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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Oral pathology
American Academy of Oral Pathology
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Genetic disorders affecting mucous membranes

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The number of genetic disorders which affect mucous membranes is legion. Within the compass of this article one can only sample at choose (albeit randomly) a few examples to illustrate the wide variety of heritable conditions which involve the mucous.

Several conditions, such as cranio-facial-digital syndrome and congential epispinal synostosis, have been excluded, for, while the oral mucous is affected, it would appear to be secondary to underlying structures.

Not all mucous are affected by these genetic disorders and, in fact, not all parts of a single mucous are affected. In Fabry's disease, for example, the tongue mucous is never involved.

There is no one genetic pattern which is common to these disorders. Examples of autosomal dominant, autosomal recessive, and X-linked recessive patterns will be illustrated here.

EPIDERMOLYSIS BULLOSA*+.

Epidermolysis bullosa is a rare condition characterized by bullous and vesicular eruption of the skin and mucous membranes. There are four types, which differ clinically and in mode of inheritance (Table 1).

The simple type is inherited as an autosomal dominant trait. Bullae and vesicles develop on the skin and mucous membranes, with secondary healing producing scars. There are scars which can lead to narrowing of the larynx.

ADDENDA.

KERATOSIS.

The tongue is a common site for keratoses in the oral cavity. Juvenile keratoses may be seen in the mouth.

The author has briefly reviewed the literature on these conditions and their implications for oral pathology.

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Not all components of the syndrome appear simultaneously. The moniliasis is nearly always the first component to appear, with most observers recording its presence during the first 6 years of life. It is followed, from 3 months to 15 years later, by the other components. Hypoparathyroidism and hypocalcemic-corticism become manifest most frequently between the ages of 9 and 12 years, the former usually preceding the latter.

Hypoparathyroidism is the component most often associated with moniliasis and it is usually manifested by tetany. The serum calcium level is reduced and the serum phosphorus level is elevated in the absence of significant disease of the gastrointestinal system. Furthermore, parathyroid hormone injection results in an increase in the level of serum calcium and in elevated urinary phosphorus excretion. At necropsy, absence of the parathyroid glands or their replacement with fat has been noted.

Addison's disease makes itself apparent soon after the appearance of hypoparathyroidism. Loss of weight, anorexia, progressive weakness, hypotension, and progressive pigmentation of the skin and mucous membranes signal its onset, and clinical laboratory tests confirm the low serum sodium and high potassium levels. A failure of 17-hydroxycoverticosterone and 17-ketosteroid urinary levels to rise subsequent to injection of ACTH demonstrates the adrenal insufficiency. Death from adrenal crisis is a common outcome in this syndrome, and necropsy shows adrenocortical atrophy of the "cytotoxic type."

Hypothyroidism in this syndrome has been infrequently diagnosed. It has been shown to be primary, for thyroid-stimulating hormone does not produce a rise in thyroid $T_4$ uptake or alter the protein-bound iodine level.

The relation of the mental infection to the endocrine glands is not known. Necropsy does not suggest mycotic involvement of these organs; nor does the fungus elaborate a toxin which is capable of producing the changes. The prior occurrence of the moniliasis by several years causes further confusion.

The skin is dry, and the hair of the body and scalp is usually brittle and diminished. The eyebrows and axillary and pubic hair are remarkably sparse. Total alopecia may develop, most notably after therapy with dihydrotestosterone. The fingernails and toenails are frequently thin, ridged, and brittle and are often the site of cutaneous infection. If infected, they become brown, iridescent, and thickened, with a crumbled outer edge. Increased cerobrospinal fluid pressure, associated with papilledema, intracranial calcification, epileptiform seizures, and mental retardation, has been noted. Muscle twitching and cramps, tetany, abdominal pain, parvochiasis, and rigidity are seen.

Keratoconjunctivitis, photophobia, corneal, ears, nose, larynx, and wheezing may also be seen in this syndrome.

