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Congenital Hereditary Lymphoedema*

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Occasionally primary lymphoedema is both congenital and familial. The first reports by Nonne (1891) and Milroy (1892) were of families in which the oedema was present at birth and was described as non-tender chronic swelling of the lower extremities, not influencing the general health of the subjects or their longevity. This is distinguished from the familial form of lymphoedema praecox (Letessier, 1865; Meige, 1898, 1899) characterized by an abrupt onset, most often at puberty, and frequently associated with signs and symptoms of acute inflammation. The congenital form of familial lymphoedema is usually called Milroy's disease and the form with later onset, Meige's disease.

The oedema of the affected individuals in the family described in this report is typical of the condition described by Milroy and is of genetic interest for several reasons, including the presence of an apparent 'skipped' generation. Linkage studies were practical in view of the size of the kindred and the number of affected persons.

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Family History

There were 15 affected individuals in three generations of this family including, by history, a stillbirth. In addition, the family tree for three preceding generations was known with a total of 245 members (Fig. 1). There was no history of consanguinity nor any suspicion of affected persons outside the progeny of I.2 (Fig. 2). There was no evidence of concomitant lymphoedema praecox.

The proposita (II.5) was a 35-year-old white woman of excellent general health and strength, with bilateral swelling of the legs and feet, which had been present since birth. There was no history of any pain or inflammation associated with the oedema, though it progressed in severity during the first decade of life. On several occasions significant but incomplete reduction in the swelling had accompanied prolonged bedrest. The physical examination was within normal limits save for the gross enlargement of her lower extremities. The massive oedema extended above the knees and pitted with ease (Fig. 3). The overlying skin had no trophic changes and was impressively warm to touch. There was a constant tachycardia (90–100 a minute). Radiographs and laboratory tests were not remarkable; in particular, serum proteins and renal function were normal.

The mother of the proposita, the probable mutant

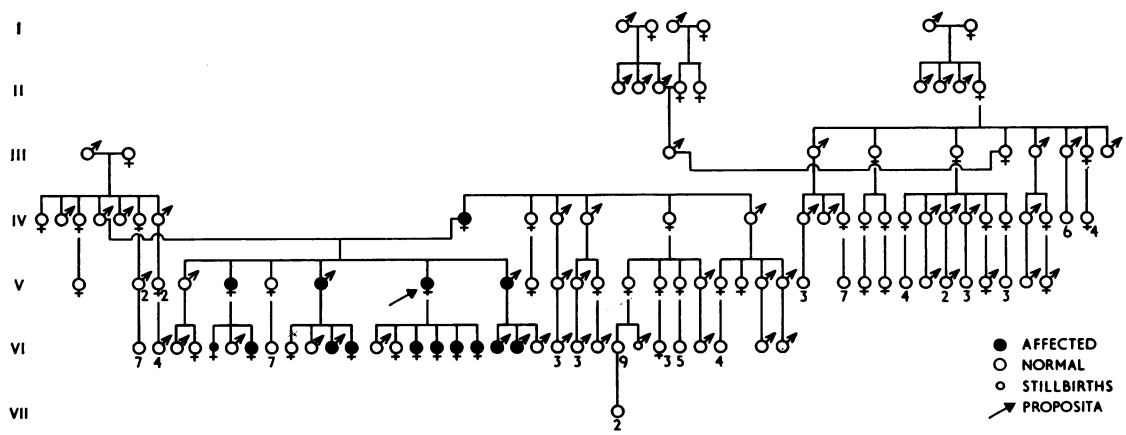


FIG. 1. Pedigree chart.

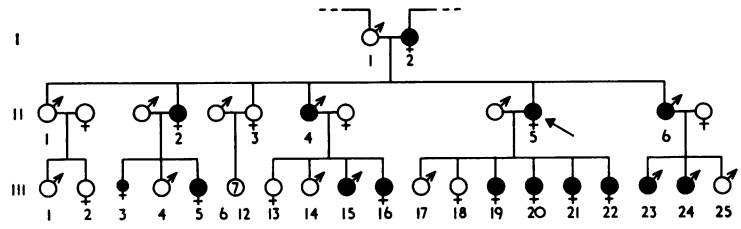


FIG. 2. Pedigree chart.

