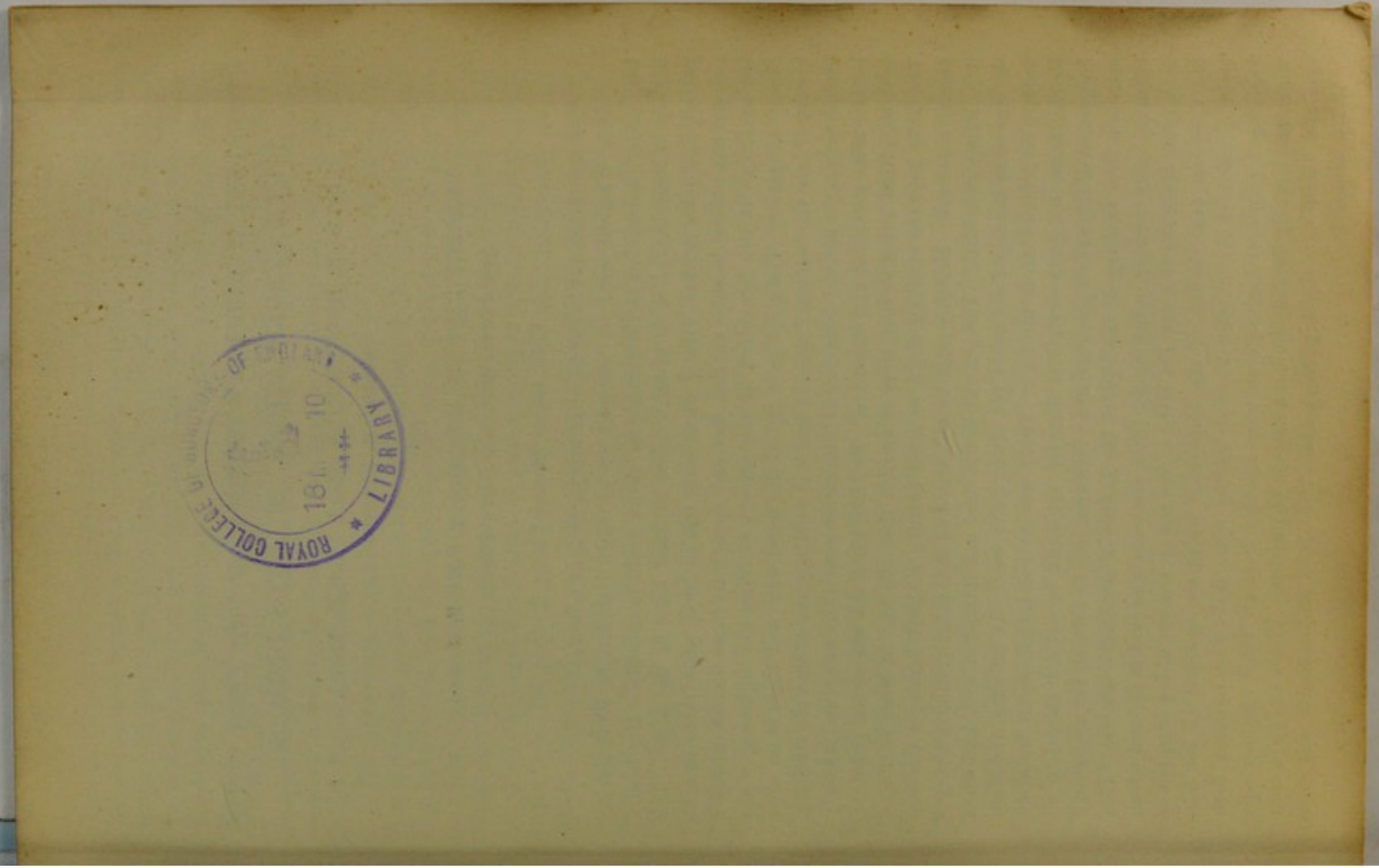
Persistent hereditary oedema of the legs with acute exacerbations : Milroy's disease / by W.B. Hope and Herbert French.

(19

Reprinted from

The Quarterly Journal of Medicine

April 1908 (*Vol. 1 No. 3*)


ROYAL COLLEGE OF
LIBRARY

PERSISTENT HEREDITARY OEDEMA OF THE LEGS WITH ACUTE EXACERBATIONS. MILROY'S DISEASE

By W. B. HOPE, M.R.C.S. (Eng.), L.R.C.P. (Lond.),
Caversham, Reading

and

HERBERT FRENCH, M.D. (Oxon.), F.R.C.P. (Lond.),
Assistant Physician, Guy's Hospital

With Plates 34 and 35.

The case which has led us to write this paper is as follows :—

Alice Wherrell, aged 18, was sent up to Guy's Hospital in 1906, having been under observation at Caversham for seven years previously. Her family history is remarkable; it is given a place to itself later in the paper. The patient was quite normal looking when born, but in 1888, when three months old, she was noticed to have swollen feet, and apparently there was no cause for the swelling. It was recognized by the parents as being the beginning of the family complaint. The child grew up in the usual way, and there is no clear history of how the 'oedema' spread; but it is definitely stated that the swelling, though varying in amount from time to time, never went quite away, and it slowly became more persistent and extensive. By 1899, when she was eleven years old, both legs, from knees to toes, were so swollen that she had to wear bandages. The latter kept the swelling down to some extent; without bandages the legs became enormous. Her only other trouble was a chronic inflammation of the eyelids, dating from birth. The general health was not interfered with, and when the legs were bandaged she could get about quite well. At no time was there oedema elsewhere than in the legs. There was no breathlessness, no tendency to chilblains, no gastro-intestinal disorder sufficient to attract attention, no suggestion of Raynaud's phenomena, no urticaria, indeed nothing but apparently causeless firm swelling of the legs of the nature of semi-solid oedema. This affection being common in the family, little attention was paid to it; and when, in August, 1900, she first saw Dr. Hope it was not on account of her legs, but of her eyes—an exacerbation of the blepharitis which she had had all her life. Ophthalmoscopic examination showed healthy optic disks and retinae; both ocular and palpebral conjunctivae were injected from an acute conjunctivitis which had recently developed upon a chronic blepharitis. Vision was $\frac{6}{18}$ in each eye, and there was slight photophobia. The acute conjunctivitis was soon

[Q. J. M., April, 1908.]

relieved, though the chronic blepharitis persisted as before. It seemed that the conjunctival condition was, in a sense, accidental, and not directly connected with the swelling of the legs. The latter had the appearance of moderate elephantiasis, similar to, but less in degree than, their condition in 1906. They remained in much the same state from 1899 to 1904, and then occurred the first of a series of 'acute attacks' of pain and additional swelling.

We propose to give a somewhat detailed account of these 'acute attacks', because they have not occurred, or, at least, they have not been prominent features, in the similar cases of hereditary trophoedema recorded by Milroy, Meige, Rolleston, and others.

The first 'acute attack' occurred on January 19, 1904. The patient at first noticed an acute pain in her pudenda, but did not regard it as serious. The next day she walked to a neighbouring town, and this made the pain in the pudenda so much worse that she had much difficulty in walking back again. When she got home she went to bed. Her temperature was only 97·4° F., and her pulse rate 74 per minute, but she was shivering in spite of hot-water bottles in the bed. The pudenda were generally swollen and painful, especially the left labium minus, and there was a red patch over the metatarso-phalangeal joint of the right great toe. The swelling of the legs was not materially increased at the time, and the local condition gradually improved until, by January 26, she had practically recovered from the acute attack, the pudenda had become normal again, pain was gone, and the legs were as before—chronically swollen from the knees downwards.