The oral moniliasis is superficial and may involve the lips, tongue, buccal mucous, palate, and larynx with thick, creamy white plaques. The mucosa between the plaques is often hyperemic, and the tongue may be smooth and devoid of papillae. Pustule or angular stomatitis, may extend over a considerable portion of the oral and vaginal mucosa has been described.
With the advent of Addison's disease, areas of splenectomized membrane pigment are seen in the mouth, especially on the buccal mucous and palate.

The teeth are chalky, with the enamel mildly pitted or exhibiting transverse grooves of enamel hypoplasia. Thickening and increased density of the lamina dura, the opposite of that seen in hyperparathyroidism, have been observed.

**ACRODERMATITIS ENTEROPATHICA**

Acrodermatitis enteropathica is a rare syndrome, occurring in childhood, the primary signs of which are (1) skin lesions, (2) hair loss, (3) nail changes, and (4) gastrointestinal disturbances. Recent comprehensive reviews of the literature have been made by Wells and Winkelman in 1961 and Margreth in 1963.

In 65 per cent of the reported cases there is a history of familial occurrence. An autosomal recessive mode of transmission appears likely.

Acrodermatitis begins early in life, usually between the ages of 3 weeks and 10 years, with an average age at onset of 6 months in reported cases. Occasionally the syndrome is reported in adults. It seems to improve by the time the patient reaches puberty. The onset is insidious and follows an intercurrent course, often with spontaneous, partial remissions succeeded by increasingly severe exacerbations. In the majority of cases the disease is fatal.

Children suffering from acrodermatitis enteropathica exhibit a striking uniformity of appearance, mainly because of the alopecia and the pruritic location of lesions. The affected child usually holds his head at an angle, with the face downward. Body growth has been found retarded in 80 per cent of the patients, and 40 per cent present mental changes, often in the form of schizophrenia characterized by the exacerbations.

The syndrome usually starts with small erythematous, moist skin eruptions localized around the natural orifices and symmetrically on the buttocks, elbows, knees, hands, and feet, especially between the fingers and toes and around the nails. The trunk is only slightly affected. In most cases, the rash is of the vesicular-bullous type. After a short period of time, the vesicular lesions begin to dry and crust, subsequently turning into sharply marginated lesions. When the lesions heal, they leave no scars.

The gastrointestinal disturbances consist of attacks of diarrhea, with increased excretion of fat. Diarrhea has been found in 91 per cent of the reported cases. The stools are often large, foul, foamy, and green, indicating malabsorption. In some cases, the only intestinal symptom is the occasional passage of loose stools.

In their review of fifty-eight cases from the literature, Wells and Winkelman found alopecia in 98 per cent; in most cases the alopecia was total. Paralytic with nail dystrophy was observed in 96 per cent of the reported cases; prolonged involvement results in complete loss of nails.

In a number of cases, conjunctivitis, blepharitis, and photophobia have been found.

The frequent finding (in 56 per cent of the cases reported) of Candida albic-
case in lesions on skin or mucous membranes or in stools has led to the assumption that the syndrome is the result of a menin
gal infection. Most investigators, however, agree that the menin
gal infection is a secondary phenomenon. It may be that acrodermatis entophasia is associated with an increased suscepti
bility to yeast infection.

The perioral area is always affected in acrodermatitis entophasia. Because of the purulent eruptions, weeping blisters
tulons at the angle of the mouth are often seen, at times with severe swelling. The oral changes are sometimes
described as “xanthisis” or “ochronosis.” Undoubtedly, a large number of chil
ren with the syndrome suffer from thrush. The buccal mucosa (less often the palate, gingiva, and tonsils) presents reddish and white spots or edema with eruptions, ulcerations, and desquamation. The white coating of the oral mucosa is reported to be rather firmly attached to underlying structures. On the buccal mucosa and borders of the tongue there may be numerous small papillomas with a whitish, thickened epithelial covering. Severe halitosis is often present.