(I.2), was 63 years of age. She had congenital involvement of the right leg and foot. A less severe swelling on the left side, present only in recent years, had been interpreted as one of several signs of chronic congestive heart failure. Two sibs of the proposita were affected: one (II.2) with bilateral pedal oedema, another (II.6) with involvement of the right leg and foot. The former had a vertex-presenting stillbirth said to have leg, ankle, and definite pedal swelling, an unaffected son, and a daughter with oedema of the left ankle and foot (III.3, 5). The latter sib (II.6) had three sons: one with striking congenital oedema of the hands, a second with similar swelling of his hands as well as bilateral involvement of legs and feet, and a third who was unaffected (III.23, 24, 25).

A third sib (II.4) of the proposita was of interest because he had no apparent lymphoedema though two of his four children had bilateral swelling of the legs and feet (III.15, 16). He was regarded at first as a 'skipped' generation similar to those noted in previous pedigrees of Milroy's disease. Closer examination, however, demonstrated a definite 3 × 5 cm. area of slight oedema on the medial aspect of the left lower leg. This area was warm to touch and could be pitted against the underlying tibia.

Four of the proposita's six children (III. 19, 20, 21, 22) showed varying degrees of bilateral leg and foot involvement. Fig. 4 demonstrates the involvement of individuals in each of the three generations. Other than the lymphoedema, the physical findings, radiographs, and laboratory studies of individuals in the family were not remarkable. The family was of Belgian ancestry and apparently unrelated to any other previously described.

Linkage Studies

Blood for red cell antigens and serum for haptoglobins and levels of previously administered isoniazid (INH) were collected from all affected subjects and their sibs (Evans, Manley, and McKusick, 1960). Thresholds of phenylthiocarbamide (PTC) tasting were also evaluated. The data are listed in Table I. The probability ratios (Z scores) give no evidence of linkage between the trait and these loci (Morton, 1955). These are listed in Table II.

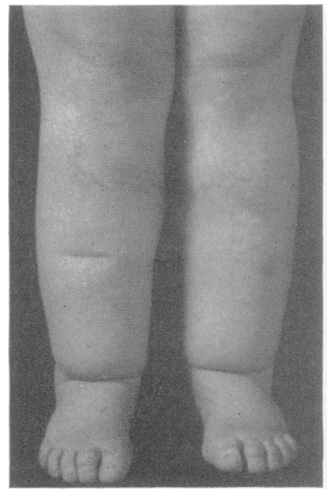
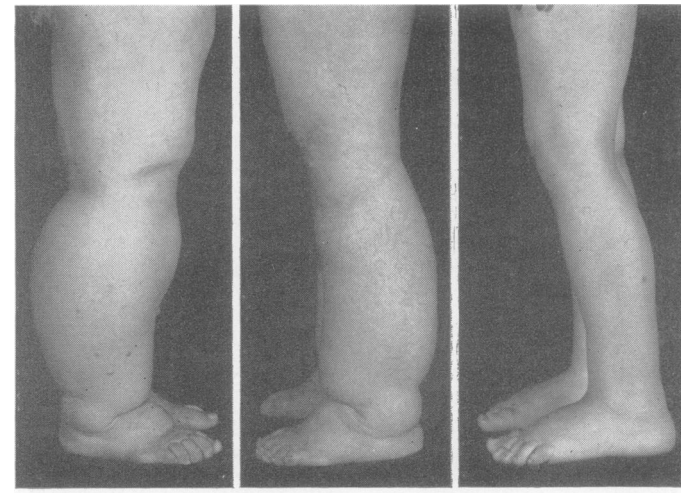


FIG. 3. Pitting oedema in the proposita (II.5).



(A) (B) (C)

FIG. 4. The appearance of congenital lymphoedema in individuals representing the three generations of the family: (A) 63-year-old woman (I.2), (B) 35-year-old woman (II.5), and (C) 4-year-old girl (III.21). The absence of secondary changes in the epidermis is characteristic of this type of lymphoedema.

