A NEW SYNDROME COMBINING PTERYGIUM COLLI WITH DEVELOPMENTAL ANOMALIES OF THE EYELIDS AND LYMPHATICS OF THE LOWER EXTREMITIES*

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IT IS THE PURPOSE OF THIS PAPER to present a hitherto undescribed complex of clinically evident abnormalities believed to represent a new hereditary syndrome. This syndrome presents an autosomal dominant pattern of inheritance and in its complete form consists of four rare congenital anomalies: (1) distichiasis of all four lids, (2) chronic lymphatic edema of both lower extremities (Milroy's disease), (3) pterygium colli, and (4) partial lateral ectropion of both lower lids. Ten affected individuals within a family of five generations are described. A second family with a sporadic case is presented for comparison.

It is to be noted that some of the facets of this syndrome do not have their onset at birth in the usual sense of a congenital disorder but simulate "abiotrophies." As originally described by Gowers,[10] certain tissues may, on occasion, be capable of normal function only for a limited time, and then undergo deterioration. The chronic lymphedema of the lower extremities in which the appearance of edema may or may not occur before puberty may be interpreted as a manifestation of lymphatic abiotrophy.

In addition to this variable age of onset, another factor to take cognizance of is the variation in the number of the component anoma-

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lies seen in each of the ten affected individuals. In syndromes, where a constellation of abnormalities coexists, it is not unusual to see incomplete forms and considerable variation in the clinical severity of each defect. Wide variation in the degree of penetrance and in the extent to which each aspect of the syndrome is expressed is the rule rather than the exception and, in general, is greater for disorders following a dominant mode of transmission than a recessive one.[17] For example, within the investigated family with ten affected individuals only two demonstrated all four features of the syndrome. Three out of ten exhibited distichiasis, chronic lymphatic edema, and webbing of the neck; four exhibited two of the anomalies (one was six years old and may yet develop edema); and one presented only distichiasis. Partial ectropion of the lateral third of both lower lids was apparent in three of the affected members and appears to be the least penetrant of the four manifestations.

Mild manifestations of the incomplete syndrome (forme fruste) were found in several of the affected persons.

CASE REPORTS, FAMILY I

CASE 1

This 23-year-old affected male (IV_{12}, Figures 1–4) came to the attention of one investigator (H.F.F.) more than fifteen years ago and in genetic parlance will be referred to as the propositus. He has been followed for intermittent episodes of photophobia, blepharospasm, lacrimation, and redness of the conjunctivas and lid margins provoked by the growing in of plucked, abnormally located cilia. This patient represents a "forme fruste"

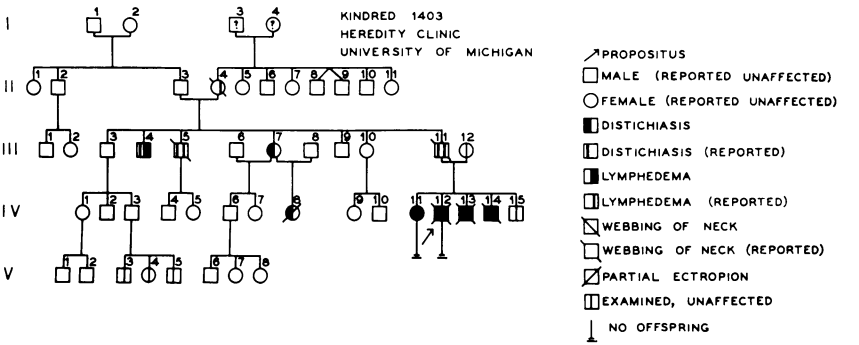

FIGURE 1. FAMILY I

Occurrence of the newly described syndrome in three consecutive generations. Transmission appears to follow an autosomal dominant pattern of inheritance.

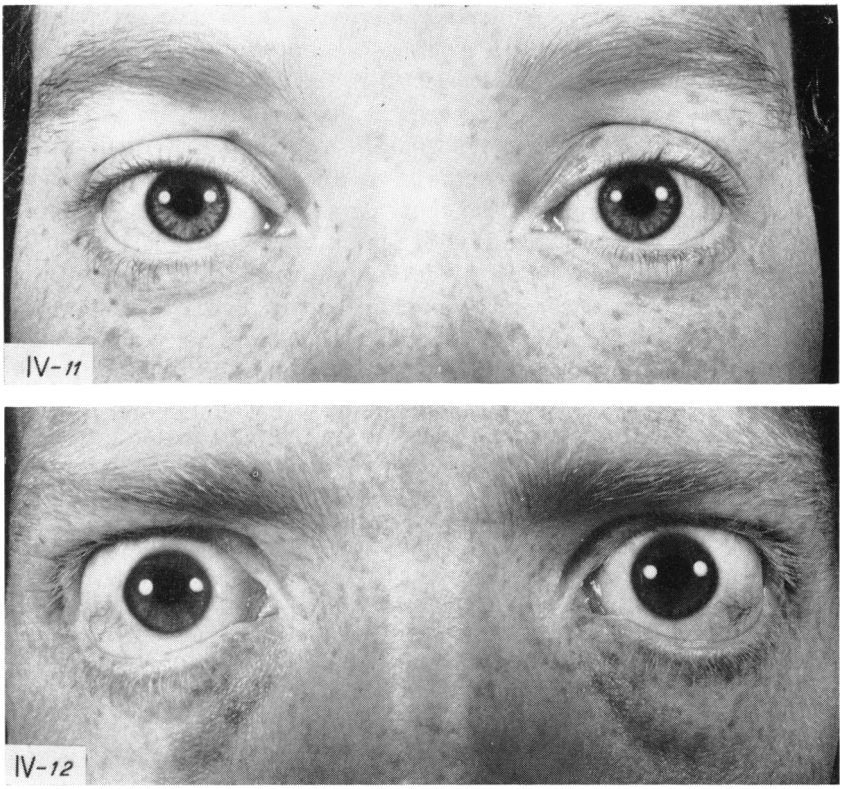

FIGURE 2. FAMILY I

IV_{11}: No definite ectropion; downward and outward slanting of cutaneous borders of both lower and outer lid margins; presence of distichiasis not evident. IV_{12}: Partial ectropion of lateral third of both lower lids; presence of distichiasis not evident.

of the syndrome and at the time of examination exhibited the following picture. Visual acuity was normal and the corneas showed no evidence of residual scarring. The margins of both lower lids had an S-shaped angulation and did not mold the eyeballs closely, giving a peculiar "pop-eyed" appearance. A partial ectropion was present in the outer third of both lower lids (IV_{12}, Figure 2A). Palpation of these areas suggested incomplete development of the inferior tarsi. The impression of tarsal abnormality was not confirmed since excision of tissue for microscopic examination was not indicated. The skin of the lids appeared normal in texture and stretchability. Orbicularis function was not impaired and closure of the lids was complete.

Distichiasis of all four lids was evident. The aberrant row of lashes was arranged in orderly progression and emerged from the natural orifices of

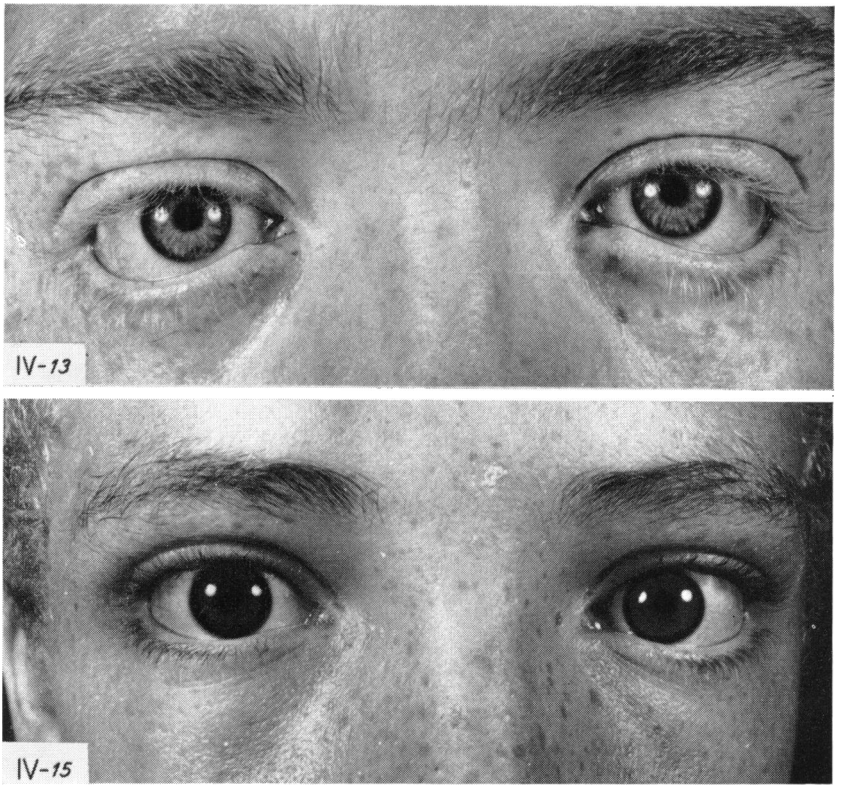

FIGURE 2. FAMILY I

IV_{13}: Partial ectropion of lateral third of both lower lids; presence of distichiasis not evident. IV_{15}: Normal eyelids.