**MULTIPLE MUCOSAL NEUROMAS, PHECOCROMOCYTOMA, AND MEDULLARY CARCINOMA OF THE THYROID**

Phaeochromocytoma may occur in combination with neurofibromatosis or with various brain tumors (cerebellar hemangioblastoma, ependymoma, astrocytoma, meningioma, glioblastoma). A considerable number of reports have been published on the association of phaeochromocytoma and multiple endocrine adenomas. Still another is the syndrome of multiple sweat gland, medul
lary carcinomas of the thyroid, and phaeochromocytoma.

Phaeochromocytoma, either alone or in combination with other tumors, may be inherited as an autosomal dominan
t trait.

The peripheral nerves principally involve the lips and the anterior portion of the tongue, although buccal, gingival, nasal, conjunctival, and laryngeal lesions have been described. Labial hamartoma produces a “blueberry” ap
pearance. The oral and labial component appears first and is often evident during the first few years of life. Microscopically, the mucosal nodules are pleomorphic nevoms.

Numerous white medullated nerve fibers traverse the cornea to amass within the papillary area. They can be seen with ease by slit lamp examination. The phaeochromocytoma may produce weakness, choking and flushing, pounding headache, hypertension, palpitation, profuse sweating, and intractable diarrhea. The attacks may last from minutes to hours and may terminate in shock or death. The tumors are often (about 40 per cent) bilateral. They may be evident as early as puberty but, in most cases, they appear after the fourth decade of life.

Medullary carcinomas of the thyroid, a tumor derived from the ultimobranchial body, elaborates both amyloid and thyrocalcitonin. It may appear as early as the eighteenth year but, in most cases it appears before the thirty-fifth year.

In several patients it has metastasized, causing death. Several patients have had necropsy, and others have had metastasized lesions of Auerbach and Meissner's plexuses.
This dominant, autonomaously transmitted disease manifests itself in the form of hyperkeratotic papules which may become confluent and widespread, occasionally involving the mucous membranes of the vulva, vagina, rectum, oral cavity, larynx, and pharynx. The oral lesions are tiny papules which somewhat resemble cobblestones. Microscopically, the skin lesions present a diagnostic picture. There are hyperkeratosis, acanthosis, dyskeratosis, and formation of clublike intracerebral lacunae, usually suprabasilar in location. Two variants of dyskeratotic cells are identifiable: intensely basophilic-staining small elongated "grains" and "corpus ruddy," which are cells with homogeneous, eosinophilic material surrounding a basophil, protoplasmic nucleus. In addition, the dermis shows nonspecific chronic inflammation, and variable degrees of papillomatosis may be present. Other diseases, such as actinic keratosis, may occasionally give rise to suprabasilar lacunae. However, corpra ruddy, grains, and papilomatosis are rarely seen in these diseases. Possibly a variant, rarely dyskeratotic, may occur as a single mucosal or cutaneous lesion.

**FACHONICHIA CONGENITA**

In 1969, H. Fuchsen and Lewandowski presented the first report on the syndrome of fachonichia congenita, palmoplantar keratosis and hyperkeratosis, follicular keratosis, and oral leukokeratosis. The name fachonichia congenita, applied to the thickened nails, was used subsequently to designate the entire syndrome.

The syndrome appears to have an autonomaous dominant inheritance pattern, although penetrance does not seem to be great. There may be a somewhat higher frequency of the syndrome among Jews.

In the vast majority of cases, at birth or soon thereafter, the fingernails and toenails are noted to be thickened, turbid, and hard, the undersurface being filled with a brown, yellowish brown material. This substance causes the nail to project upward from the nail bed at the free edge. Not uncommonly the nails are lost, with similar but more severe involvement appearing on regrowth. Inflammation at the sides of the nails is common.

Hyperkeratosis of the palms and soles nearly always occurs and is in marked contrast to the rest of the skin, which is quite dry and often described as "nail-like ichthyotic."

Palm and plantar hyperkeratosis are common, and during warm weather bullae appear on the feet, especially on the plantar surface of the toes and heels along the sides of the feet. These bullae burst, become infected, and are extremely painful, often making walking an extremely difficult task.