TABLE I

	Linkage Data															
	A_1	H	C	c	D	M	N	S	Fy^a	Jk^a	C^w	P	Le^a	Le^b	PTC	INH	HAPT
I.1	+	o	+	o	+	+	+	+	+	+	o	o	o	o	tt	R	2-2
I.2	o	+	+	+	+	o	+	o	o	+	o	+	o	+	T	S	1-1
II.1	o	+	+	+	+	+	+	+	+	+	o	+	o	+	T	S	2-1
Wife of II.1	o	+	+	+	+	o	+	o	+	o	o	+	o	+	T	S	2-1
III.1	o	+	+	+	+	o	+	o	+	+	o	o	o	+	T	—	2-1
III.2	o	+	+	+	+	o	+	o	+	+	o	—	o	+	tt	R	2-2
II.2	+	o	+	+	+	+	+	+	+	+	o	—	o	o	T	S	2-1
Husband of II.2	o	+	o	+	o	+	+	o	o	+	o	+	o	+	tt	S	1-1
III.4	+	o	+	+	+	+	o	+	o	+	o	o	o	o	T	S	2-1
III.5	+	o	+	+	+	+	+	+	+	+	o	o	o	+	T	I	1-1
II.3	+	o	+	o	+	+	+	+	+	+	o	—	o	o	tt	R	2-1
II.4	+	o	+	o	+	o	+	o	+	+	o	o	o	o	T	S	2-1
Wife of II.4	o	+	o	+	o	+	+	o	+	o	o	+	o	o	T	R	2-1
III.14	o	+	+	+	+	+	+	o	+	+	o	+	o	+	T	R	2-1
III.15	o	+	+	+	+	o	+	o	o	+	o	o	o	+	T	S	2-1
II.5	+	o	+	+	+	o	+	o	+	+	o	+	o	o	T	R	2-1
Husband of II.5	o	+	+	o	+	+	+	+	+	+	o	+	o	+	T	R	2-1
III.17	+	o	+	o	+	o	+	o	+	+	o	+	o	o	T	R	2-1
III.18	o	+	+	+	+	+	+	+	+	+	o	+	o	+	T	R	1-1
III.19	+	o	+	o	+	o	+	o	o	+	o	+	o	+	T	S	2-1
III.20	+	o	+	+	+	+	+	+	+	+	o	o	+	o	T	R	2-2
III.21	o	+	+	+	+	+	+	+	+	+	o	o	o	+	T	—	2-1
II.6	+	o	+	+	+	+	+	+	+	+	o	—	o	o	T	R	2-1
Wife of II.6	o	+	+	+	+	+	+	o	+	+	+	—	o	+	tt	R	2-1
III.23	+	o	+	o	+	o	+	o	+	+	+	+	o	o	tt	R	2-1
III.24	o	+	+	+	+	o	+	o	+	+	o	+	o	o	tt	R	2-2
III.25	o	+	o	+	o	o	+	o	o	+	o	+	o	+	T	R	2-1

+ present, o absent, — not tested. The antigen Kp^b was present in all individuals; the following antigens were tested but not present: B, E, K, Lu^a, Wr^a, Be^a, Vw, Mg. T and tt indicate phenylthiocarbamide (PTC) 'tasters' and 'non-tasters'. The letters R, I, and S indicate rapid, intermediate, and slow inactivation of isoniazid (INH).

Inheritance

There are 22 previously documented pedigrees along with the present family giving 152 affected individuals. The detail in these reports represents a spectrum from multiple case reports to extensive genealogical inquiry. In the review of this subject, the problem of limited documentation was complicated by the varying severity of the trait.

Several of the pedigrees were unsatisfactory for tabulating the ratio of affected members in the progeny of affected individuals. Four reports describe exclusively the affected individuals (Phillips, 1914; Still, 1929; Evans, 1930; Rosenberg, 1940). Those of Sutherland (1908) and Caselli (1945), and probably that of Glaser (1944), contain affected persons in only a single generation and so cannot be used to examine transmission. In Jopson's family the sex of the normal sibs is unknown (Jopson, 1898). Furthermore, since the affected conductor 'recovered', the family might be classed with the single generation group. The remaining omissions are those of Milroy (1892, 1928) and Lortat-Jacob (1902) in which the number, sex, and exact ancestry of descendants is not always stated.