the meibomian glands. These cilia were shorter, thinner, and lighter in color than the normal lashes and resembled lanugo-like hairs. They pointed upward or downward, depending on their location, and were directed in random fashion either outward, away from the eyeball, or toward the eyeball, rubbing against the cornea and bulbar conjunctivas. Treatment of the distichiasis has consisted of periodic epilation principally by the patient's mother.

The onset of edema of both lower extremities was noted at 12 years of age, with the approach of puberty, and has never progressed above the knees (IV_{12}, Figure 3). The edema has been mild and kept under control by the use of elastic stockings.

The patient has developed into a burly looking male with bull-like webbing of the neck (IV_{12}, Figure 4). He recently married.

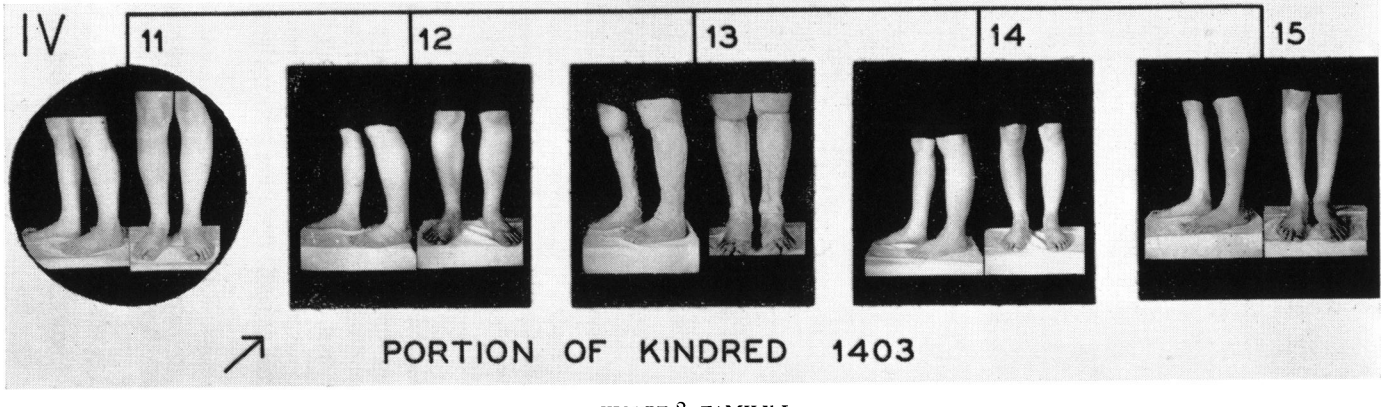

FIGURE 3. FAMILY I

IV_{11}: Mild lymphedema of both lower extremities ceasing at level of knees (Edema more apparent a few hours after removal of elastic stockings). IV_{12}: Mild lymphedema of both lower extremities ceasing at level of knees (Edema more apparent a few hours after removal of elastic stockings). IV_{13}: Appearance of legs following surgery with visualization of disfiguring scars. IV_{15}: Normal lower extremities.

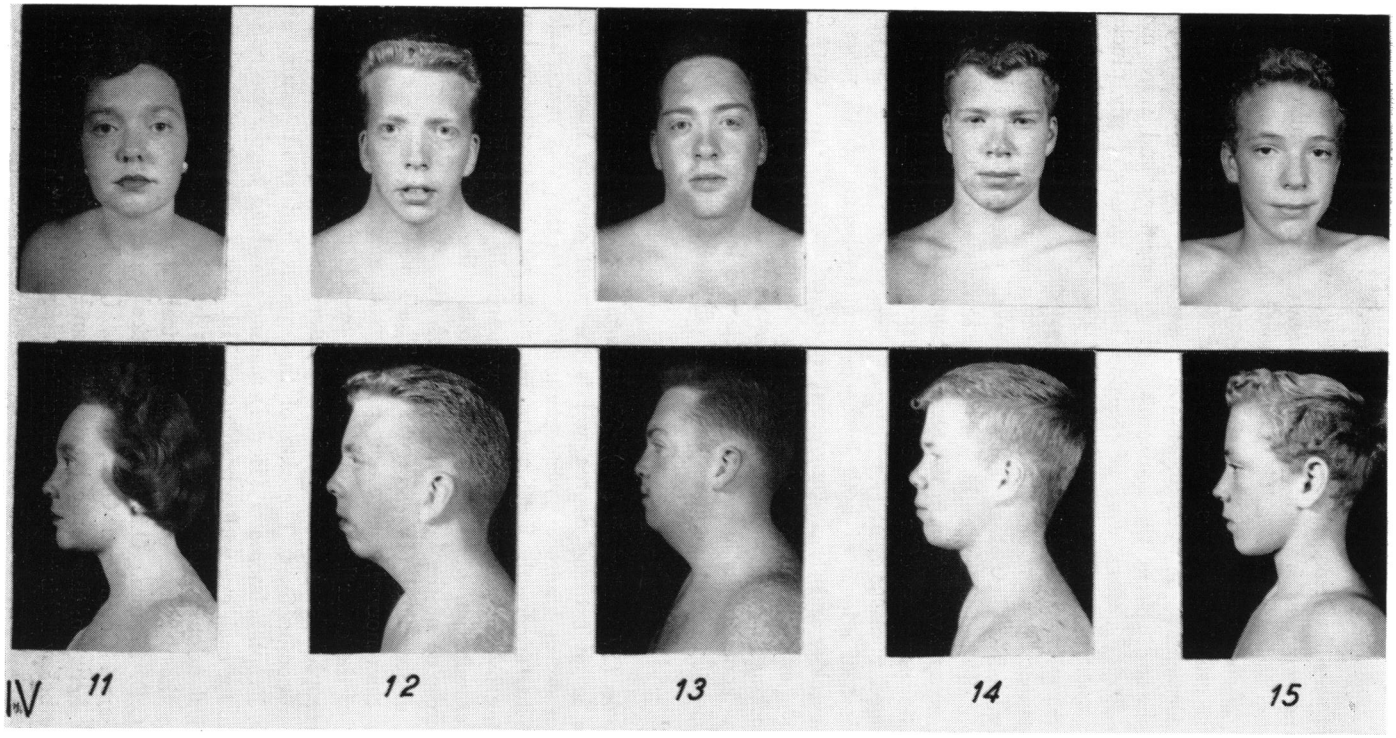

FIGURE 4. FAMILY I

IV_{11}: Normal neck. IV_{12}: Marked webbing of neck. IV_{13}: Moderate webbing of neck. IV_{14}: Slight webbing of neck. IV_{15}: Normal neck.

CASE 2

This 24-year-old female patient (IV_{11}, Figures 1–4) exhibited a mild form of the two most frequently expressed features of this syndrome: distichiasis and Milroy's disease. The neck showed no webbing but was short and thick in conformity with the patient's pyknotic build (IV_{11}, Figure 4).