This was the only occasion on which the pudenda have been affected at all, and also the only occasion on which there was no rise of temperature during one of these acute attacks.

The second 'acute attack' began on June 10, 1904. At 6 a.m. the patient had a severe fit of shivering which lasted an hour and a half. She then vomited four times at short intervals, after which she became very hot and experienced severe continuous pain down her right thigh and leg, from Poupart's ligament to the ankle. Her temperature was 104° F., her pulse rate 126, and her respiration rate 52, per minute. The right thigh, leg, and foot, beginning sharply at Poupart's ligament, were red, enormously swollen, very hot to the touch, painful, and so tender that any pressure that could be borne failed to cause any pitting. The left thigh and leg felt hot also, but they were neither red nor painful, and the swelling on the left side was only the same as had been present for years. The measurements taken at the time showed:—

Maximum circumference measurements.

	Right side.	Left side.
Instep	13 inches.	12 inches.
Calf	$16\frac{5}{8}$ „	$17\frac{1}{4}$ „
Knee	$21\frac{5}{8}$ „	$21\frac{1}{8}$ „
Thigh	$23\frac{1}{3}$ „	$24\frac{1}{4}$ „

We have no record of measurements previously to this, but clinically the left leg had always been considerably more bulky than the right hitherto.

There were no abnormal physical signs in the lungs nor in the abdominal organs. The only abnormal physical sign noted in the heart was a faint blowing systolic murmur, which was heard both at the impulse and at the base; it was thought not to indicate any valvular disease.

Next day, June 11, 1904, the temperature had fallen to 100° F., the pulse rate to 106, the respiration rate to 40. The right lower limb was still hotter than the left, the redness above the knee had disappeared, and that below the knee was fading markedly. Pain was also much less.

On June 12, 1904, the systolic bruits were scarcely to be detected. The temperature was 99° F., the pulse rate 100, and the respiration rate 20 per minute. The right lower limb was desquamating, and the pain in it was almost gone.

By June 16, 1904, the attack was quite over, the temperature was 98° F., the pulse rate 60, and the respiration rate 20 per minute.

Measurements showed:—

Maximum circumference measurements.

	Right leg.	Left leg.
Instep	11½ inches.	10½ inches.
Calf	14¼ „	14¼ „
Knee	17 „	16½ „
Thigh	21 „	21½ „

Both legs had diminished in size, as was always the case, to some extent, when the patient lay in bed for a week.

The third 'acute attack' occurred on Aug. 22, 1904, and was very similar to the second. It may be noted that up to this time there had been no breach of surface in either leg, no boil nor sore place that could be detected, and no enlarged lymphatic glands in the groins or elsewhere. The urine had a specific gravity of 1010; it was pale and clear, with a neutral reaction, and it contained neither albumen nor sugar.

The first breach of surface that was noticed was some time after the patient had been up and about after recovery from the third 'acute attack'; on Nov. 1, 1904, there were numerous small superficial ulcers in the skin about both knees. These ulcers were mostly no more than an eighth of an inch in circumference, the largest measuring half an inch across; each had a sloughy base, an indefinite edge, and a thin serous discharge, which was small in amount. Each excoriation was surrounded by an area of redness due to inflammation. There was nothing suggestive of syphilis in the appearance of the very shallow sore places; they seemed to be pyodermic from accidental infection of the poorly nourished skin.

The fourth 'acute attack'. On Nov. 4, 1904, about 3 p.m., the patient complained of shivering, and of severe pain down her left side. Half an hour

later both lower limbs became hot and began to swell. A typical attack followed, like the previous ones in every respect, except that both legs were affected equally instead of one more than the other.

The fifth, sixth, seventh, eighth, ninth, and tenth 'acute attacks'. These occurred at intervals of a month or two during the year 1905. Each was confined to the right leg, was of short duration, and very similar to those already described. It is worthy of note that the patient was now eighteen years of age and had only menstruated once.

A short but acute attack of mental derangement occurred in February, 1906. On Feb. 19 of that year she became very excited and talkative, without apparent cause, and next day she was garrulous, with a happy, but unintelligent, facial expression, much exaltation, and delusions. The following day, Feb. 20, she was passing her motions and urine under her, and she had delusions about money. On Feb. 21 she was very noisy and persistently dirty in her habits. She continued in this abnormal mental condition throughout March, April, and May, but in June she gradually improved, and entirely regained her reason.

She was in Guy's Hospital from Nov. 1 to Dec. 1, 1906. The condition of her legs at that time is shown in the accompanying photographs (Figs. 1 and 2).

There was brawny, elephantiasis-like swelling of the whole of both lower extremities from Poupart's ligament and the gluteal fold above to the toes below. The pudenda were not affected, nor did the swelling extend on to the trunk. If any parts of the lower limbs were less affected than the rest, they were the plantar surfaces of the feet and toes themselves. The swelling appeared to be subcutaneous, the skin itself being dry, but only moderately thickened, and not discoloured. The swelling obliterated the normal outlines of the parts, bony prominences such as the malleoli, the patellae and the great trochanters not being made out. The swelling was comparatively uniform in the straight parts of each limb, with deep transverse sulci across the roots of the toes, in front of and behind the ankles, and behind the knees. On lightly handling the parts they felt almost hard, but on firmly pressing with the finger, for a longer time than is necessary in the case of ordinary oedema, deep pitting was obtainable, so that, even if there was a real increase in the subcutaneous connective tissues, there was considerable oedema as well, of the kind that is sometimes called semi-solid.

The legs were skiagraphed, and the X-rays showed no abnormality in the bones. It was impossible to examine the muscles digitally; they were certainly deficient in power, for the patient could stand with difficulty and could scarcely walk at all. It seemed likely, however, that this apparent weakness of the muscles might well be due to the mechanical difficulties in the way of their free action rather than to any real disease in the muscle fibres themselves. The electrical reactions were tested, but the resistance in the dry coarse skin was so great that no contraction was obtainable with any current, Faradic or galvanic, that the patient could bear over the quadriceps extensor femoris, or the ham-

string muscles of the legs. The tibialis anticus muscles responded to a bearable faradic current, and so did the long extensors of the toes and the muscles at the back of the calf, though the resultant movements of the toes or ankle were but slight. These muscles also gave a slight galvanic reaction, in which the kathodal closure contraction was more easily obtained than the anodal closure contraction. So far as could be judged, therefore, the electrical reactions were normal, though the difficulties in the way of obtaining them were great. The muscles of the upper extremities all gave a normal reaction with readiness.

As regards sensation, there was no abnormality. Cutaneous sensibility was present everywhere, and localization was correct. Heat and cold were properly distinguished, pain was felt distinct from touch, muscle sense was correct, and pressure sense was normal when allowance for the thickness of the superficial tissues was made. There was no cutaneous hyperaesthesia, and there was no pain at all. The feet themselves were not markedly colder than those of other patients in the wards at the same time.

The respiratory system was perfectly natural.