The sex ratio of affected individuals in the 23 families (Table III) is 66 males to 81 females. The families are grouped as simple dominant pedigrees (A), those with skipped generations but otherwise resembling the former (B), and those omitted from further tabulations (C).

TABLE II

PROBABILITY RATIOS (Z SCORES) OF LINKAGE WITH MILROY'S DISEASE

X =	0·05	0·1	0·2	0·3	0·4	0·5
ABO	−5·61	−3·62	−1·76	−0·82	−0·28	0
MNS	−1·16	−0·63	−0·18	−0·01	+0·04	0
Rhesus	−6·07	−3·17	−1·57	−0·75	−0·26	0
Duffy(Fy^a)	−2·72	−1·82	−0·94	−0·46	−0·17	0
P*	−2·75	−1·84	−0·99	−0·52	−0·21	0
Haptoglobins	−2·44	−0·30	−0·03	+0·07	+0·08	0
PTC	−2·63	−1·56	−0·64	−0·24	−0·05	0

* Excluding the family of II.6.

The progeny of affected individuals are listed in Table IV grouped by sex and the trait, and the ratio of affected to normal members in these sibships. Sibs of unknown sex are included in this total but not in the groups divided by sex. In addition, the families in Group B are recalculated on the assumption that the skipped conductors represent individuals with minimal lymphoedema (B-I). In no case were these 'skips' in either Group B or Group C (Table III) examined or described in detail; in most cases the information was historical. It is likely that many if not all of these skipped individuals

TABLE III

REPORTED FAMILIES OF CONGENITAL HEREDITARY LYMPHOEDEMA

	Generations Affected	Affected ♂	Affected ♀	Affected ⚥	Total
A (Simple dominant pedigrees)					
Nonne (1891)	3	3	4	1	8
Page (1928)	3	2	2		4
Jennett (1931)	5	5	8		13
Faber and Lusignan (1933)	3	1	2		3
Dassanayake (1940)	2	8	4		12
Schroeder and Helweg-Larson (I, 1950)	5	4	1		5
Present family	3	5	10		15
		28	31		60
B (Presumably dominant with skipped generations)					
Tobieson (1899)	3	3	1		4
Boks (1913)	2	1	5		6
Van Vliet (1913)	3	3	11		14
Schroeder and Helweg-Larsen (II, 1950)	3	2	3		5
Cook and Moore (1951)	3	3	6		9
		12	26		38
C (Pedigrees excluded from detailed consideration)					
Milroy (1892, 1928)	6	12	8	4	24
Jopson (1898)	2	3			3
Lortat-Jacob (1902)	3	1	5		6
Sutherland (1908)	1		2		2
Phillips (1914)	2	2			2
Still (1929)	2	1	1		2
Evans (1930)	3	2	1		3
Davis (1933)	3	3	2		5
Rosenberg (1940)	2		3		3
Glaser (1944)	1	1	1		2
Caselli (1945)	1	1	1		2
		26	24	4	54
Total		66	81	5	152

TABLE IV

PROGENY OF AFFECTED CONDUCTORS

Conductor / Progeny	♂ ♂	♂ ♀	♀ ♂	♀ ♀	⚥ ♂	⚥ ♂	⚥ ♀	⚥ ♀	⚥ ⚥	⚥ ⚥
A										
Nonne (1891)					3	0	2	2	6	5
Page (1928)	1	2	1	0	1	0	0	0	3	2
Jennett (1931)	2	2	3	0	3	6	4	2	12	20
Faber and Lusignan (1933)					1	1	1	0	2	1
Dassanayake (1940)	5	2	4	1	0	2	0	2	9	7
Schroeder and Helweg-Larsen, I	3	3	1	0					4	3
Present family	3	2	1	1	2	3	8	2	14	8
	14	11	10	2	10	12	15	8	50	46
B										
Tobieson (1899)					1	2	0	1	1	3
Boks (1913)										
Van Vliet (1913)	1	0	2	1	1	10	5	2	9	13
Schroeder and Helweg-Larsen, II	0	1	1	3	1	1	0	3	2	8
Cook and Moore (1951)	0	0	0	1	2	0	2	0	4	1
	1	1	3	5	5	13	7	6	16	25
A + B	15	12	13	7	15	25	22	14	66	71
B–I										
Tobieson (1899)					3	2	1	0	4	2
Boks (1913)					0	3	3	2	3	5
van Vliet (1913)	1	0	2	1	1	13	8	3	12	17
Schroeder and Helweg-Larson II	0	1	1	3	2	8	2	7	5	19
Cook and Moore (1951)	0	0	1	0	2	1	5	1	8	2
	1	1	4	4	8	27	19	13	32	45
A + B–I	15	12	14	6	18	39	34	21	82	91