The eye examination was normal except for the presence of sparsely scattered distichiasis of both upper and lower lids. The abnormal lashes arose haphazardly from the meibomian gland openings and were most numerous laterally. They were of the fine, lanugo variety, easily plucked by the patient, and caused no irritating eye symptoms. Although no definite ectropion could be diagnosed, downward and outward slanting of the cutaneous borders of both lower and outer lid margins was observed (IV_{11}, Figure 2). The patient had a "wide-eyed" gaze similar to that seen in her two affected older brothers, but to a lesser degree. Correction of a moderate myopia was given in the form of contact lenses which in addition to cosmetic purposes offer protection to the corneas from growing-in, stubby-edged, injurious cilia.

The onset of edema of both lower extremities began at 12 years of age at the ankles and slowly progressed up to the knees (IV_{11}, Figure 3). It has been mild in nature and adequately controlled by the wearing of elastic stockings during waking hours. Removal of the elastic support for only a few hours results in considerable ankle and leg edema. This patient has also married recently and as yet has no offspring.

CASE 3

This male (IV_{13}, Figures 1–4), 21 years of age, displays the complete syndrome in an extreme degree and is the most severely affected case within the entire kindred. Upon examination, attention was immediately drawn to his apparently large protruding eyes and husky, athletic build accentuated by the presence of the pterygium colli (IV_{13}, Figures 2, 4).

Close examination of the lower lids showed the S-shaped curve and partial ectropion of the lateral third of each side with a pooling, but no overflow, of tear fluid (IV_{13}, Figure 2). The lower tarsi felt less firm to palpation than normal, suggesting poor development. The loose fit and drooping of the outer borders of the lower eyelids gave the impression of bilateral exophthalmos because of the greater than usual visualization of the bulbar conjunctivas. The skin of the eyelids had good texture and resiliency. Exophthalmometer (Hertel) reading was high borderline normal of 22 mm. for each eye with a baseline of 110. Measurements of the height and vertical extension of the upper eyelids by Fuchs's technique (8) to determine the presence or absence of vertical shortness were as follows. Height: O.D. 27 mm.; O.S., 27 mm. Vertical extension: O.D., 40 mm.; O.S., 40 mm. Coefficient: O.D., 1.5; O.S., 1.5. The coefficient signifies the ratio between the vertical extension and the height of the lid. A coefficient below 1.5 is indicative of vertical shortness which results in faulty

lid approximation (8). Although the coefficient in this patient was within normal limits the lateral margins of the lower lids did not exactly approximate and establish precise contact with the upper lids due to the existence of the bilateral partial ectropion.

Distichiasis involved all four lids and arose from the orifices of the meibomian glands in regular fashion. A few resembled lanugo-like hairs, but the majority were well-developed and appeared as vigorous as normal lashes. Several of the well-developed aberrant cilia turned inward toward the globe and caused injury to the cornea. The patient suffers repeated episodes of punctate keratitis, congested palpebral and bulbar conjunctivas, and inflamed lid margins. Fortunately, he has no residual scarring of the corneas. Repeated electrolysis has been performed without complete success. Epilation is still necessary and is routinely done by the patient's mother. Corrective lenses are worn for mixed astigmatism with normal visual acuity.

The chronic lymphatic edema appeared at 12 years of age and involved both lower extremities from the feet to the knees. At 16 years of age, the patient had a sudden onset of pain in the right leg associated with a fever of 104° F., shaking chill, malaise, headache, and vomiting. Upon examination the right leg was found to be red, swollen, and hot up to the knee with tenderness upon palpation into the thigh and inguinal region. The skin was thickened, indurated, and unsightly. The patient was hospitalized with a diagnosis of acute erysipelas and was treated with penicillin, Chloromycetin, hot soaks, and elevation of the affected extremity. There was no obvious portal of infection such as skin ulceration, ingrown toenail, or trichophytosis. Six months later a second episode occurred in the same leg which mimicked the first one. Again no precipitating cause could be detected and recovery followed within a few days after hospitalization with the type of treatment previously mentioned.

Because the heavy weight and growing size of both legs, uncontrolled by elastic stockings, made walking increasingly difficult, the patient was hospitalized for drainage of the lower extremities by means of periodic application of the Jobst gradient pressure boot. Oral diuretics were also given. Within 12 days of treatment the patient lost 25 pounds with a significant decrease in the circumference of both legs. Within the next five months two similar treatments were administered.

Despite efforts of medical management only temporary relief was obtained. In view of this, and because of the unsightly appearance and recurrent inflammatory episodes, surgery was performed on the right lower extremity followed one month later by the some procedure on the left lower extremity. Prior to surgery on the left leg, a lymphangiogram was attempted. The contrast material extravasated into the soft tissues and cuffed around the vascular channels. Consequently, no conclusion could be drawn regarding the status of the lymphatic system. The surgical procedure included extensive dissection of the skin down to the fascial layers.

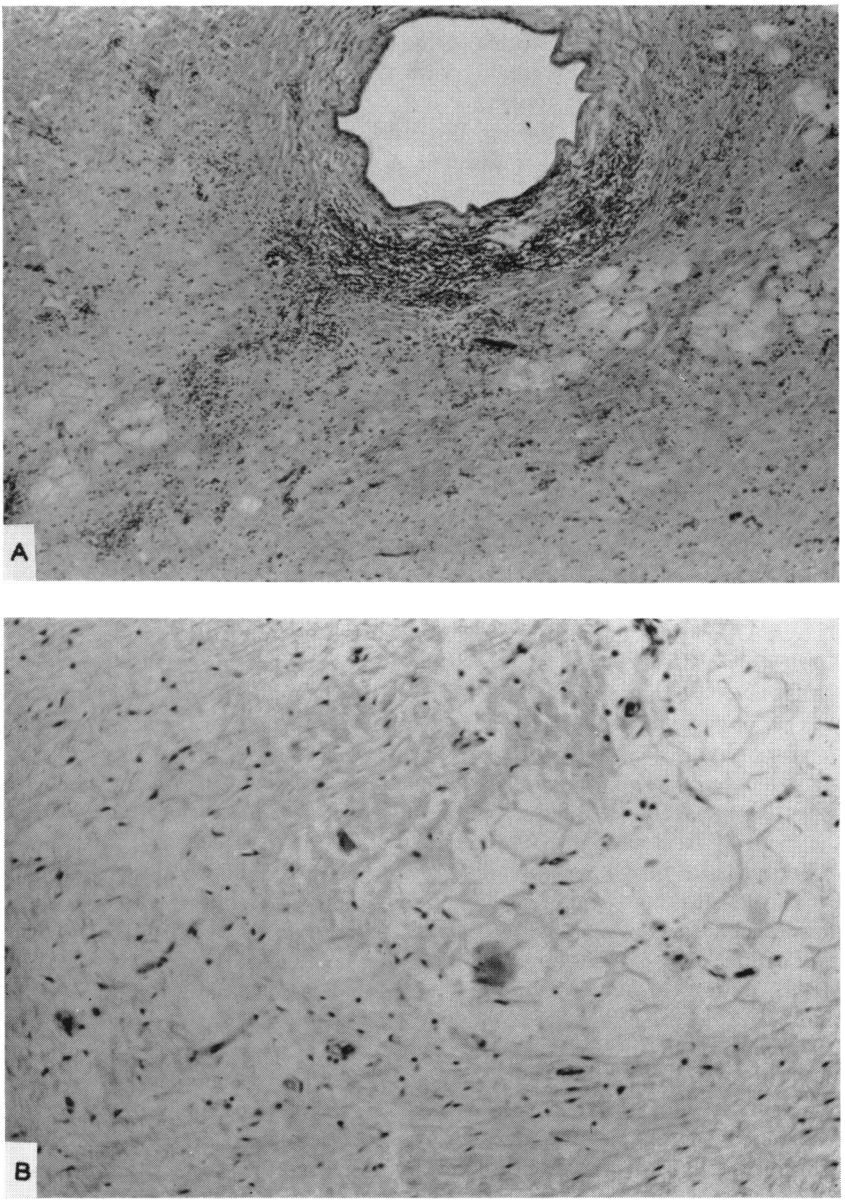

FIGURE 5

A, Dilated lymphatic vessel with lymphocytic infiltration. Edema of deep corium and upper subcutaneous tissue with fibrous replacement. (Scan.) B, Edema of deep corium and upper subcutaneous tissue with fibrous replacement. (L.P.)

