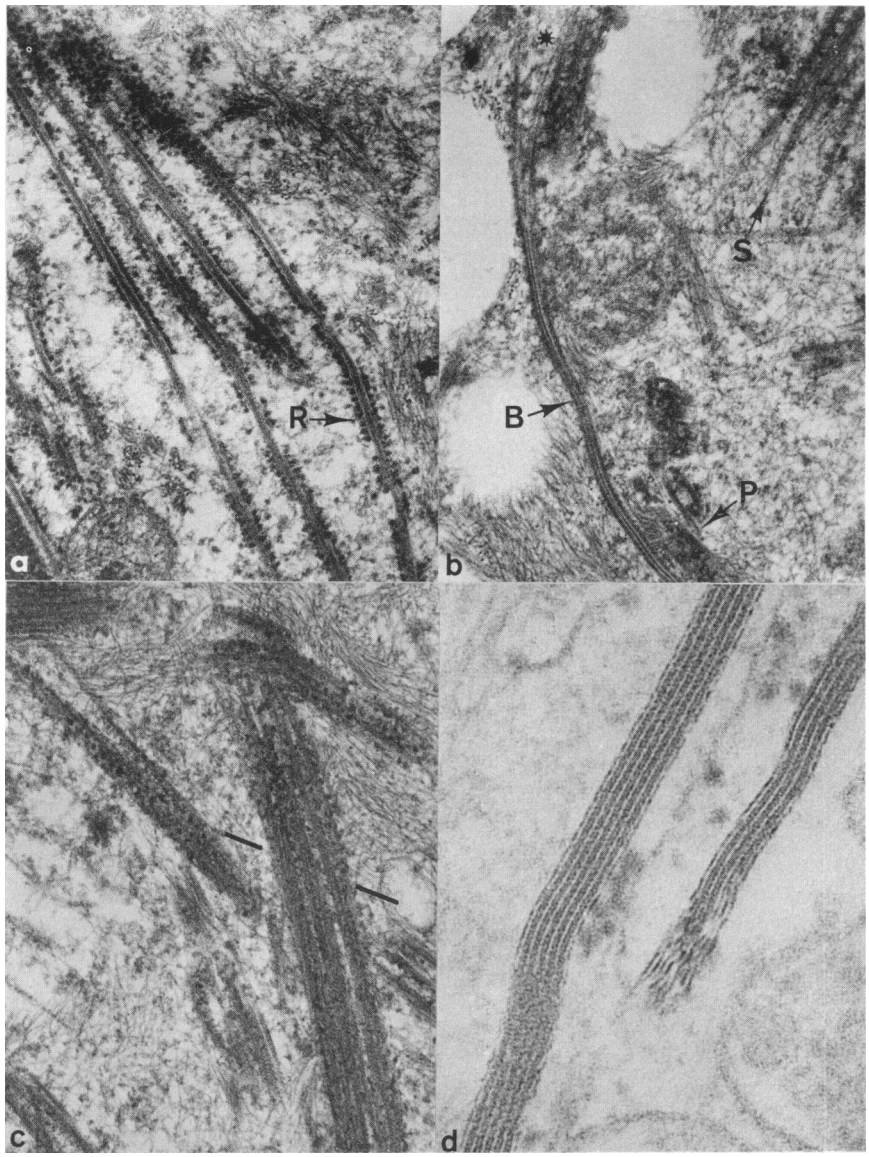


FIG. 10.—Details of structural elements in bladder epithelium and gingival keratinocytes. *a*, Long bars of amorphous material are the major structures in perinuclear zone of bladder epithelial cell. Thin, clear line on each side of bars separates them from regularly associated ribosomal (*R*) particles. *b*, Undulating band, split at upper end (*), courses through cytoplasm of bladder epithelial cell. The band has a highly ordered substructure of two dense outer layers and a thin central dark line separated from outer layers by clear spaces. Plaque-like structure (*P*) radiates filaments which appear to interdigitate with the band. Strands (*S*) are also present. *c*, Wheatsheaf-like bundles in a gingival keratinocyte reveal diagonal periodicity at higher magnification (*diagonal lines*). Dark particles associated with fibrous strands and bundles are ribosomes. *d*, Undulating bands in gingival keratinocyte. Outer layers of band are thin, although appearance may depend on the plane of the section. Inner dense layers are thicker and separated from each other by narrow clear zones. Although band structure superficially resembles a neuron's myelin sheath, the basic organization and thickness of layers is quite different. Magnifications: *a–c*, × 52,000; *d*, × 180,000.

lens fibers [24]. They probably play a major role in the anoxic lens epithelium where glycolysis through oxidative phosphorylation [25] provides the major source of energy production to maintain this tissue [26]. A defect in gap junctions could conceivably lead to the gradual production of cataracts as seen in this disorder. The recurrent diarrhea suggests that the gastrointestinal mucosa may also be involved.

The histologic and cytologic changes in the cornea and oral mucosa most closely resemble those seen in hereditary benign intraepithelial dyskeratosis [8, 9, 27, 28] but are distinctive for this disease. The oral cytologic changes share features with erythema multiforme [29]. Corneal transplants have failed in four instances in two patients (IV-10 and V-15). In light of the histologic findings in the cornea (fig. 3), this failure may have been conditioned by the dysplastic corneal epithelium.

Throughout the records of IV-10, IV-15, and IV-16 is the suggestion that they had a Marfan or Marfanoid syndrome. Investigation of the kindred accounts for this finding as a familial tallness which is not an integral part of the mucoepithelial dysplasia syndrome. The familial tallness was introduced into the kindred by II-2. III-9, who was unaffected with the mucoepithelial syndrome, is 6 feet 6 inches tall, his son 6 feet 8 inches tall, and two daughters 6 feet tall. They also have long fingers. None have had pneumothorax, chronic lung disease, or mucosal lesions.

A mother and two children with similar clinical findings were reported by Okamoto et al. [30] as a "New Syndrome of Chronic Mucocutaneous Candidiasis." The mother in that kindred had nail changes typical of candidiasis and the organism was isolated. However, the evidence for an immune or endocrine defect in that family is tenuous, and none of the present kindred members has a defect in those systems. Further, at the suggestion of one of us (C. J. W.), a vaginal Pap smear of the mother was obtained and noted to have cytoplasmic inclusions (J. G. Hall, personal communication, 1978).

A review of the microflora of eye, oral, vaginal, skin, and lung lesions of the patients show a wide variety of species. The organisms in order of frequency reported were: *Pseudomonas aeruginosa*, coagulase positive *Staphylococci, Neisseria*, alpha *Streptococci, Pneumococci, Hemophilis influenzae,* and *Candida albicans*. Because of the susceptibility to mucosal infections, these patients should be treated promptly and vigorously for any infection, especially those involving the respiratory tract and eye.

The folliculitis clinically and histologically resembled keratosis pilaris and was absent on the tanned skin surfaces of IV-15. Three minimum erythema doses of ultraviolet light (spectrum B) to the affected skin of the buttocks of IV-15 and IV-16 induced resolution of the lesions. Thus, ultraviolet light may have some beneficial effects in the treatment of this disease.

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