represent involvement no more striking than that in one member of the present family (II.4).

The ratio of affected and normals among the progeny of affected persons is 82:91, in agreement with the 1:1 expectation of a simple dominant trait. The transmission from affected female to female (34) is about twice as frequent as to male (18) or from affected male to female (14) or male (15). The significance of this observation is not known, nor is female predominance more than suggested by the over-all sex ratio (66 males:81 females).

Comments

Clinical Features. Despite minor exceptions and qualifications which are detailed later, Milroy's criteria for the recognition of congenital hereditary lymphoedema remain valid. The oedema is chronic, firm but pitting, confined to the lower extremities, present at birth, and permanent. It is accompanied by no constitutional symptoms, is compatible with long life, and its behaviour demonstrates conspicuous hereditary transmission. Milroy recognized the three exceptions in his large family: a case with onset at puberty, another with additional involvement following a fracture at the age of 20, and an instance of scrotal involvement, also at puberty, with simultaneous recovery of a congenitally affected foot (Milroy, 1892, 1928).

In retrospect, these exceptions appear to represent a mixture of lymphoedema praecox. The acute attacks described by Phillips (1914) and observed by the author in another family may have a similar explanation. In the reported pedigrees there remain occasional atypical cases of which the interpretation is necessarily uncertain. These families are not immune to related disease which might be reflected in the status of the oedema. Nevertheless as treatment is ineffective, true recovery would be most remarkable.

Genital involvement in the male is not uncommon (Boks, 1913; Glaser, 1944; Milroy, 1928; van Vliet, 1913), but lymphoedema in the upper extremities is distinctly unusual. Radner (1946) described it in lymphoedema praecox, but the slight oedema of the hands in Case 1 of Schroeder and Helweg-Larsen (1950) is the first account of congenital oedema. In the present family III.17 is similar and more severe. Case III.15, with congenital involvement of the hands alone, is unique.

The absence of changes in the overlying skin is a characteristic feature of chronic lymphoedema. When lymphoedema is severe the diagnosis is readily made, but when minimal it is frequently difficult to detect even when it is congenital and familial.

There have been several recent classifications of lymphoedema (Goodman, 1962; Martorell, 1951; *Brit. med. J.*, 1963). In addition, that of Griffith and Newcomet (1897) is of historical interest. Allen's Mayo Clinic series (1934) is probably the largest.

Pathogenesis. Several theories have been proposed for the pathogenesis of congenital lymphoedema. Welch and Osler (in Milroy, 1892) suggested that Milroy's oedema was similar to angioneurotic oedema, reflecting Osler's contemporary interest in the familial form of the latter condition (1888). Pointing out the differences, Milroy considered a local cause such as obstruction 'or an error in the activity of blood vessels or lymphatics dependent on a perverted nerve supply' (Milroy, 1928). Subsequent attempts to implicate an endocrine or other systemic mechanism have been unsuccessful.