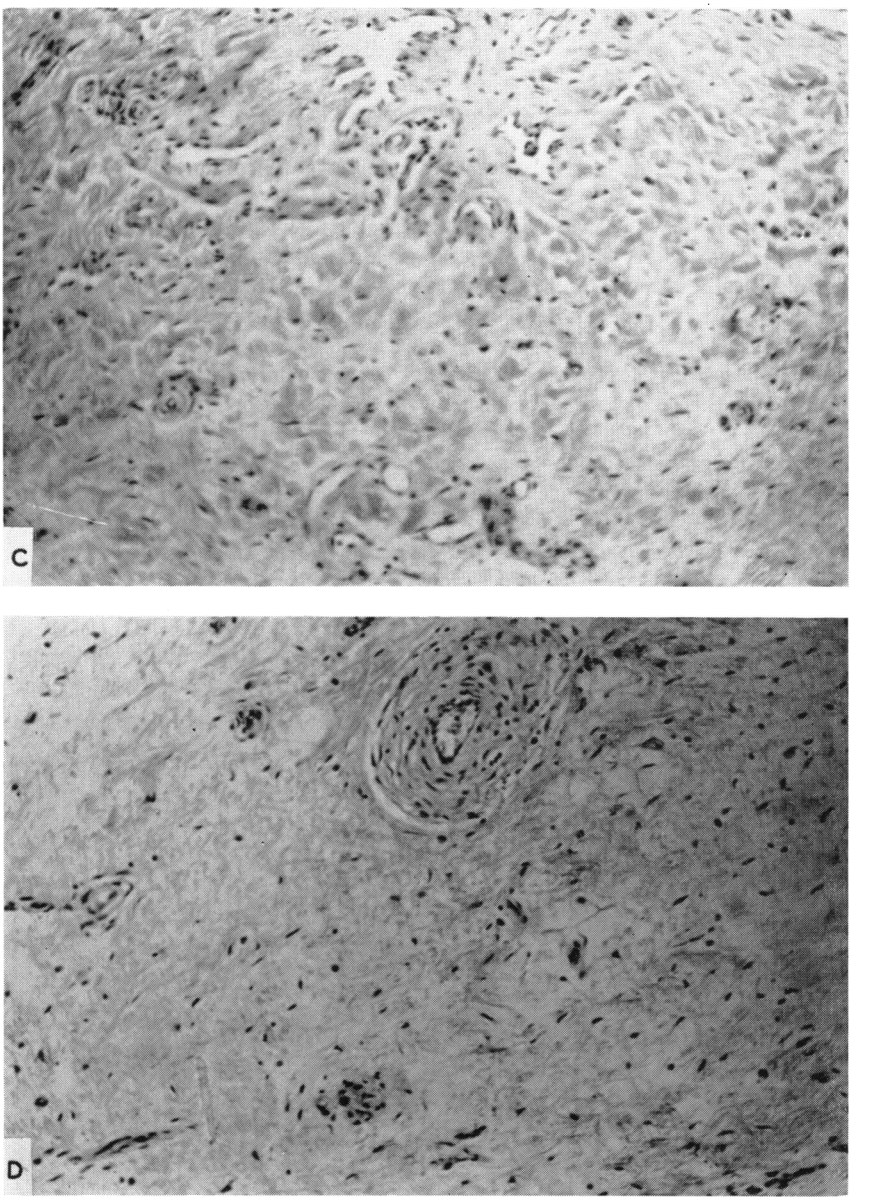

FIGURE 5

C, Dilated veins and lymphatics in edematous corium. (L.P.) D, Thickened vein in edematous corium. (L.P.) Chronic inflammatory cells are seen scattered throughout all microscopic sections. (Courtesy of Dr. Henry Bryant, Department of Pathology, St. Joseph Mercy Hospital, Ann Arbor, Michigan.)

The exposed fascia was covered with a split thickness graft which was stripped from selected areas of the dissected tissue. Clinically, this tissue appeared thickened and leathery. The underlying adipose tissue felt water-logged, oozed clear fluid upon compression, and reached up to two inches in thickness. Microscopic examination of the skin revealed edema of the deep corium and upper subcutaneous adipose tissue with fibrous replacement (Figure 5, A-D). Dilated lymphatics were clearly seen in the corium some of which were distinctly surrounded by infiltrations of lymphocytes (Figure 5, A and C). Several medium-sized blood vessels showed intimal proliferation. Chronic inflammatory cell infiltration was also evident around the blood vessels and scattered throughout the corium (Figure 5, C and D).

Postoperatively, the patient responded well psychologically and physically in spite of the disfiguring scars left by the surgical procedures. The marked reduction in size of both lower extremities has enabled him to carry his weight around with much greater ease.

Because of the presence of several congenital malformations and the association of webbing of the neck in Turner's syndrome, chromosome analysis was done on the peripheral blood. The findings indicated a chromosome number of 46 and a normal male karyotype.

CASE 4

This 17-year-old male (IV_{14}, Figures 1, 3, 4, 6) is the youngest affected offspring within the sibship of the propositus and manifests three of the

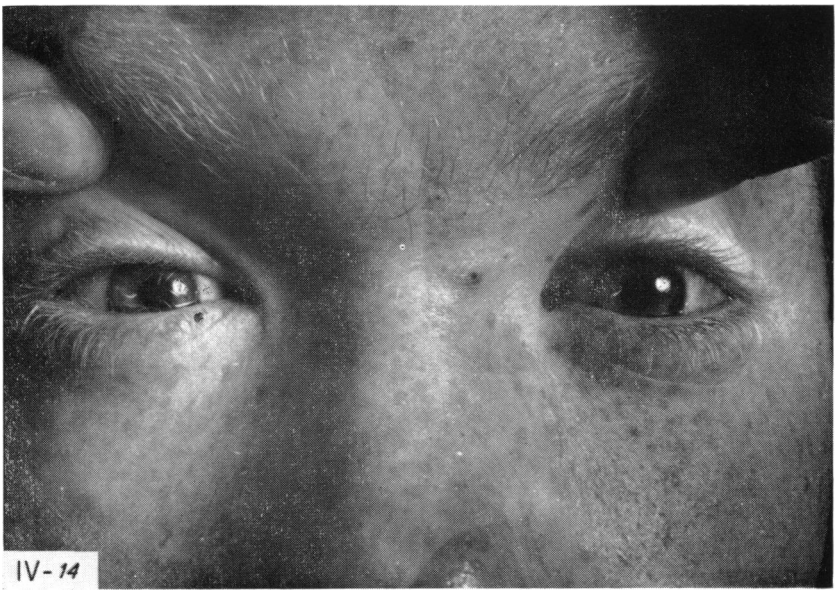

FIGURE 6. DISTICHIASIS PRESENT IN ALL FOUR LIDS.

four abnormalities exhibited by this syndrome: distichiasis, chronic lymphatic edema of the lower extremities, and webbing of the neck (IV_{14}, Figures 3, 4, 6). These features exhibit an intermediate degree of expressivity compared to the two oldest mildly affected siblings and the third oldest severely affected sibling.

The aberrant row of lashes emerged from the meibomian glands in regular succession, and, for the most part, were well developed (IV_{14}, Figure 6). Their color, form, and texture closely resembled normal cilia but a few appeared similar to fine lanugo-type hairs. The margins of the lids approximated well upon closure. Vertical lid measurements were within normal range. Height: O.D., 17 mm.; O.S., 16 mm. Vertical extension: O.D., 27 mm.; O.S., 29 mm. Coefficient: O.D., 1.6; O.S., 1.8.

The chronic edema of the lower extremities began at 10 years of age and has been under excellent control with elastic stockings (IV_{14}, Figure 4).

The youngest sibling of the propositus is 14 years old and shows no manifestation of any part of the syndrome (IV_{15}, Figures 1–4). He is still free of lower extremity edema but this does not preclude its onset at a later age. Although the appearance of edema occurred between the ages of 10 and 12 years in the four older siblings, it will be noted that the onset of edema in another affected member (III_4) in this family kindred developed after puberty. Interestingly this sib has blond hair as contrasted to the four affected older siblings who all have red hair. Red hair is transmitted by autosomal recessive genes and speculation arises about the association of the recessive gene for red hair to the abnormal autosomal dominant gene responsible for this syndrome.