Usually during the first few years of life, pinhead-sized follicular papules appear over the elbows, knees, popliteal areas, and buttocks. In the center of each papule a horny plug is seen. Venous lesions may also occur in the same areas.

General dystrophy has been reported by several authors. A hoarse voice has been described in several patients, and thickening of the posterior commissure of the larynx has been noted. Thickening of the tympanic membranes has also been observed. Vocal stridor has been found to be thickened as well.
The oral mucoa, especially that of the dorsum of the tongue, is thickened, presenting a white or grayish white appearance. Less commonly involved is the buccal mucosa of the intermandibular line. Oral “herpetiform” lesions are frequent. Natal or neonatal teeth are commonly observed.

**WHITE SPONGE NEVUS**

This disorder may be present at birth or may appear by puberty. It is characterized by white spongy plaques on nearly any part of the oral mucosa, with variable involvement of the anal, vulval, and vaginal mucosa. The waxes are equally affected, and the disorder is clearly inherited as an autosomal dominant trait. At least thirty pedigrees have been published under a variety of names.

The white plaques are symptomless; hence, the disorder is often discovered by accident. The mucosa is thickened, corrugated or folded, and soft. The superficial keratin has a tendency to desquamate, at times leaving a raw surface. The free gingival margin appears to be spared. Buccal mucosal involvement is constant and nearly always symmetrical; in rare instances, it is unilateral.

In addition to the genital mucosal involvement in both sexes, the laryngeal and nasal mucosa can also be affected.

Microscopically, the epithelium is thickened and parakeratotic, the superficial cells appearing “washed out” with pyknotic nuclei. The prickle cells are usually vacuolated.

Differential diagnosis would include cheek biting, pachyonychia congenita, leukodema, and hereditary benign intraepithelial dyskeratosis.

**HEREDITARY BENIGN INTRAEPITHELIAL DYSKERATOSIS**

The syndrome of hereditary benign intraepithelial dyskeratosis was described in a North Carolina trilaminar isolate (Cousen-Hyman-Indian) in 1969 by Wilkens and associates and by von Sallmann and Patton. The chief components are (1) plaques of the buccal conjunctiva and (2) oral mucosal thickenings, clinically similar to white folded hypertrophy (white sponge noma of Cannon), typically affecting the palate and nasopharynx.

The syndrome is inherited as an autosomal dominant trait with a high degree of penetrance. The eye lesion is usually noted within the first year of life. About the fifth year, both nasally and temporoally, there are many gelatinous plaques, more superficial than pterygia, on a hyperemic bulbar conjunctiva. The dyskeratotic process may involve the eponym, producing blindness from shedding and resultant vascularization of this structure. Photorobia, especially in children, is common.

The oral mucosal thickenings are asymptomatic. They appear as soft white folds and plaques resembling white sponge nema. Although the thickenings appear at birth, they are mild, increasing in severity to the age of about 36 years. There does not appear to be a tendency for the oral lesions to undergo malignant degeneration.

Tissue sections or Papanicolaou-stained smears of buccal mucosal or con-
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Jejunal scrapings are characteristic. Acanthosis, vacuolization of the stratum spinosum, and intraepithelial dyskeratosis, characterized by waxy cytoplasmic cells called "abnormal cells" and a "cell-within-a-cell" pattern, are noted. These latter changes are especially evident in Parakeratohyaline

ized squames.

Witkop and Griswold found similarities in oral squames from hereditary benign intraepithelial dyskeratosis and keratosis follicularis (Darier-White disease). The grains of the latter resemble the so-called "tobacco cells" of the former, and the cores from the latter resemble the "cell-within-a-cell" body seen in the syndrome under discussion. However, the cell-within-a-cell is far more common in oral squames of hereditary benign intraepithelial dyskeratosis, in addition, one rarely sees the small blue parakeratinized cells so often seen in keratosis follicularis. Patients receiving methotrexate also exhibit the "cell-within-a-cell" phenomenon in exfoliated buccal cells.

DYKERATOSIS CONGENITA WITH PIGMENTATION.