It has been suggested that increased filtration is the cause of congenital lymphoedema, because groups of peculiar arteriole-like structures have been noted deep in the dermis (Schroeder and Helweg-Larsen, 1950). It was suggested that an abnormality of arterioles results in an abnormally high filtration pressure in the capillary bed. Though the findings were confirmed by biopsy in the proposita (II.5) in this family, this hypothesis remains unproven and the nature of the vascular changes is obscure. It seems likely that the arteriolar changes are secondary to the high flow that accompanies oedema of varied aetiology (Harrison and Pilcher, 1930), and not a primary defect. Evidence of a lymphatic malformation has been demonstrated with lymphangiograms by Kinmonth, Taylor, Tracy, and Marsh (1957); in two cases of familial lymphoedema no well-developed lymphatic pattern was visualized. Other congenital malformations have been recorded in both affected and unaffected persons in families with lymphoedema (Faber and Lusignan, 1933; Jennett, 1931), but these have been infrequent and of no consistent type. These reported findings and the failure to demonstrate lymphatics in the proposita of the present family (J. E. Wood and J. R. Esterly, 1960, unpublished data) support the view that hypoplasia (or aplasia) of lymphatics is the basic lesion.

Genetics. It is clear from Tables II and III that the ratio of affected to normal members of sibships (82:91) is in accordance with a dominant trait. Though the over-all male:female ratio is 66:81, within transmitted sibships the ratio rises to 33:47. Female predominance in the pedigrees of Boks (1913) and van Vliet (1913) prompted Cockayne to

suggest a form of sex influence (Cockayne, 1933).

In the families in Group A, the proportion of affected individuals (50:46), the sex ratio of affected individuals (24:25), and the modes of transmission, are all those expected of an autosomal dominant trait. Specifically male-to-male transmission and unaffected daughters of affected males exclude X-linked dominant inheritance. Whereas in the families in Group B, either as described or as recalculated with the assumption of complete penetrance (B-I), the ratio of affected to normal is only 32:45, there are fewer males (9:23), and the female-to-female transmission is higher.

These data support the hypothesis of Schroeder and Helweg-Larsen of more than one type of inheritance. However, it is worth quoting their qualification that the 'material is too small, too heterogeneous and too incomplete' to establish any hypothesis (Schroeder and Helweg-Larsen, 1950). Goodman's view that autosomal recessive inheritance best explains his family (one of the praecox, i.e. Meige type) does not apply to the vast majority of these pedigrees (Goodman, 1962).

In conclusion, congenital lymphoedema is clearly inherited as a dominant trait, most frequently as a simple autosomal dominant. Although all pedigrees are compatible with this type of inheritance, it is not possible to rule out a second mode explaining the female predominance in some families.

Summary

A family is described in which congenital hereditary lymphoedema affected 15 members in three generations. It is proposed that transmission is as a simple autosomal dominant trait with complete penetrance but variable expressivity. The previously reported pedigrees are reviewed and analysed genetically. No linkage could be demonstrated between the lymphoedema and blood group antigens, haptoglobins, PTC tasting, and rate of INH inactivation.

The assistance of Dr F. H. Allen, Jr., of Boston, for the blood group determinations, and of Dr James H. Renick and Mrs Jane F. Schulze for the linkage calculations is gratefully acknowledged. The continued guidance and encouragement of Dr V. A. McKusick are largely responsible for this investigation.

References

Allen, E. V. (1934). Lymphedema of the extremities. *Arch. intern. Med.*, **54**, 606.

Boks, D. B. (1913). Aangeboren familiar oedeem der odnerste ledematen. *Ned. T. Geneesk.*, **57**, I, 416.

Brit. med. J. (1963). Leading article. Milroy's disease and lymphoedema. **2**, 1483.

Bulloch, W. (1909). Chronic hereditary trophoedema. *Treas. hum. Inher.*, **1**, 32.

Caselli, E. G. (1945). Enfermedad de Milroy. *Arch. argent. Pediat.*, **24**, 106.

Cockayne, E. A. (1933). *Inherited Abnormalities of the Skin and Its Appendages*, pp. 375–78. Oxford University Press, London.

Cook, W., and Moore, A. T. (1951). Milroy's disease. *J. Amer. med. Ass.*, **147**, 650.

Dassanayake, W. L. P. (1940). Persistent hereditary oedema of the legs. *J. trop. Med. Hyg.*, **43**, 221.

Davis, D. B. (1933). Chronic hereditary edema. *J. Mich. med. Soc.*, **32**, 237.

Evans, D. A. Price, Manley, K. A., and McKusick, V. A. (1960). Genetic control of isoniazid metabolism in man. *Brit. med. J.*, **2**, 485.