The alimentary system was apparently sound. The tongue was clean and moist, the teeth good, the appetite good; there was no tendency to nausea or vomiting, and the bowels were opened regularly. Neither liver nor spleen could be felt; indeed, no abnormality could be made out, and the abdominal wall was supple and natural right down to Poupart's ligament, where the swelling of the legs suddenly began.

The genital system was abnormal only in respect to menstruation, which had occurred but once, though the patient was 18.

The urine was also natural; its specific gravity was 1014, its colour pale yellow, its reaction acid; it was clear, of normal amount, and it contained no albumen, blood, pus, or sugar; microscopical examination showed no abnormal constituents. No excess of indican was present.

The temperature varied from 97° F. to 98·8° F., being for the most part slightly sub-normal. The pulse rate varied from 66 to 88, and the respiration rate from 20 to 24, per minute.

The heart appeared to be of normal size, and the sounds were clear and entirely free from bruit. The peripheral arteries that could be felt were natural; the maximum systolic blood pressure in the brachial artery, taken on many different occasions by Martin's modification of the Riva-Rocci apparatus, was never higher than 132 mm., and never lower than 120 mm. of mercury. There were no varicose or other distended veins to be seen anywhere, nor were there any telangiectases. The patient stated that her hands and feet readily became numbed and blue in cold weather, but no decided symptoms of Raynaud's disease could be found. The blood examination showed nothing distinctive. The red blood corpuscles numbered 4,120,000 per cub. mm., the leucocytes 8,437, and the haemoglobin was 80 % (male standard).

The differential leucocyte count was as follows :—

Polymorphonuclear cells	74 per cent.
Small lymphocytes	21 „ „
Large lymphocytes	3 „ „
Coarsely granular cosinophile corpuscles .	2 „ „

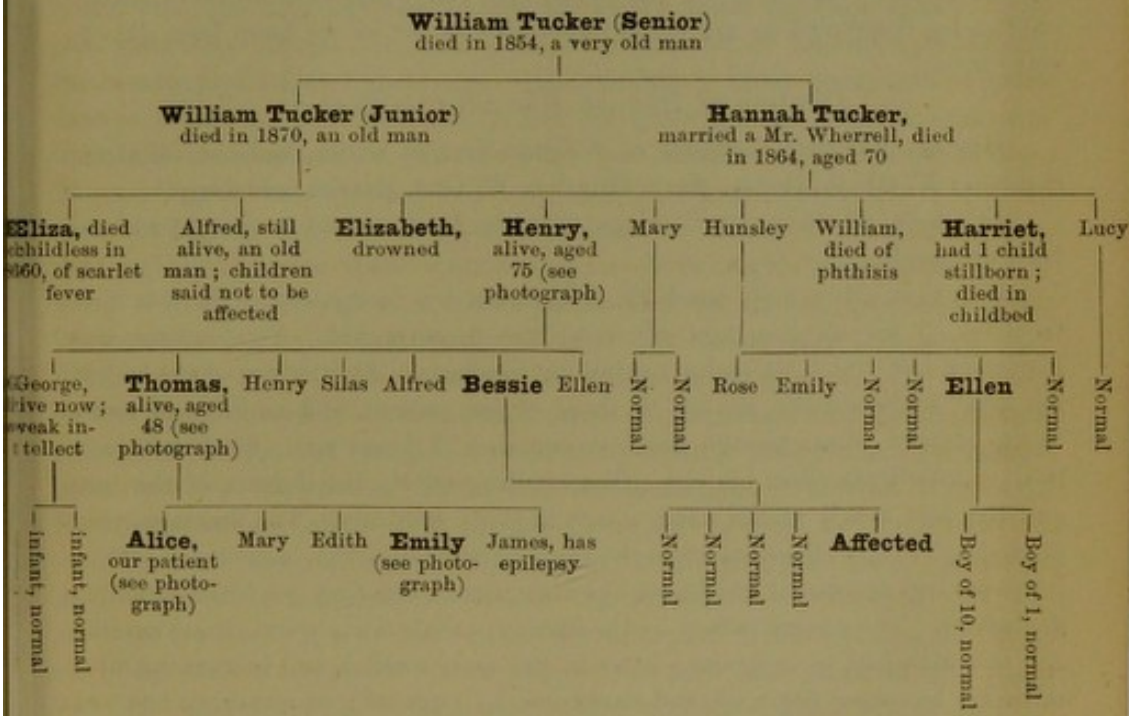
Filaria embryos were searched for in both night and day specimens of blood, and none were found. The patient, it may be mentioned, had not been out of England, so that filariasis seemed out of the question. The blood coagulation time was approximately normal.

The eye condition—chronic blepharitis and conjunctivitis—has already been alluded to.

The thyroid gland could be felt in the neck, and it seemed to be natural.

The patient's height was 5 ft. 3 ins.

Genealogical table of the family.



The individuals whose names are printed in thick type had, or have, the family complaint of 'swollen legs', mostly with 'acute attacks' as well.

The diagnosis of this patient's condition was much simplified when the family history was obtained. There were thirteen similar cases in five generations. When an individual had the hereditary complaint we summarize this by merely stating that there were 'swollen legs', without going into detail in each case. The swollen legs, when mentioned, began young and lasted long.

First Case traced.

GENERATION 1.—The first member of the family of whom we had any account was William Tucker. It is reported that he 'had very swollen legs all his life', but no further particulars are available. He died in 1854 at an advanced age.

Children of William Tucker, senr.

GENERATION 2.—William Tucker had two children, William and Hannah. This William was affected by 'swollen legs' and 'attacks'. He died in 1870. Hannah also had 'swollen legs' and 'attacks'. She died in 1864 when 70 years of age. She had married a Mr. Wherrell, and our patient is one of her descendants.

Children of William Tucker, junr.

GENERATION 3.—William Tucker, junior, had two children, Eliza and Alfred. Eliza had 'swollen legs' and 'attacks'. She married, but had no children, and died in 1860 of scarlet fever. Alfred is still alive, and is quite free from the swollen-leg complaint, as are his children also, so far as we have been able to trace them.

Children of Hannah Wherrell (née Tucker).

Hannah Wherrell, daughter of William Tucker, senior, had the following children: Elizabeth, Henry, Mary, Hunsley, William, Harriet, and Lucy.

Elizabeth, who had 'swollen legs', went to America, and is thought to have been drowned.

Henry is alive now, aged 75, a cowman by occupation. He was first troubled by his swollen legs when he was 9 years old. The oedema was persistent, but was kept under control by bandages. At 20 years of age he had his first 'acute attack', similar to those of our patient, and he has had many 'acute attacks' since, though the last one was 25 years ago. He is hale and hearty, notwithstanding his age. The swelling affects the dorsum of the feet, and the legs nearly to the knee, where it stops suddenly. The accompanying photograph (Fig. 3) does not make the swelling very apparent, because the patient keeps his legs constantly bandaged, knowing what a size they get if the bandages are left off. The creases caused by the bandages show fairly well. Some months ago this man had to take some cows to the local market, and in running after them his bandages came off and could not be replaced; on returning home at night the legs, up to the knee, were a great size, but there was no opportunity of getting a photograph of them then. The vigour of the man, notwithstanding his age, is shown by the way he could run after the cows.

His children, George, Thomas, Henry, Silas, Alfred, Bessie, and Ellen, are mentioned again below.

Mary was normal and had two normal children.