DYSTROPHIA LINGUIAE, APALEIC ANEMIA, HYPERSENSITIVISM, AND LEUKOPLAKIA ORIS.

Zinner, in 1906, reported what appears to be the first case of a syndrome comprising "reticular atrophy of the skin with pigmentation, dystrophy of the nails and oral leukoplakia."

Although one cannot be too certain concerning the hereditary pattern of this syndrome, it appears to be an X-linked recessive trait.

The most prominent skin changes closely resemble those seen in psoriasis, atrophoderma vespertilonicum, involving especially the face, neck, and about and appearing approximately at puberty. A prominent reticulated hyperpigmentation of skin, usually described as "meatal color, involves the same areas. Microscopically, one notes atrophy of the epidermis and subcutaneous tissue accompanied by capillary hyperplasia. Melanin pigment is heavily deposited, especially near blood vessels.

Hyperhidrosis of the palms and soles has been noted in all cases, and palmar keratoses have been described. Keratosis of the hands and feet appears to be exceedingly common. In most cases the fingernails and toenails become dystrophic at about the age of puberty.

Chronic blepharitis and ectropion and profound atrophy due to keratinization, with obstruction of the lacrimal points, have been described. Acute atrophy occurs in several patients and seems to be part of the syndrome.

Crops of vesicles and bullae appear on the oral mucosa, most frequently during the 5- to 7-year age period. In some cases, earlier. These flexural bullae are recurrent and especially painful. Because of moisture and maceration, they rupture early, leaving ulcerated areas along the border of which may be seen epithelial tags. After several attacks, the mucosa becomes atrophic and the tongue loses its papillae and becomes smooth. Under a Wood light, the normal orange fluorescence of the tongue is missing. Eventually, the mucosa becomes thickened, fissured, and white.
MUCOCUTANEOUS MELANOTIC PIGMENTATION AND GASTROINTESTINAL POLYPOSIS

The most important component of the syndrome is polyposis of the gastrointestinal tract. The polyps are hamartomatic in origin. The following sites, in order of frequency, are involved: jejunum, ileum, large bowel, rectum, stomach, duodenum, and appendix.

Polyps may produce intussusception and occasionally lead to severe intestinal obstruction and death. The age at onset cannot be precisely determined, but generally there is a history of gastrointestinal problems before the third decade of life.

There is no evidence that the polyps are premalignant. Some patients have polyps of the shoulder, nose, cervix, and bronchi, but this is unusual.

Fifty per cent of affected persons exhibit discrete brown to bluish black macules of the skin, chiefly around the oral, nasal, and orbital orifices. The number of pigmented spots varies in different patients. Pigmentation of the extranails (elbows, knees, ears, and palms) also can be found.

The lips, especially the lower lip, and the oral mucosa are involved with pigmented macules in about 90 per cent of the patients. Less frequently involved are the gingiva and palate, and rarely the tongue and oral floor. The melanotic spots are larger than those on the skin. The cutaneous pigmented macules tend to fade after puberty, but the intranasal pigmentation remains for life.

Pigmented spots have also been reported in the conjunctival and nasal mucosa.

The syndrome is inherited as an autosomal dominant trait with high penetrance and variable expressivity.

HYALINOSIS CUTIS ET MUCOSAE

The syndrome consisting of (1) yellowish nodular infiltration of skin and mucous membranes and (2) hearing loss was first described by Stobbe and Tiegens in 1959, and has since been designated by Ullrich and Wiethe, who defined the condition and applied the terms hyalinosis cutis et mucosae and lipoid proteinosis. About 125 cases have been described to date.

The syndrome is transmitted as an autosomal recessive trait. It has appeared in siblings, and in several cases there has been consanguinity in the parents.

Discrete or confluent yellowish, ivory or waxy nodules, from pinhead to walnut size, usually occur on the face, neck, axillae, and hands early in life.

Bullous exorcescences appear on the margin of the eyelids, followed by loss of hair. Brownish, yellow wartlike hyperkeratotic lesions appear on the knees, elbows, and proximal interarticular surfaces of the fingers.