In the third generation four out of seven individuals within the paternal sibship were affected including three out of five males and one out of two females. The mother of the propositus and the entire maternal lineage are entirely free of any abnormality found within this syndrome. Therefore it is evident that the responsible gene or genes were transmitted to the fourth generation through the paternal ancestry.

CASE 5 (IV_8, Figure 1)

This six-year-old female cousin of the propositus was reportedly unaffected. However, a field trip visit to the family and examination of the youngster revealed distichiasis of all four lids. Retrospectively the child was said to be photophobic since three years of age. The corneas were clear but the bulbar conjunctivas were laterally injected. A few fine cilia were irregularly distributed along the entire length of the lid margins with greatest concentration within the outer third. There was a suggestion of an S-shaped angulation and minimal out-turning of the lateral cutaneous

lid borders. A peculiar antimongoloid slant of the fissures was present which had not been noted in any other member in this kindred.

CASE 6

This affected uncle (III_4, Figure 1) of the propositus was married but had no offspring. He reportedly had distichiasis, a "large" neck, and swelling of both lower extremities since early adulthood. Edema of the lower extremities began around the ankles and slowly advanced to the level of the knees. The right foot and leg were more edematous than the left and the ankles were more severely involved than the legs. The patient was known to suffer recurrent acute attacks of reddened, painful, and swollen lower extremities which became more frequent during his last few years of life. He died at age 40 from metastatic fibrosarcoma which originated in the right ankle and which was diagnosed one year prior to death. Concurrently, a colloid goiter was observed to which the "large" neck could possibly have been attributed or accentuated by the presence of a webbed neck. The thick neck was thought, by one sibling, to be present during this patient's entire life.

To our knowledge, fibrosarcoma in a lymphedematous extremity of the Milroy type has not been previously reported in the literature. However, primary lymphangiosarcoma has been seen coexisting with congenital lymphedema and also with acquired edema of the upper extremities following radical mastectomy for carcinoma of the breast. The development of fibrosarcoma in this affected male may have been coincidental or related to the chronic edema and repeated trauma of the ankle region.

CASE 7

Alive and well at the age of 57, this uncle (III_5, Figure 1) of the propositus reportedly has distichiasis, mild chronic lymphatic edema of the lower extremities, and a "thick" neck. He has been married twice and from his first marriage has a son and daughter who are presumed to be normal.

CASE 8

This individual, a 49-year-old aunt (III_7, Figure 1) of the propositus, has only one feature of the syndrome: distichiasis. It is very mild in character and primarily involves the lateral aspects of both upper and lower lids. The cilia cause little irritation and require infrequent plucking, easily performed by the patient. She has two grown offspring from a first marriage who are reportedly normal. The oldest, a male, is married and has one boy and two girls, also reportedly normal. Her six-year-old daughter from a second marriage was found, upon examination during a field trip visit, to have distichiasis (Case 5, IV_8). The mother was unaware of its presence.

CASE 9

The father (III_{11}, Figure 1) of the propositus died in early adulthood from a coronary thrombosis and reportedly had mild manifestations of

distichiasis, swelling of the lower extremities requiring no treatment, and webbing of the neck. The presence of distichiasis was not known until treatment was received for a metallic foreign body injury to the eye in adulthood. Following this discovery, the patient's wife occasionally epilated a few aberrant lashes. The presence or absence of an incomplete ectropion could not be confirmed upon questioning members of the family or from photographs.

CASE 10

The paternal grandmother (II_4, Figure 1) of the propositus died at 68 years of age and was claimed to have had chronic lymphatic edema of the lower extremities since childhood as well as a "thick" neck. It is not known whether she had either of the two other defects of the syndrome which could have been present in mild enough form to escape notice. Nothing is known of the family beyond this generation.

CASE REPORTS, FAMILY II

CASE 1

This previously unreported sporadic case is included for comparison with the cases described above. She is 28 years old (III_5, Figures 7–9) and presents two of the clinical manifestations of the described syndrome: distichiasis and chronic lymphatic edema of the lower extremities.

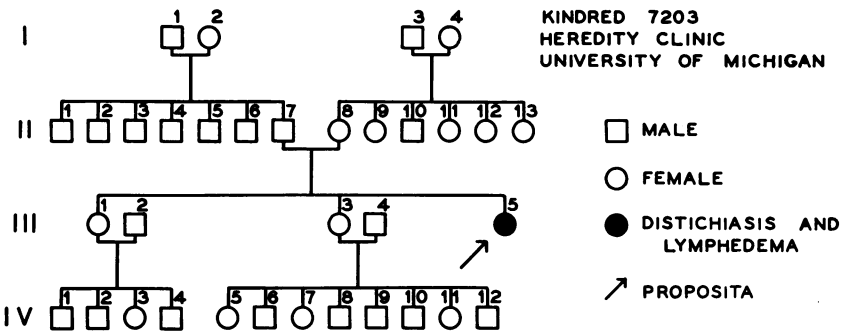

FIGURE 7. FAMILY II

A female sporadic case with distichiasis and Milroy's disease.

The abnormal rows of lashes were well developed and emerged from the meibomian orifices of both upper and lower lids. Minimal bilateral inferior corneal scarring as a result of repeated episodes of injurious inturned lashes were observed. The usual methods of treatment (epilation and electrolysis) were to no avail and recently plastic surgery of the lids was performed with some symptomatic relief.

The chronic asymptomatic lymphedema began at 16 years of age around the ankle of one extremity. Within one year the edema progressively

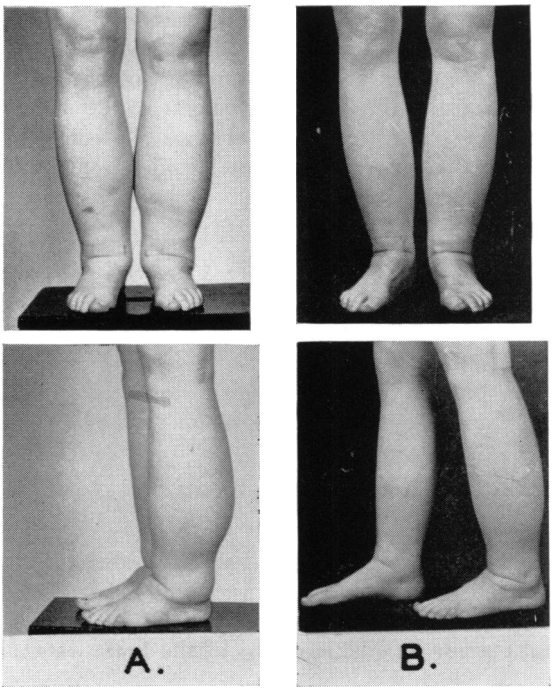

FIGURE 8. MILD LYMPHEDEMA OF BOTH LOWER EXTREMITIES CEASING AT THE LEVEL OF THE KNEES.
A, appearance before Jobst pressure gradient support; B, appearance immediately following removal of support.

spread to involve both feet and legs up to the level of the knees (III_5, Figure 8). Chemical determinations of total protein and differential cell count on lymph fluid withdrawn from the involved extremities were within normal values. Lymphangiography performed at Henry Ford Hospital revealed tortuous and markedly dilated lymphatic vessels indicative of developmental aberration (III_5, Figure 9).

At age 18 years, a ligation and stripping of the superficial veins of the right leg was performed without significant reduction in the size of the leg swelling. Since then the patient has been managed medically with Jobst pressure-gradient supports (removed only at bedtime) with clinical improvement of the edema.

CONSIDERATION OF EACH FEATURE OF THE SYNDROME

Two of the four components of this syndrome, distichiasis and lymphedema, are known to be inherited as isolated traits.