Hunsley was herself normal, but of her six children, Ellen, Rose, Emma, and three more, one (Ellen) had the 'swollen legs' and 'acute attacks' (vide *infra*).

William was free from oedema, and died of phthisis, childless.

Harriet suffered from girlhood with the 'swollen legs' and 'acute attacks'. She died in her first confinement, and the child was stillborn.

Lucy is normal, and has a normal child.

Children of Henry Wherrell.

GENERATION 4.—George Wherrell is alive and in good bodily health, but he is of extremely poor intellect. He is free from oedema, but he is so dull and slow that he is barely able to earn his living, and he is the butt of his fellow-workmen. He has two infant children, neither of whom has the hereditary complaint so far.

Thomas Wherrell, who is now 48 years of age, has the 'swollen legs' to a moderate extent and has also had the 'acute attacks'. His present condition does not show any better in the photograph (Fig. 4) than does that of his father Henry, and for the same reason, namely, that the legs are kept constantly bandaged. The trouble is more marked in the right leg than it is in the left, but both legs are affected up to the knees and not higher. The photograph was taken immediately after the removal of bandages; it shows the creases and folds of the latter. His intellect is fairly good, but he lacks enterprise and energy; so much so that he gave up a position of trust and took one in which the wages were less in order to escape responsibility. The swelling of the legs was first bad when he was 18 years old. On three occasions during the last two years he has had 'fits', which we have not seen but which have been described by a person who saw one of them. About 7 p.m. he went out to his allotment and was talking to a man when he suddenly fell down and struggled with both arms and both legs, and frothed at the mouth. The convulsion lasted about 20 minutes. On recovery he had no knowledge of what had happened. It is possible that the attack was epileptic. On the last occasion he was going down a ladder when the seizure came on. He fell to the bottom and contused himself severely. He says that for two days before a 'fit' comes on he has 'a catch in his voice'.

We have notes of two 'acute attacks' in his legs, similar to those we have described in his daughter Alice. On November 10, 1904, at 11 a.m., when at his work, he was suddenly seized with pain in his right groin. This was immediately followed by shivering. He next had pains in the back and hip. On examination there was a large painful swelling at the back of the right thigh, and the right knee was red, painful and a little swollen. There were no varicose veins, though some of the veins looked unduly full. The upper part of the leg was normal. The lower third of the leg, the ankle, and the foot were swollen, red, and painful. Next day the patient's temperature was 100° F., the pulse rate 100, and the respiration rate 28, per minute. There was no abnormality in the cardiac sounds; indeed all the visceral system seemed natural. The thigh was now less swollen, and the knee both less swollen and less red. The foot and ankle were still red and swollen, but no longer painful or tender. On November 12 the temperature

was 100·2° F., the pulse rate 90, and the respiration rate 24, per minute. Herpes had now developed on the lips and nose. The swelling of the thigh had almost gone, the knee seemed normal, and the swelling of the foot and ankle was less, and could be pitted on pressure. The redness had spread higher up the leg. On November 13 his temperature was 99° F., his pulse rate 80, and his respiration rate 20, per minute. There was an area of redness over Scarpa's Triangle on the right side, extending thence down the course of the femoral vessels and round to the popliteal space. On November 14 the temperature had fallen to normal. The redness above the knee had all gone except for a little at the upper part of Scarpa's Triangle. The foot and leg were less swollen and less red. The next day the patient had returned to his normal state of oedema, the 'acute attack' having lasted four days, and having got well spontaneously without leaving additional oedema behind it.

The second 'acute attack' that has been watched began on May 31, 1907. On leaving work at 6 p.m. he began to shiver, and on the way home he vomited. The shivering continued until 8 p.m., when he became very hot. His right leg, which had been aching since 4 p.m., began to swell worse at 8 p.m. Next morning his temperature was 103° F., and his pulse rate 108 per minute. The right leg was hot, more swollen than usual, and painful up to the upper border of the patella. Two days later, June 3, the temperature was 98° F., the pulse rate 78 per minute, the pain in the leg was gone, and the swelling was almost back to its usual amount.

These attacks are all of the same character, and as transient as they are severe for the time being.

Henry was himself normal. His descendants, if any, are not known.

Silas has no swollen legs. He had convulsions in infancy. He is slow in speech and movement, but healthy.

Alfred is normal.

Bessie began to have 'swollen legs' when 9 years old, and the swelling steadily increased till it reached the hips, as in our own patient. She also had several of the 'acute attacks', but we have not been able to get any good account of them. She married, took to drink, and died in 1901, leaving five children, of whom one, a girl, has the 'swollen legs' already. The children are in Egypt and we have not been able to obtain further particulars of them.

Ellen is normal.

The children of Mary Wherrell.

Mary, the daughter of Hannah Wherrell, had two children, both of whom were free from the leg trouble.

The children of Hunsley Wherrell.

Hunsley, the daughter of Hannah Wherrell, had six children.

Of these, Rose, Emily, and three others were all normal.

Ellen suffers both from the 'swollen legs' and from the 'acute attacks';

we have been allowed to examine her by kind permission of her medical attendant, Dr. Mead. She is now 39. Up to 21 years of age she was perfectly healthy, and then, apparently without cause, her legs began to be affected by the family complaint. As far as she can remember, the trouble was first noticed at the level of the knees and thence very gradually spread down to the feet and toes. Her first 'acute attack' was when she was 36, fifteen years after the seemingly causeless oedema began. The 'acute attacks', though so long delayed in their first onset, are now very frequent, the longest interval between them having been three months, except during her last pregnancy, when she had none. Both legs have been attacked; on one occasion the left leg was seized before the right had quite recovered, but otherwise each 'acute attack' has been strictly unilateral. She herself says they come on either just before or just after the monthly period. They begin with a desire to yawn and stretch repeatedly, after which there is a shivering fit and intense pain in the groin. The shivering lasts about 15 minutes, the hands go blue, and the leg goes red, hot, and more swollen than its average. She has to stop in bed for three days, after which she is able to get about again, though not really well for a day or two longer.

Her present condition is as follows: The toes are swollen on their dorsal aspect; there is a deep tranverse sulcus marking the site of the metatarso-phalangeal joints; the plantar surfaces of the feet are almost normal, but the dorsum is swollen and rounded with a deep sulcus over the anterior aspect of the ankle joint; the calves are uniformly swollen, notwithstanding constant bandaging; the patellae and the outlines of the bones at the knees cannot be felt; the thighs are much enlarged, the swelling extending as high as Poupart's ligament on both sides and there suddenly ceasing. The vulva is not involved. There are no ulcers nor sore places. The patient unfortunately refuses to be photographed, and we regret this most particularly because she exhibits the condition much better than do any of the other cases we have photographed, except Alice Wherrell herself. Measurements of Ellen's legs, taken September 17, 1907, immediately after removal of the bandages she always wears, are as follows:—

Maximum circumference measurements.

	Right leg.	Left leg.
Instep	$9\frac{7}{8}$ inches.	$9\frac{7}{8}$ inches.
Calf	$17\frac{1}{2}$ „	17 „
Knee-cap	$16\frac{1}{2}$ „	17 „
Middle of Thigh	$19\frac{1}{2}$ „	$20\frac{3}{4}$ „

The patient's height is 5 feet $0\frac{1}{2}$ inch.

William and Harriett, children of Hannah Wherrell, died childless.

The children of Lucy.