Intramural calcification has been found in a considerable number of patients. It is located above the pituitary fossa in the hippocampus, floor cerebelli, or temporal lobes.

The voice may be hoarse from birth, or it may become so at puberty. The inability to cry at birth in the majority of cases testifies to early laryngeal involvement. Laryngoscopic examination reveals yellowish white plaques in the
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Epiglottitis, aryepiglottic folds, and interarytenoid region. The carin is thickened and nodular, and closure is insufficient. Dyspnea may be severe, and laryngopytis may be necessary.

The mouth is the most extensively affected area. Nearly all oral tissues become infiltrated with yellowish white, elevated, pus-filled plaques, which appear most frequently before puberty and gradually increase in severity. The lower lip, usually more severely affected, assumes a cobblestone appearance. Radiating fissures may appear at the angles of the mouth.

The tongue becomes firm or woody, thick, large, and bound to the oral floor with marked infiltration of the frenum and sublingual and submandibular plexus. The thalamus loses its papillae.

With infiltration of the buccal mucosa, the papilla of the palatal duct may become atrophied, with ensuing retrograde parotitis. Extension of the infiltration to the pharynx may result in dysphagia.

The dentition may be severely affected. Teeth may fail to develop or may be hypoplastic, especially the upper lateral incisors, canines, and upper second premolars, or the enamel may be severely hypoplastic.

Microscopically, one notes hyalinosis of the upper layers of the corium or dermis, beginning about the small arterioles of the sweat glands. The elastic fibers are destroyed. Argyrophilic fibrils appear throughout the dermis. The hyaline material stains intensely with the periodic acid-Schiff stain and appears to be a glycoprotein with associated free or loosely bound lipid.

ANGIokeratoma corporis diffusum universale

The syndrome of (1) angiokeratomas of the skin, (2) pain in the extremities, (3) disturbance in sweat excretion, (4) elevated blood pressure, (5) heart enlargement, and (6) gliomia was first described by Anderson in England in 1899 and by Fabry in Germany in 1898. Sversly and Klimovi, in 1963, suggested the name of angiokeratomas.

The condition is inherited as an X-linked recessive trait with full expression in males and partial expression in heterozygous females in accordance with the Lyon hypothesis. Its occurrence in a few homozygous females has also been described.

The syndrome is produced by an abnormally high concentration of two closely related neutral biuret-reacting glycolipids (ceramide trihexoside and ceramide dihexoside) in (1) smooth muscle, (2) endothelium, (3) supporting cells of blood vessels in the kidney, skin, gastrointestinal tract, heart, and central nervous system, and (4) reticuloendothelial tissues. This lipid deposition is caused by deficiency of a ceramide trihexosidase-degrading enzyme.

Angiokeratomas of the skin may be present from early childhood, becoming clinically evident at 7 to 10 years of age. The skin lesions are manifest as numerous minute, slightly grouped, round to oval, macular to papular, bluish red to black, blood-filled cavities up to 4 mm in diameter, spread over the iliac area, posterior thorax, buttocks, scrotum, thighs, and umbilical area.

The face is not affected, and the skin surfaces of the forearms are involved to a lesser degree. In some male patients the skin rash is absent. Histological
females generally do not present skin lesions. Vascular motility of palms and soles has also been reported.

Pain, usually affecting the hands and feet, is the main complaint of affected persons. The pain is colicky in type and may be due to abnormal conduction resulting from defective myelination. It is not modified by vancomycin drugs. Elevated temperature and diminution in sweating are frequent.

Superficial corneal opacity resembling that seen in chloroquine intoxication has been noted in both sexes, but less commonly in female carriers. The fundi may present marked tortuosity of retinal vessels with dilatation of veins. Variocities of the palpebral and bulbar conjunctive are also common.

Most patients present enlargement of the left heart and elevated blood pressure. Proteinuria has been noted in the majority of patients. Swelling of the ankles and about the eyes is first seen during puberty. Various veins and hemorrhages have been noted in about 25 per cent of all affected persons.