DISTICHIASIS

Distichiasis is a Greek word meaning "double row" and specifically applies to the congenital occurrence of an aberrant row of lashes. It should not be confused with trichiasis which signifies the inversion

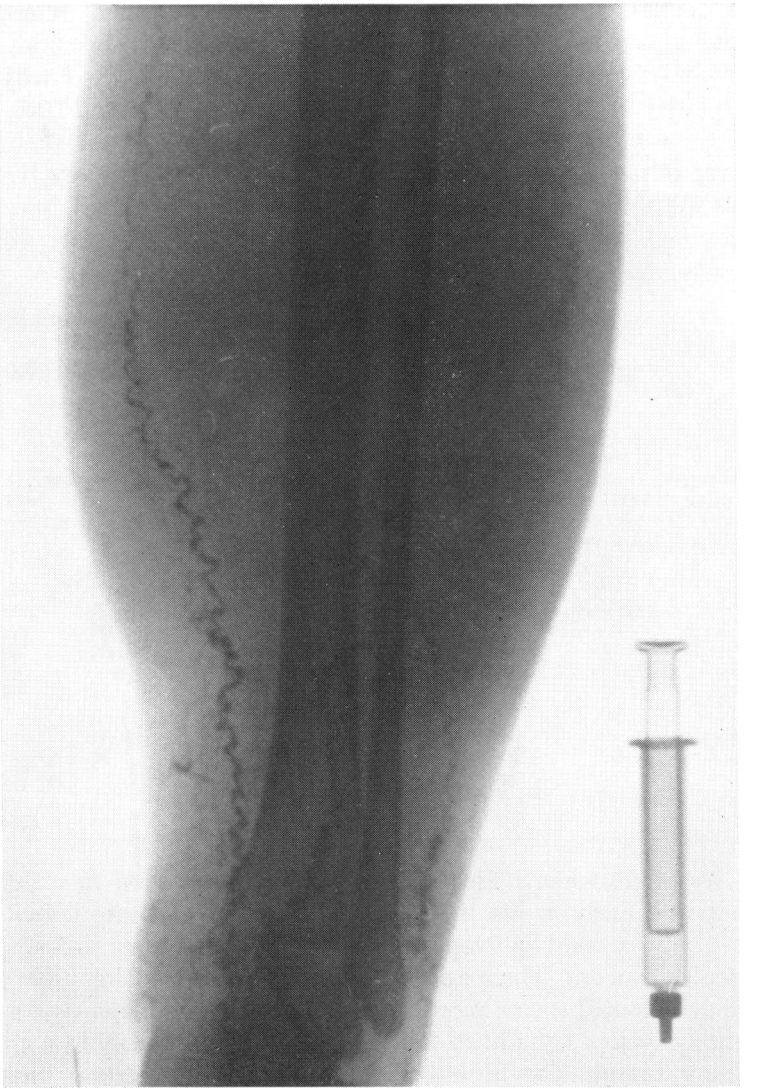

FIGURE 9

Lymphangiogram of sporadic case within Family II revealing tortuous and markedly dilated lymphatic vessels. (Courtesy of Henry Ford Hospital, Detroit, Michigan.)

of lashes secondary to scarring of the lids from acquired causes such as burns, injuries, and infections.

Distichiasis is rare and since the first reported case by Becker in 1867[2] fewer than 50 cases are found in the literature occurring either as an isolated entity or in association with other anomalies. The rarity of the aberration is further exemplified in a report by Brailey in 1906.[4] In it he draws attention to a comment made by Fuchs that in his clinic in Vienna, with an annual attendance of over 20,000, only four cases of distichiasis were revealed within a 20-year period. A 10-year survey of the University of Michigan Ophthalmology Records (1953–1962) uncovered five cases (excluding affected members ascertained through the propositus) out of approximately 225,000 patients.

TABLE 1. FEATURES OF THE SYNDROME OBSERVED IN THE AFFECTED MEMBERS OF FAMILY I AND FAMILY II

Pedigree number	*Age (yrs.) at time of investigation*	*Sex*	*Bilateral distichiasis (upper and lower lids)*	*Bilateral lymphatic edema (lower extremities)*	*Bilateral partial ectropion (lower lids)*	*Pterygium colli*	*Other*
Family 1 (Figure 1)							
IV_8	6	F	×	—	×	—	
IV_{11}	24	F	×	×	—	—	red hair
IV_{12}	23	M	×	×	×	×	red hair
IV_{13}	21	M	×	×	×	×	red hair
IV_{14}	17	M	×	×	—	×	red hair
III_4	d. 40	M	×	×	—	—	
III_5	57	M	×	×	—	×	
III_7	49	F	×	—	—	—	
III_{11}	d. 39	M	×	×	—	×	
II_4	d. 68	F	—	×	—	×	
Family 2 (Figure 7)							
III_5		F	×	×	—	—	red hair

Cases of distichiasis usually come under observation in childhood or puberty. Early in life the abnormally located delicate lashes may cause only a mild photophobia and blepharospasm, arousing no particular concern. Their existence may go unnoticed for years until these symptoms become more pronounced or until conjunctivitis and keratitis develop. Usually all four lids exhibit the anomaly to a greater or lesser extent. The accessory cilia are found emerging from or adjacent to the orifices of the meibomian glands along the inner border of the lid margins. Histological examination of tissue sections of this condition have shown meibomian gland and tarsal defects. The

meibomian glands may be smaller than normal, absent, or replaced by abnormal sebaceous glands.[13] The tarsus may be absent or appear as a vestigial structure.

Family studies of the isolated condition follow an autosomal dominant mode of inheritance.

CONGENITAL ECTROPION

Congenital ectropion appears to be more rare than distichiasis. In Picó's extensive review of the literature (1957) for both anomalies,[23] he found 12 recorded cases of congenital ectropion. With his own detailed study of 11 cases the number reported rose to a total of 23. The propositus in the present study (Family I), excluding relatives, was the only recorded case of congenital ectropion in the 10-year survey of the University of Michigan Ophthalmology Records.

Picó[23] classified the 12 cases of congenital ectropion recorded in the literature into two etiologic groups: (1) absence or anomaly of the tarsus, and (2) traumatic passage through the birth canal. In 1914, Urmetzer reported the first case exemplifying the group 1 category.[24] Adams, in 1896, first brought attention to the type that characterizes the group 2 category.[1] Picó[23] classified his 11 cases of congenital ectropion into group 1. Six of these had both lower lids involved (minimally in all but one) and five had marked ectropion of all four lids. Among these eleven cases, three had isolated congenital ectropion and eight had it in association with distichiasis. In two cases examined histologically no meibomian glands or inferior tarsi could be demonstrated. Other characteristics of Picó's syndrome included narrowing of the palpebral fissures horizontally and vertical shortness of the lids. These features were notably absent in our cases.

It seems reasonable to assume that congenital ectropion is related to underdevelopment or absence of the tarsal plates which act as a supporting framework and contribute to the shape and firmness of the lids. However, not enough cases are known with histological confirmation of tarsal anomaly to warrant such a conclusion.

From a genetic point of view there is no doubt that congenital ectropion may be inherited. However, its heredity has only been demonstrated in families manifesting other congenital ocular anomalies. It was found associated with bilateral ptosis in the family reported by Gordon and Cragg in 1944[9] and with distichiasis in the study reported by Picó.[23] In Picó's cases, transmission followed an autosomal dominant pattern.

The combination of congenital ectropion and distichiasis was first

reported by Erdman in 1904.[7] The next reported case, by Landau, appeared in 1947.[14] The eight cases reported by Picó[23] brought the total count to ten.

PTERYGIUM COLLI (WEBBING OF THE NECK)

To our knowledge webbing of the neck has never been reported as an isolated inherited condition in any family and its hereditary nature as an independent trait remains obscure. Yet it is known to have a relatively high occurrence in Turner's syndrome (ovarian dysgenesis in females and hypogonadism in males with associated somatic malformations) and in the Bonnevie-Ullrich syndrome (similar to Turner's but without evidence of gonadal dysfunction).[12] The cases described herein represent the first known association of pterygium colli with the combination of somatic anomalies observed in this new syndrome.

CHRONIC HEREDITARY LYMPHEDEMA OF THE LOWER EXTREMITIES (MILROY'S DISEASE)

Although a relatively rare congenital anomaly, many reports of hereditary lymphedema are found in the literature. The first recorded description of it was given in a doctorate of medicine thesis by E. E. Letessier in 1865 to the faculty of medicine in Strasbourg.[15] Unfortunately, this author's identity has remained in obscurity and the disease has become synonymous with the names of Nonne, Milroy, and Meige. In Letessier's account of this disorder, the onset of edema in the lower extremities occurred around puberty, was associated with periodic attacks of erysipelas, and presented itself in several family members. A variation of this same condition was first described by Nonne in 1891.[22] He studied a family with eight affected members in four generations in whom the edema of the feet and legs was evident, in most of the cases, at birth, and appeared to follow an autosomal dominant mode of inheritance. In 1892 Milroy reported the first American family with congenital lymphedema and in the American literature the disease is generally referred to by his name. Milroy's original report consisted of a family of six generations comprising 97 individuals of whom 22 were afflicted with the edema.[19] Thirty-six years later, in 1928, he published a follow-up report of the same family with 30 additional members.[20] In Milroy's study the edema was asymptomatic and present at birth in all affected members with the exception of one female who was normal until 12 years of age. The mode of inheritance appeared to be autosomal dominant.