Lucy, daughter of Hannah Wherrell, has one child, who is still young; it has so far escaped from the 'swollen-leg' complaint.

The children of George Wherrell.

GENERATION 5. These are two infants who, as yet at any rate, show no tendency to swollen legs.

The children of Thomas Wherrell.

Thomas Wherrell has five children, two of whom have the complaint.

Alice, aged 18, is the patient whom this paper centres round, and whose condition has been fully described above.

Mary, the next younger, is at present normal.

Edith, the next younger, is at present normal.

Emily is now 12 years old, and has begun to develop the swollen legs. Their condition is not as yet very bad, but they have to be kept constantly bandaged or they would swell out of bounds. The accompanying photograph (Fig. 5) shows very clearly the depressions produced in the oedema by her boot. The swelling is symmetrical, does not affect the feet so much as it does the legs, and stops suddenly just below the knees. The general health and activity are good. No cause could be assigned for the oedema. Emily has, like her father and sister, been subject to what we have called 'acute attacks', one of which was observed. It began on July 6, 1906, at 6 a.m., with a shivering fit which lasted till 8 a.m. She vomited, complained of headache, and had a pain along the outer aspect of the right thigh. At 9 a.m. her temperature was 101° F. At 4 p.m. her temperature was 103·2° F., and her pulse rate 116 per minute. Her visceral systems all seemed natural. Her right foot was red and swollen. An irregular circle of redness, about 9 inches wide in front and 2 inches wide behind, surrounded the right calf, and felt much hotter to the touch than did the surrounding skin. It did not project like erysipelas. The veins on the thigh and leg became unduly visible, but they were not prominent. A single lymphatic gland, not very big, could be palpated in the groin, and little pellet-like nodules could be felt in the skin around the reddened area. Next day, July 7, the temperature was 102° F., and the pulse rate 96 per minute. The redness of the right leg was more general, the foot more swollen, and a red patch was present over the patella. The patient was very sick, being unable to keep even water in her stomach. On July 8 the temperature was 98·4° F.; the swelling and redness were still present, but considerably diminished. On July 9 the leg and foot were still swollen and faintly red, but not painful. The red patch that had been on the calf was surrounded by minute raised spots, bright red in colour, discrete, and rounded. On July 10 the leg began to ache during the afternoon; during the night it 'burned', and on July 11 it was red and swollen as at first. The temperature of the reddened skin was 99·4° F. when taken with an ordinary clinical thermometer under a pad of wool, whereas that of the left leg taken in the same way was 95·4° F.; the mouth temperature at the same time was 102° F. On July 12 the mouth temperature

was 100° F. By July 16 the redness and pain had almost gone; the swelling persisted, and, as is shown in the photograph, it is present about equally in each leg. A similar 'acute attack' occurred on the left side, beginning on July 18, 1907.

James, the youngest, is as yet normal as regards his legs, but he is subject to epileptic fits.

The children of Bessie.

Bessie, the daughter of Thomas Wherrell, had five children. These are all in Egypt and cannot be seen by us personally. We have made inquiries, and we learn that four of the five are normal, but that the fifth already has the 'swollen legs', which began without apparent cause, and seem to be running the same course as have those of the other members of the family who have been affected.

The children of Ellen the daughter of Hunsley Wherrell.

Ellen has two children, both boys, one aged 10 years, the other 12 months; both of these show no tendency to 'swollen legs' at present, but it is too early to say that they are really free from the complaint.

The relationships between the different individuals we have been able to trace is shown in the Genealogical Tree, p. 317.

The diagnosis in the case of our patient, Alice Wherrell, would have been difficult if the family history had not been so definite; but with that it was clear that the condition was very similar to, if not identical with, that described at length by Milroy in America in 1892, as 'An undescribed variety of Hereditary Oedema', and in France in 1898 and later years by Henry Meige as 'Trophœdème chronique héréditaire'. The only account that we have found of any similar family in England is that of H. D. Rolleston in his paper upon 'Persistent hereditary oedema of the lower limbs', in 1902. The literature contains fairly numerous isolated cases, but the fullest accounts of the condition are given by the authors just mentioned.

Milroy's cases are the most numerous—22 affected persons amongst 97 individuals in six generations. Meige's cases numbered 8 affected persons in four generations. Rolleston's cases numbered 3 in two generations. Our own number 13 out of 42 persons traced in five generations. In France the condition is termed Meige's disease. If priority of description is to count for anything, and if the disease is to be named after a person, it should be called Milroy's disease. If no person's name is to be included in the title it may be well styled 'persistent hereditary oedema of the lower limbs', after Rolleston, until its pathology is better known and a shorter scientific name for it can be devised.

The Differential Diagnosis.

It will scarcely be necessary to go into the differential diagnosis in great detail. This has already been done by Meige in a very able manner. Suffice

it to say that cardiac, pulmonary, renal and haemic causes for the oedema can be rapidly excluded, and that myxoedema, though possibly a real difficulty in some cases, can usually be excluded by the normal conditions of the rest of the body, by the presence of the thyroid gland, by the fact that the oedema is real and not merely apparent, and by the fact that the administration of thyroid extract does not ameliorate the condition of the legs.

It soon becomes clear that there is almost certainly a local cause for the oedema, and the three chief local causes that might produce a similar condition would seem to be:—

(1) Venous obstruction or thrombosis.

(2) Lymphatic obstruction.

(3) Errors in the behaviour of the blood vessels or lymphatics, without there being any actual obstruction to them—vasomotor neurosis.

The relation between the 'swollen legs' and the 'acute attacks'.

Before we can go further with the discussion of the last paragraph it will be necessary to say a word or two as to the relation between the 'swollen legs' and the 'acute attacks' which so many of the above patients have had. If an 'acute attack' were always the first thing, then it would be very difficult to exclude venous thrombosis or lymphatic obstruction, secondary to inflammation, as a cause for the oedema. The remarkable thing is that the 'swollen legs' have come on gradually, without any assignable cause; and in one case the 'swollen legs' had been present for five-and-twenty years before any 'acute attack' occurred at all.

It seems clear, therefore, that the 'acute attacks' are either accidents, or at most concomitants, rather than essential factors in the oedema. We do not know what is the nature of the 'acute attack', and we shall discuss it again when we mention angioneurotic oedema; but we are bound to admit that, though possibly a 'vasomotor phenomenon', each acute attack bears some resemblance to a temporary microbial infection comparable with erysipelas. The rigor, the pyrexia, the painfulness of the part affected, the vomiting that may occur at the same time, all suggest microbial infection. On the other hand, the attacks are remarkably transient, lasting but three or four days; they pass away spontaneously without any particular treatment; and they seem to be quite free from danger, for not one of the patients has died of septicaemia, even when the 'acute attacks' have been constantly repeated. Upon the whole we are inclined to think that the 'acute attacks' are not due to sepsis, or at least that they are not primarily due to micro-organisms, but rather to vasomotor troubles. Be this as it may, our point is that the oedema precedes any 'acute attack', and may precede it by as much as twenty-five years. There seems, therefore, to be none of the ordinary causes of venous thrombosis or of lymphatic obstruction underlying the oedema.

Other reasons for excluding venous thrombosis or lymphatic obstruction.