Evans, E. L. (1930). Three cases of congenital oedema (Milroy's disease) in two generations of the same family. *Proc. roy. Soc. Med.*, **23**, 1585.

Faber, H. K., and Lusignan, H. R. (1933). Hereditary elephantiasis. *Amer. J. Dis. Child.*, **46**, 816.

Glaser, K. (1944). Congenital hereditary lymphedema (Milroy's disease). *J. Pediat.*, **25**, 337.

Goodman, R. M. (1962). Familial lymphedema of the Meige's type. *Amer. J. Med.*, **32**, 651.

Griffith, J. P. C., and Newcomet, W. S. (1897). Types of oedema in infancy and childhood. *Trans. Ass. Amer. Phycns*, **12**, 399.

Harrison, T. R., and Pilcher, C. (1930). Studies in congestive heart failure. *J. clin. Invest.*, **8**, 259.

Jennett, J. H. (1931). Persistent hereditary edema of the legs—Milroy's disease. *J. Mo. med. Ass.*, **28**, 601.

Jopson, J. H. (1898). Two cases of congenital elephantiasis. *Arch. Pediat.*, **15**, 173.

Kinmonth, J. B., Taylor, G. W., Tracy, G. D., and Marsh, J. D. (1957). Primary lymphoedema. *Brit. J. Surg.*, **45**, 1.

Letessier, E. E. (1865). De l'éléphantiasis des Arabes et de son hérédité. Thesis, Strasbourg.

Lortat-Jacob (1902). Deux cas de trophoedème héréditaire chez des infants. *Rev. neurol.*, **10**, 279. (Quoted by Bulloch, 1909).

Martorell, F. (1951). Chronic edema of the lower limbs. *Angiology*, **2**, 434.

Meige, H. (1898). Dystrophie oedémateuse héréditaire. *Presse méd.*, **6**, 341.

—— (1899). Le trophoedème chronique héréditaire. *Nouv. Iconogr. Salpêt.*, **12**, 453.

Milroy, W. F. (1892). An undescribed variety of hereditary oedema. *N.Y. med. J.*, **56**, 505.

—— (1928). Chronic hereditary edema: Milroy's disease. *J. Amer. med. Ass.*, **91**, 1172.

Morton, N. E. (1955). Sequential tests for the detection of linkage. *Amer. J. hum. Genet.*, **7**, 277.

Nonne, M. (1891). Vier Fälle von Elephantiasis congenita hereditaria. *Virchows Arch. path. Anat.*, **125**, 189.

Osler, W. (1888). Hereditary angio-neurotic oedema. *Amer. J. med. Sci.*, **95**, 362.

Page, C. W. (1928). Milroy's disease. *Calif. west. Med.*, **29**, 101.

Phillips, J. (1914). Persistent hereditary oedema of the legs (Milroy's disease) with acute exacerbations. *Cleveland med. J.*, **13**, 316.

Radner, S. (1946). Chronic hereditary edema of extremities (Milroy's disease). *Acta derm.-venereol.* (*Stockh.*), **26**, 261.

Rosenberg, W. A. (1940). Hereditary edema of the legs (Milroy's disease). *Arch. Derm. Syph.* (*Chic.*), **42**, 1113.

Schroeder, E., and Helweg-Larsen, H. F. (1950). Chronic hereditary lymphoedema (Nonne-Milroy-Meige's disease). *Acta med. scand.*, **137**, 198.

Still, G. F. (1929). Some forms of oedema in childhood. In *Diseases of Children*, 2nd ed., ed. A. E. Garrod, F. E. Batten, H. Thursfield, and D. Patterson, p. 143. Arnold, London.

Sutherland, G. A. (1908). A case of oedema persisting since birth. *Brit. J. Child. Dis.*, **5**, 290.

Tobieson, F. (1899). Elephantiasis congenita hereditaria. *Jb. Kinderheilk.*, **49**, 392. (Quoted by Bulloch, 1909).

Vliet, J. C. van (1913). Aangeboren familiair oedeem der onderste ledematen. *Ned. T. Geneesk.*, **57**, 1092.