Six years after Milroy's first report, Henry Meige in France[18] reported a family with eight affected individuals in four generations in whom the characteristics of the edema mimicked the picture described by Letessier in 1865, namely, late onset and periodic inflammatory attacks in the edematous areas.

The relative rarity of chronic lymphedema of the Milroy type is illustrated by our survey of the University of Michigan Hospital Records. Of more than one-half million patients within the period 1958–62, only 22 cases were recorded.

The characteristics of the edema show some variability. This is not surprising since manifestations of a disease process, whether hereditary or infectious, are not generally identical in every particular. Therefore, digressions in the clinical manifestations from the early reported descriptions cannot be construed as different diseases but should more appropriately be interpreted as variations in expression of the same entity. With reference to the age of onset, Milroy specifically states in his 1928 follow-up report of cases that "the age of the individuals at which the swelling first appears is one of the variations noted."

The typical features of the edema may be summarized as follows:

1. Variable age of onset, usually at birth or around the age of puberty.
2. Chronic, firm, and permanent edema restricted to the lower extremities and most frequently confined to the level of the knees.
3. Asymptomatic edema with or without acute, recurrent, erysipelas-like attacks of the edematous limbs associated with constitutional symptoms of vomiting, shaking chills, headaches, and elevated temperature, pulse rate, and respiratory rate. The first attack may not occur for a number of years after the appearance of the edema, may recur at intervals of a few months or years, and last a few days to a week. The patient is desperately ill but in so far as is known the attacks have never been fatal. The cause of the attack and its relation to the edema are not known. Possible precipitating factors occasionally seen include a break in the skin or a fungus infection between the toes. Hemolytic streptococcus was isolated by McGuire and Zeek from tissue removed during an attack.[16] Treatment of the acute attacks is palliative and symptomatic. The administration of antibiotics and cortisone does not noticeably alter the duration or the pattern of the attack.
4. Minimal reduction of edema with bed rest and minimal to moderate reduction with elastic stockings.
5. Not unfavorable to a long life span.
6. Hereditary.

Initially the skin may appear normal or in some instances it appears translucent because of the edema. At this stage pitting is easily obtained. Later the skin becomes thickened, whiter, and more opaque with little to no pitting. Fibrous tissue production is possibly stimulated by the edema, and the affected area becomes firm and hard. The skin eventually resists wrinkling and gives the appearance of pigskin.

INHERITANCE

Heredity as an etiologic factor in this newly described syndrome is evident from the family pedigree. The responsible gene manifests the characteristics of autosomal dominance with relatively high penetrance and variable expression. Within the sibships available for analysis, 10 out of 25 individuals manifested some aspect of the syndrome. Among 15 males, 6 were affected and among 10 females, 4 were affected. These figures, albeit small, approximate the expected 1:1 ratio for normal siblings *versus* affected siblings regardless of sex. The gene also appears to be directly transmitted from one affected person to another without skips or breaks in generations. The lack of affected offspring by the marriage of individual III_5 (presumed heterozygous) to a normal female may be attributed to the vagaries of chance.

Males within the affected kindred were more severely affected than females. Phenotypically, the full complement of the abnormalities was seen only in males. Generalization of these observations is, of course, hazardous, since the sample consisted of only 10 affected individuals.

The sporadic case (an unmarried female) in Figure 7 exhibits two of the most constant features of this syndrome: distichiasis and chronic lymphatic edema of the lower extremities (Figure 8). It is believed that this combination arose on the basis of an autosomal dominant mutation. The heritability of the two anomalies, presumably through a single autosomal dominant gene, has been reported by Neel and Schull.[21] The question as to whether the sporadic case, as well as those reported by Neel and Schull, represents the same or a different syndrome cannot be answered on the basis of available evidence. Possibilities other than mutation should, however, be considered. These are: (1) homozygosity for a recessive gene which is more likely to occur in consanguineous marriages; (2) inheritance due to an incompletely penetrant gene with skipping of generations; (3) phenocopy resulting from environmental rather than genetic influences; and (4) illegitimacy.

Absence of one or more features of the syndrome as seen in the isolated case and in 8 out of 10 affected members within Family I is

not inconsistent with the hypothesis that a single gene with incomplete penetrance may be responsible. However, another possible explanation is that the several traits arise from different, closely linked genes. This appears unlikely since it would then be expected that each trait would occur separately more often than in combination with other traits. The occurrence of combinations of traits was clearly in excess of the presence of a single trait among the 10 affected individuals within Family I. As a matter of fact only one affected person showed a single aspect of the syndrome (III_7). Still there is a third consideration. It may be that the observation of incomplete forms of the syndrome are due to multiple allelic mutations.

REPORTS OF OTHER OCULAR ANOMALIES COEXISTENT WITH SOME FEATURES OF THE DESCRIBED SYNDROME

Other ocular anomalies have been reported in the literature in association with the different abnormalities seen in this newly described syndrome. The various combinations found in the literature are listed in Table 2. It is readily seen that Milroy's disease has been found concurrently with ptosis, congenital glaucoma, and strabismus.

TABLE 2. OTHER ANOMALIES COEXISTENT WITH VARIOUS FEATURES OF THE SYNDROME DESCRIBED

Author	*Associated anomalies*
1. Bloom, D.[3]	Milroy's disease and ptosis
2. Zeeman, W. P. C.[25]	Milroy's disease and congenital glaucoma
3. DeVoe, G. A., and H. Horwick[6]	Milroy's disease and convergent strabismus
4. Halberg, G. P.[11]	Distichiasis with an incomplete form of mandibulofacial dysostosis
5. Brailey, A. R.[4]	Distichiasis with an incomplete form of mandibulofacial dysostosis plus two accessory bicuspid teeth
6. Gordon, S., and B. H. Cragg[9]	Congenital ectropion associated with bilateral ptosis
7. Urmetzer, J.[24]	Congenital ectropion associated with madarosis
8. Collins, T.[5]	Congenital ectropion associated with partial ptosis and epicanthus

In 1941 Bloom reported a study of a family of five generations which showed the association of hereditary lymphedema of the lower extremities with ptosis of the eyelid in six members of three consecutive generations.[3] In this family the lymphedema and ptosis followed an autosomal dominant mode of inheritance.

We have one family on file in the Heredity Clinic of the University of Michigan with an isolated case of bilateral ptosis and Milroy's

disease (Figures 10 and 11). The father of the propositus is deceased and reportedly had only ptosis. In view of the family described by Bloom and the isolated case noted by us with the same combination of defects, the association of Milroy's disease and ptosis may represent more than a coincidence.

The same reasoning applies to other anomalies seen in combination with distichiasis and congenital ectropion (Table II). These combinations may be fortuitous and non-hereditary; however, due to the relative rarity of each anomaly and sparsity of reports in the literature,

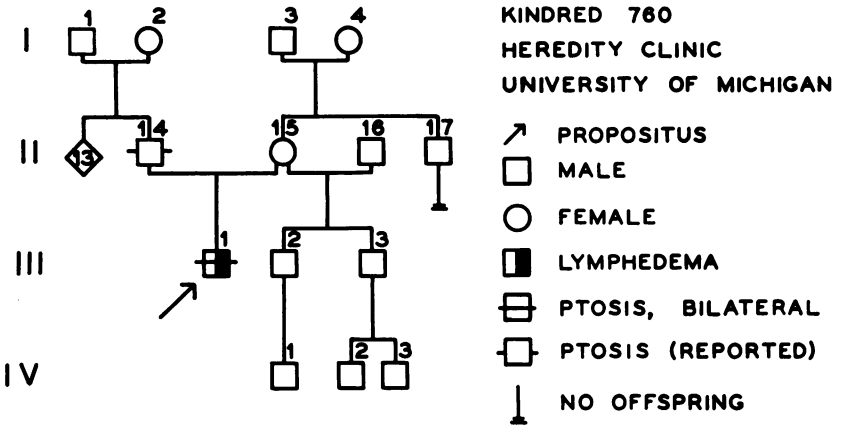

FIGURE 10
A male sporadic case with bilateral ptosis and Milroy's disease.

especially from a genetic viewpoint, hereditary factors cannot be excluded. Further family as well as twin investigations are needed for clarification of the genetic problem.