Besides the above, there are other reasons for excluding venous thrombosis or lymphatic obstruction as the original cause for the oedema. First, there is the distribution of the swelling. The cases recorded by Meige agree with ours in the fact that the oedema receives a sudden limitation at the level of a joint. In Alice Wherrell it for some time ceased at the ankle; we have several cases in which the oedema stops at the knee, and several others in which it stops at the hip or groin. The oedema does not stop gradually, moreover, but suddenly, and does not involve the vulva or the abdominal wall, although it may become extreme immediately one passes down over Poupart's ligament. This would be difficult of explanation if the obstruction were in the pelvis; and, when the swelling is bilateral, it is difficult to understand how any obstructive lesion in veins or lymphatics should be well marked right up to Poupart's ligament on both sides and yet not extend into the pelvis in any single one of the patients recorded by Milroy, Meige, Rolleston, ourselves, or any of the observers we can find. Venous obstruction seems unlikely on this further ground, namely, that the circulation in the affected legs seems to be quite good; a patient over 70 who has had the oedema all his life has been able to run about after cows, so that his muscles must have been well supplied with blood. Visible distension of the veins in the legs is a rarity in the cases. The feet are not unduly cold. It is conceivable that there might be some congenital abnormality in the structure of the lymphatics from Poupart's ligament downwards; but against this view are the facts that it may be twenty years before the oedema sets in, that when it does set in it may be restricted to the level of the knee for years before it reaches to Poupart's ligament, and that when it spreads at all it spreads at one time the full distance from one joint level to the level of the next joint above (Meige). Upon the whole, therefore, although it cannot be called a very satisfactory explanation, we think, with Milroy, Meige, and others, that the oedema in these cases is secondary, not to gross structural changes in the blood vessels or lymphatics, but to an error in the functions of these vessels, presumably, or at least possibly, resulting from erroneous functions in the nerves supplying them —in other words we think the condition is primarily a *vasomotor neurosis.*

The relation of these cases to those of angioneurotic oedema and of other vasomotor neuroses.

There are three well-known conditions in which vasomotor neurosis is generally held to be at the root of the affection. These are Raynaud's disease, factitious urticaria, and angioneurotic oedema.

These are so distinct in their objective manifestations that it would not be at all surprising if other, and at first sight wholly different, manifestations of vasomotor neurosis were possible. Our cases show little in common with Raynaud's disease; that is to say they could scarcely be mistaken for cases

of Raynaud's disease, although, in addition to their oedema, cold weather causes several of the patients to suffer from blueness of the hands, which to some extent resembles Raynaud's disease. Similarly, they could not be taken for cases of factitious urticaria. Nor could they, we think, be taken for a variety of angioneurotic oedema in the ordinary sense of the latter term. Nevertheless, there are distinct points at which angioneurotic oedema and our cases of Milroy's disease come close together—notably in the strongly marked hereditary disposition, and possibly in the 'acute attacks' to which many of the above patients were subject. It seems likely that Raynaud's disease, factitious urticaria, angioneurotic oedema, and Milroy's disease are related to one another pathologically, but that their objective manifestations are so well defined and so different that these different kinds of vasomotor neuroses merit distinctive names. It may be noted that, apart from the 'acute attacks', our cases had absolutely painless swelling of the legs, and no general disturbances of health at all, whereas during the 'acute attacks' there was considerable constitutional disorder, sometimes with marked vomiting for a short time, comparable to the colic, nausea, and vomiting often seen during exacerbations of angioneurotic oedema. So like the latter were the 'acute attacks', except in so far as they were confined to the legs instead of varying in place and affecting body, face, hands, arms or throat, that we felt very much inclined to call them definitely 'angioneurotic attacks'. This, however, we have refrained from doing, because we cannot bring forward absolute proof that they were angioneurotic.

The incidence of other nervous complaints in the family.

It is often a very difficult thing to elicit a history of insanity or fits in a family. Nevertheless it is interesting to observe that Alice Wherrell's uncle George is of weak intellect and the village butt; that her father Thomas has had three 'fits', which seem to have been very like epilepsy; that Silas is slow-witted; that Bessie was a dipsomaniac; that Alice herself has had an attack of garrulous mania, with delusions; and that her brother, James, a young boy, has already had many epileptic fits. A similar history of epilepsy in members of a family in which other members are subject to the trophoedema of the legs has been noted by other observers, and the point is of interest in connexion with the angioneurosis that is supposed to be at the root of the trophoedema.

The points in which our cases resemble, and the points in which they differ from, those recorded by others.

The points in which our cases and those recorded by others closely resemble one another are as follows:—

(1) The restriction of the oedema entirely to the legs.

(2) The absence of any traceable cause for the oedema, general or local.

(3) The strong family predisposition to the complaint.

(4) The painlessness of the pale swollen legs (apart from the 'acute attacks' in our cases).
(5) The absence of constitutional symptoms.
(6) The sharpness of limitation of the upper level of the oedema.
(7) The incidence in both males and females.
(8) The permanence of the oedema when once it has appeared.

There are certain points, however, in which our cases differ from those of others. Meige, for instance, lays stress upon the absence of 'acute attacks', which occurred on more than one occasion in most of ours. Milroy lays stress upon the oedema being present at birth; Meige lays stress upon its appearing at puberty; in our cases not once was it actually noted at birth, and the age at which it first attracted attention was sometimes in infancy, sometimes in boyhood or girlhood before puberty, sometimes not until the teens were passed.

The fact that there are differences such as these is not to be wondered at, seeing that the cases recorded by each individual observer all belong to one family, and are, therefore, likely to resemble one another, but to differ in details from cases arising in a different family observed by some one else. Small points of difference by no means indicate differences in kind; they may well be but family variations in the same condition.

Comparison with muscular dystrophies.

Several observers have aptly compared this disease to that of the muscular dystrophies; the latter may be present at birth (congenital), or they may develop later (hereditary). Similarly, it seems that trophoedema of the legs may be congenital and present at birth, as in Milroy's cases, or it may be hereditary and only develop later at a constant period after birth (puberty), as in Meige's cases, or at a variable period after birth, as in ours.

The treatment of the condition.

Little treatment is required in the majority of the cases, beyond firm and constant bandaging of the legs. Several of our cases lived to over 70 years of age, having suffered from the complaint for 60 years or more, but having kept the swelling in check by constant bandaging.

The 'acute attacks', dangerous though they look, pass away spontaneously in a few days, and all that can be done for them is to relieve the pain by putting the patient to bed and applying anodynes to the affected part.

Our own patient's condition had passed all bounds so far as keeping the oedema in check by bandaging was concerned, and all treatment for the condition was a failure as regards ameliorating it. The oedema always diminished to some extent with rest in bed, and firm bandaging was a relief to the patient when she was able to get up after such rest. Medicinal treatment of various kinds was tried in vain—thyroid extract, diuretics, purgatives, potassium iodide, mercury, intestinal antiseptics, bromides, valerianate of zinc, and so forth. None made

the least impression on the leg condition. One observer has recorded benefit in one case from electrical treatment, and one or two have recommended massage. The latter may alleviate the oedema temporarily, but when the swelling has got beyond bounds, as in the case of Alice Wherrell, it seems next to impossible to restore the normal conditions again. The important point seems to be to recognize the nature of the trouble early, and to keep the legs bandaged constantly from the first, so that no large increase in the oedema can occur. It may then be held in check for a great many years, as may well be seen in the photograph of the two men. These two know full well what would happen if the bandages were long off whilst they were upright, and they will not leave the bandages off at all; otherwise the photographs of them would show a great deal more oedema than they do.