Anemia is commonly associated with uremia. Raynaud's phenomenon has been noted during hemolytic episodes. Sometimes有 reported cases of thrombosis in phlebitis-like condition.

Most patients present angioneurotic edema of the lips, especially the lower lip, near the skin-mucosal junction on both sides of the midline. The tongue is not affected, and only rarely are other oral tissues involved.

Light and electron microscopic studies have shown the characteristic lipids in various affected tissues.

Hereditary Hemorrhagic Telangiectasia

The syndrome is characterized by multiple capillary and venous dilatations of the skin and mucous membranes with repeated hemorrhage. The disease is inherited as an autosomal dominant trait; it is more common among Jews and very rare among Negroes. Onset is usually in the second and third decade, sometimes later.

Penpoint, spiderlike, and nodular telangiectases are observed on the face, nasal orifices, ears, scalp, fingers, toes, and nail beds. Lesions on the nasal mucosa produce frequent and, at times, severe epistaxis that may persist for several days. Generally, nasalbleeding precedes the appearance of cutaneous telangiectases.

Telangiectases affect the mucous membranes of the mouth and anterior chamber of the eyes and occasionally, the palate, gingiva, and buccal mucosa. Bleeding from the oral cavity, especially from the lips and tongue, is second in frequency after epistaxis.

Mucous membranes in the gastrointestinal tract, conjunctiva, vagina, uterus, and bladder may also be involved and give rise to hemorrhagic. Any organ—liver, brain, spinal cord, lungs—may be affected by the disease.

The syndrome should be differentiated from angioneurotic edema (Fisher's syndrome) and from the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia).

Familial Dysautonomia

This condition, first recognized by Riley and associates in 1949, is also known as the Riley-Day syndrome. It is transmitted as an autosomal recessive trait.
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and is virtually limited to persons of Ashkenazi Jewish extraction. No specific enzyme defect has been demonstrated.

The condition becomes evident soon after birth, with difficulty in swallowing and regurgitation. Absence of tears and corneal anesthesia with resultant corneal ulceration, skin blotching, insensitivity to pain, which may result in Charcot's joints as the child grows older, motor incoordination, excessive sweating, high fever of unknown cause, diminished gag reflex, frequent vomiting and breath-holding spells that may result in loss of consciousness and a mild degree of retardation are the most frequent findings during the first 3 years. There may also be athetosis and an abnormal nasal speech (dysarthria).

Postural hypotension and paroxysmal hypertension may develop later in life. Statute is small, and physical growth and psychosexual development are delayed. Severe progressive kyphoscoliosis commonly appears around the eighth or ninth year of life. Twenty-five percent of affected persons die of pulmonary infection by the end of the first decade. There is a marked tendency to recurrent bronchopneumonia, probably due to the frequent aspiration of food. Boys seem to have a significantly poorer chance of survival up to the sixth year of age.

The face is quite characteristically exhibits a transverse elongated mouth with symmetrical facial drooping. The tongue shows an almost complete absence of fungiform and circumvallate papillae. Associated with this is a decreased sensitivity to sweet and bitter tastes. This is a consistent pathognomonic feature of the Riley-Day syndrome.

Other characteristics include a slight to absent reaction to histamine skin test and a marked reaction to neopentylphosphate and related drugs. Low 3-
methoxy, 4-hydroxyamphetamine acid (VMA) and increased homovanillie acid (HVA) levels have been detected in the urine of affected patients. Moses and colleagues, however, found normal HVA levels.

Genetic studies have shown an autosomal recessive inheritance pattern. All but two parents have had Ashkenazi Jewish ancestry, but in each of those cases the other parent was Jewish. An estimation of the frequency of dysautonomia among American Jews, according to McKeon and associates, is approximately 1 in 10,000. A similar finding was noted in Israeli Jews of Ashkenazi origin.

The carriers do not exhibit any clinical signs of the disorder, but Moses and colleagues noted a lower VMA level than in normal adults.

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