SUMMARY

A new syndrome is described consisting of (1) distichiasis of all four lids, (2) chronic lymphatic edema of both lower extremities (Milroy's type), (3) pterygium colli, and (4) partial ectropion of both lower lids. From the detailed study of a single family in which ten individuals were affected within five generations, it is evident that the syndrome is hereditary and follows an autosomal dominant mode of inheritance. The several component anomalies appear to exhibit varying degrees of expression and penetrance. Speculatively, the order of penetrance for the four features is the same as that in which they are set out above, highest for distichiasis and least for partial ectropion.

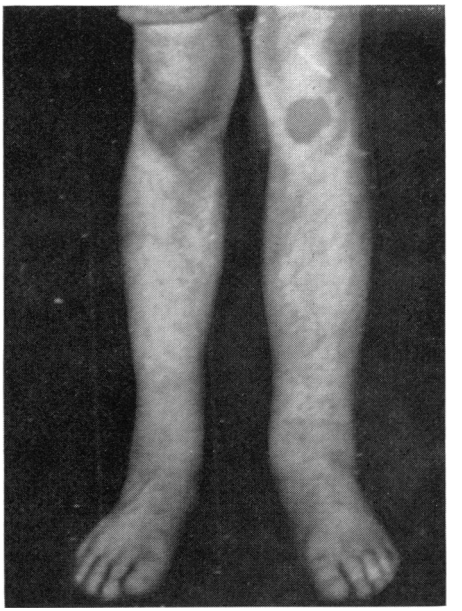

FIGURE 11
Bilateral lymphedema of lower extremities ceasing at level of knees. Left leg more severely affected than right.

The sporadic case represented in Family II is believed to be the result of an autosomal dominant mutation and may or may not represent the same syndrome.

The literature is surveyed for the separate anomalies and for other defects found in combination with those of the syndrome.

A brief discussion of the genetics of the syndrome is included.

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DISCUSSION

DR. CLEMENT MCCULLOCH. Dr. Falls and Dr. Kertesz are to be congratulated for bringing before the Society this syndrome with its widespread manifestations. As this is a new entity, or a new combination of findings, we are advised to be alert for such a concurrence of abnormalities appearing in our own clinical experiences.

The Falls and Kertesz syndrome seems particularly important as a step towards clarifying our understanding of a number of genetic diseases. The various abnormalities that they have included in their entity have been described as occurring as isolated findings or in other syndromes. Since expression is frequently quite variable in these syndromes a clear-cut pedigree, such as that of Falls and Kertesz, brings order to the material.

Two of the entities in which abnormalities described by Falls and Kertesz are included, are of particular interest.

TURNER'S SYNDROME. Seen in females showing infantilism, small stature, rudimentary secondary sex characteristics; seen in males showing small stature, undescended testes, and undeveloped penis. These individuals may have drooping eyelids, both upper and lower, pterygium colli, and lymphedema of the legs. The females show an abnormality of the chromosomes, having only one X chromosome. The males have X and Y chromosomes and the reason for the syndrome appearing in the male is not apparent. It is carried as an irregular dominant.

BONNEVIE-ULLRICH SYNDROME. Has many of the findings of Turner's syndrome, particularly pterygium colli. Sexual development is normal and there is no evidence of abnormality of the chromosomes. Inheritance would seem recessive and the status of this syndrome is not clear.

We have been interested in Turner's syndrome. This illustration is of a case showing pterygium colli and ptosis with antimongoloid droop to the lids. She does not have lymphedema of the legs but of course may still develop it at puberty. A second case in a female shows the pterygium colli, with the typical wide carrying angle. These girls have the XO chromosome picture. A third case in a male shows undescended testicles, small genitalia, pterygium colli. Distichiasis is not found in these cases.

Particularly in view of the number of other syndromes that include abnormalities similar to those described by Falls and Kertesz I would like to ask them concerning the karyotypes of the patients. Chu, Warkany, and Rosenstein (*Lancet*, 1: 786–8, 1961) reported negative findings in their case of Turner's syndrome and I would think one would need to do chromosome analyses on all affected members of the family to rule out Turner's syndrome. Also, is there any spinal abnormality or evidence of status dysraphicus in the family or of mandibulofacial dysostosis?

Finally, if this is a mendelian inherited disease and if the changes are more prominent in the males, could the defect be carried on the X chromosome as an intermediate inheritance? In view of the fact that the defect in Turner's syndrome would seem related to a loss of one X chromosome, the findings in the Falls-Kertesz syndrome have multiple similarities to those in Turner's syndrome, it would seem reasonable to suspect that even if this is a mendelian inherited disease the defect is on the X chromosome.

DR. GUILLERMO PICÓ. I wish to congratulate Dr. Harold Falls for the excellent presentation of this interesting new syndrome and to thank him

for his kind remarks about my thesis for membership in this Society, on the syndrome of congenital ectropion and distichiasis, which was accepted in 1957.

My paper was based on the study of three generations of a family of eighteen members. Dominant autosomal type of inheritance was evident. The pathogenic gene showed a high degree of penetrance. Only five of the family had normal eyes. Eleven suffered from congenital ectropion, which in eight instances was associated with distichiasis. Two persons had distichiasis alone. The genetic expression varied in degree from slight ectropion in the lower eyelids to marked ectropion in all four eyelids. The number and appearance of the aberrant eyelashes was also variable. Histologic examination of segments of affected eyelids in two of my cases showed absence of meibomian glands and replacement of the dense collagenous tissue of the tarsal plates by loose areolar tissue. No bony abnormality was found in the face or rest of the body.

The syndrome that Dr. Harold Falls has presented has clinical manifestations that were not found in my series of cases; none of my cases showed pterygium colli or lymphatic edema of the lower extremities. More than one gene is probably involved in his syndrome.

I would like to ask Dr. Falls if a pathologic study was done of a specimen from an affected eyelid in his cases and if X-rays of the malar bones were taken to determine any underdevelopment, as occurs in mandibulofacial dysostosis.

DR. FALLS. I would like to thank Drs. McCulloch and Picó for their valuable additions to this paper.

First I should like to answer Dr. McCulloch's question regarding the possibility of X chromosome inheritance in this family. In the first place, there is definite evidence that males can transmit the gene to their respective offspring, and there is no increased incidence of female affectation; in fact, the male was more affected than the female in this particular syndrome. I think that more pedigrees will help us to ascertain statistically whether or not this is a possibility. The evidence I have at the present time, I think, shows it is definitely an autosomal dominant inherited trait.

As to the possibility of there being other features simulating that of mandibulofacial dysostosis, we are extremely aware of this possibility, and we investigated this particular aspect. There are no other features in these individuals (and we have meticulously gone over them) which I felt could be put into the category of Franceschetti's syndrome, mandibulofacial dysostosis.

This will help to answer Dr. Picó's question as to whether X-rays of the orbits and zygomatic bone and in particular the malar remnants have been taken to rule out the possibility again of mandibulofacial dysostosis. We do not find any evidence of aberration of the orbital margin or of the malar remnants. In making the diagnosis of Franceschetti's syndrome, even

though there is no obvious external change, merely taking your finger and pressing at the outer one-third of the lower eyelid or in turn on the orbital margin will make the diagnosis for you.

As to the pathological study, raised by Dr. Picó, we have not had the opportunity ourselves specifically to do this, because we have been refused. However, in the Fort Collins family, two of which I reported as being hearsay evidence, the physician tells me definitely there is absence of meibomian glands, and that the tarsus is incompletely developed.

I think I have covered the points that have been raised in the form of questions. I would like to summarize for the benefit of our European guests, and say that I am cognizant of D. Klein's report associating congenital lymphedema with lower extremity with edema of the conjunctiva, and unilateral involvement. I concluded, in reviewing this report, that I could not completely rule out the possibility of neurofibromatosis, and for this reason, we just cast aside this one particular report.