The effects of pregnancy on the condition.

Several female members of the family married when the trophoedema was well advanced. It might have been thought that the oedema of the legs would certainly have been made materially worse by pregnancy. This has not been the case, and in one instance, in which the 'acute attacks' had been frequent previously, they were in complete abeyance throughout a pregnancy. The fact that the leg condition is not made materially worse by pregnancy may, perhaps, be an additional argument against lymphatic or venous obstruction being its cause, and, therefore, indirectly in favour of the angioneurotic view.

Transmission by an unaffected mother.

It is a point that will, perhaps, interest those who pay attention to the family transmission of peculiarities that Hunsley, the daughter of a woman who had the family complaint, was not herself affected, but transmitted the trouble to her daughter Ellen. If one had the opportunity it would be interesting to see whether any of Ellen's children, escaping the trouble themselves, will one day have children who are affected.

Conclusion.

The family of which we have given an account seems comparable, with minor differences, to those described by Milroy, Meige, Rolleston, and others. The chief points in the malady from which certain members of the family suffered—13 out of 42 individuals in five generations—are summarized on pages 326 and 327, the most obvious being painless persistent oedema of one or both legs, arising apparently without cause, and apart from any constitutional ill health. The malady has received various names, of which we select Persistent Hereditary Oedema of the Legs, or Milroy's disease. The disease affects both males and females, and is not itself inimical to life; though in some cases the oedema becomes so like elephantiasis that locomotion is greatly impeded, or even rendered almost impossible, as in the case of Alice Wherrell. There is often a history of epilepsy or other nervous disorder in the same family. Our cases, unlike those

of some observers, were subject to what we have described as 'acute attacks', many of which we have described in detail. The condition differs objectively very much from Raynaud's disease, factitious urticaria, and angioneurotic oedema, but we think that there is evidence that underlying both these three conditions and our cases of Milroy's disease there is a common pathology, namely that of a vasomotor neurosis.

LITERATURE

Crozier Griffith and Newcome, 'Types of Oedema in Infancy and Childhood,' *Transactions of the Association of American Physicians*, Phil., 1897, xii. 411.

Debove, 'Œdème segmentaire des membres inférieurs,' *Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris*, Paris, 1897, series 3, xiv. 1172.

Desnos, 'Œdème rhumatismal chronique,' *Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris*, Paris, 1891, series 3, iii. 65–73.

Follet, 'Œdème névropathique consécutif à des poussées d'œdème angio-névrotique,' *Thèse de Paris*, 1895.

Hertoghe, 'Contribution à l'étude du trophœdème chronique,' *Nouvelle Iconographie de la Salpétrière*, Paris, 1901, series 3, vi. 496.

Higier, 'Œdème aigu et chronique dans quelques névroses et en particulier dans l'hystérie,' *St. Petersburger medicinische Wochenschrift*, 1894, iv. 50.

Lannois, M., 'Hereditary Chronic Oedema of the Lower Limbs,' *Nouv. Icon. de la Salp.*, Paris, 1900, xiii. 631; and *Medical Review*, 1901, iv. 99.

Mabille, 'Observations de Trophœdème,' *Gazette hebdomadaire de Médecine et de Chirurgie*, Paris, 1902, vii. 159.

Manheimer, 'Troubles vasomoteurs d'origine hystérique,' *Archives de Neurologie*, 1896, series 2, ii. 186–198.

Mathieu, 'Sur une forme d'œdème névropathique' (pseudo-éléphantiasis névropathique), *Annales de Dermatologie et de Syphiligraphie*, Paris, 1893, series 3, iv. 11–16.

Meige, Henry, 'Dystrophie œdémateuse héréditaire,' *Comptes rendus du IX^e^ Congrès des Médecins aliénistes et Névrologistes tenu à Angers le 4 août* 1898.

Meige, Henry, 'Dystrophie œdémateuse héréditaire,' *Presse Médicale*, 1898, no. 102, 341.

Meige, Henry, 'Le Trophœdème chronique héréditaire,' *Nouvelle Iconographie de la Salpétrière*, Paris, 1899, xii. 453.

Meige, Henry, 'Sur le Trophœdème,' *Nouvelle Iconographie de la Salpétrière*, Paris, 1901, xiv. 465.

Meyer, Georges, 'Elephantiasisartige Anschwellung beider Unterschenkel nebst eigenartigen vasomotorischen Störungen an den Händen und Füssen,' *Deutsche medicinische Wochenschrift*, Leipzig and Berlin, 1894, xx. 519–521.

Milroy, W. F., 'An Undescribed Variety of Hereditary Oedema,' *New York Medical Journal*, 1892, lvi. 505–508.

Rénon, 'Éléphantiasis nostras,' *Séances et Mém. de la Société de Biologie*, Paris, 1897, iv. 343.

Rolleston, H. D., 'Persistent Hereditary Oedema of the Lower Limbs,' *Lancet*, Lond., 1902, ii. 805.

Sainton et Voisin, 'Contribution à l'étude des Trophœdèmes,' *Nouvelle Iconographie de la Salpétrière*, Paris, 1904, xvii. 189–192.

Sicard et Laignel Lavastine, 'Trophœdème chronique, acquis et progressif,' *Nouvelle Iconographie de la Salpétrière*, Paris, 1903, xvi. 30–36.

Souques, 'Éléphantiasis nostras symétrique du pied et de la jambe,' *Iconographie de la Salpétrière*, Paris, 1890, iii. 281–288.

Tobiesen, 'Ueber Elephantiasis congenita hereditaria,' *Jahrbuch für Kinderheilkunde*, Leipzig, 1899, xlix. 392.

Tschirkoff, 'Œdèmes vaso-moteurs sans albuminurie,' *Revue de Médecine*, Paris, 1895, xv. 625–642.

DESCRIPTION OF PLATES

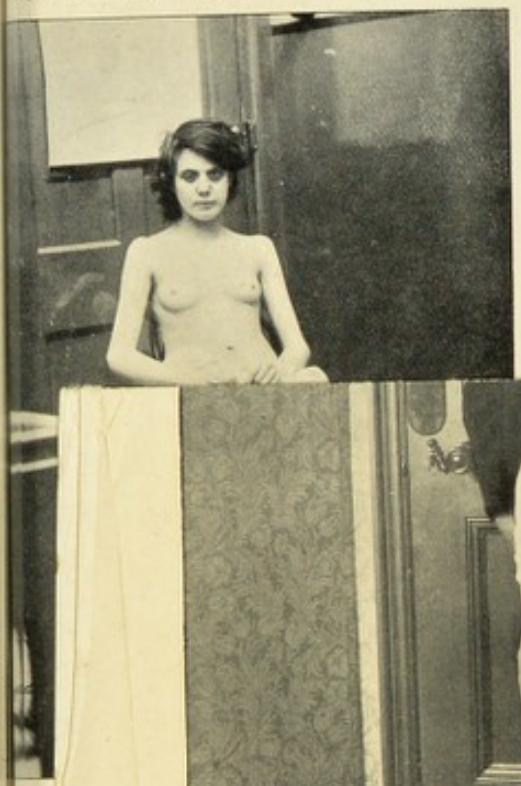
FIG. 1. Alice Wherrell, Persistent Hereditary Oedema of the legs.

FIG. 2. Alice Wherrell, Persistent Hereditary Oedema of the legs.

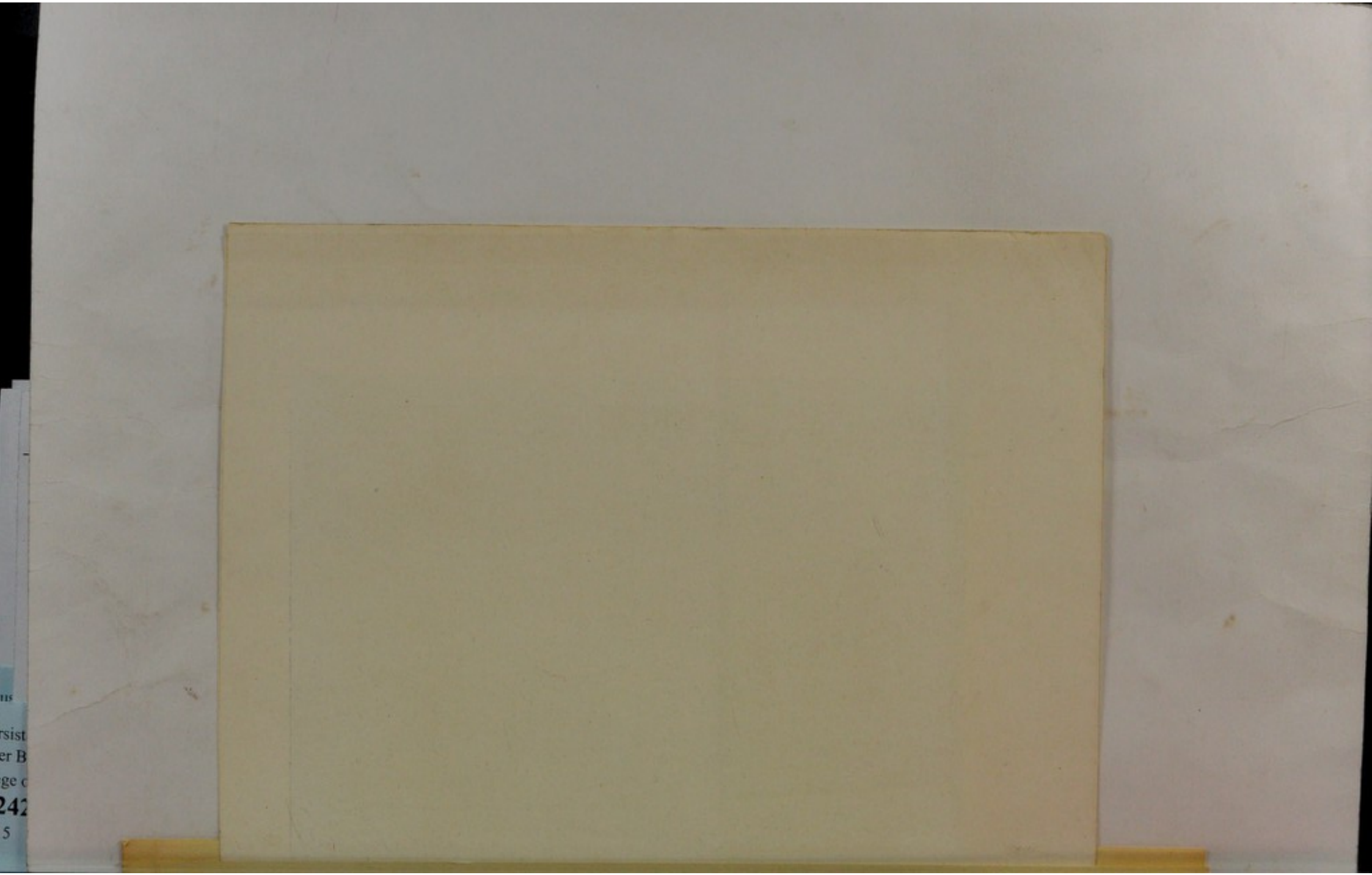
FIG. 3. Henry Wherrell, grandfather of Alice. The leg-bandages have just been removed. The Oedema has been present for 66 years.

FIG. 4. Thomas Wherrell, father of Alice. The leg-bandages have just been removed. The Oedema has been present for 30 years.

FIG. 5. Emily Wherrell, sister of Alice. Persistent Hereditary Oedema of the legs is beginning to develop.



F



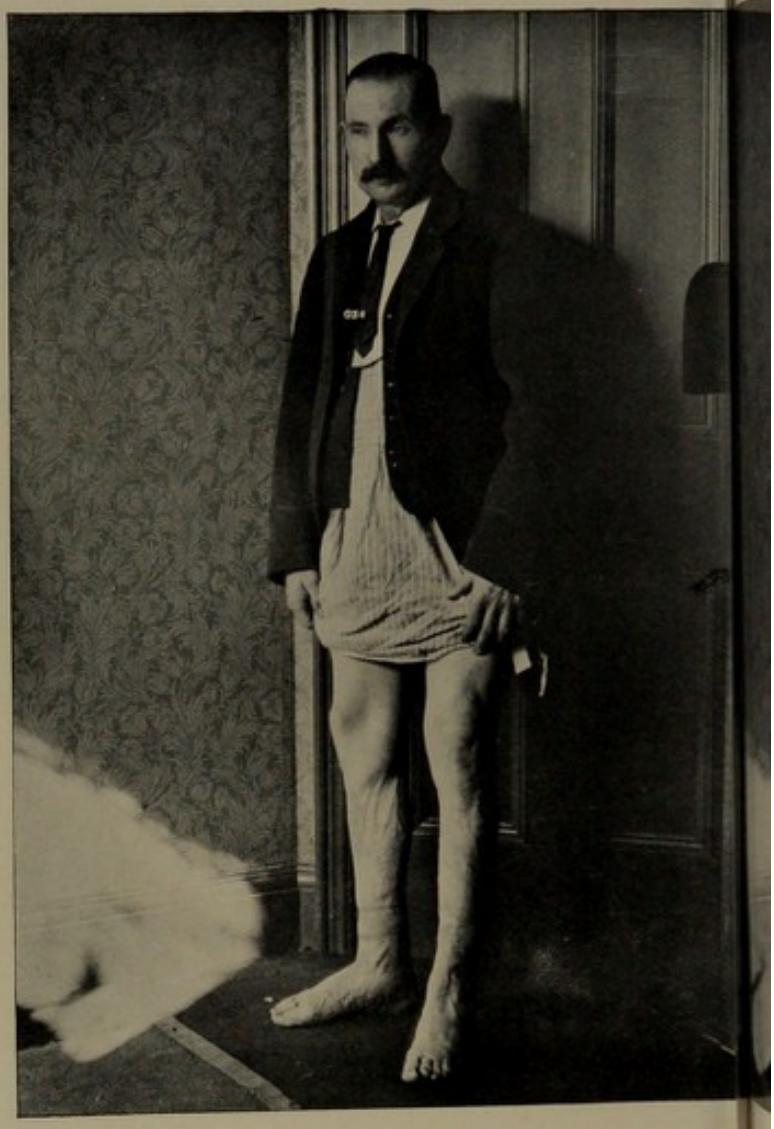


Fig. 4

Fig. 5