promyelocytes, and myeloblasts formed from about 20 to 50% of the total for the first two weeks, gradually falling with the count (Table I). It has already been mentioned that the question of agranulocytosis following sulphadiazine was raised after the first count. In our experience, however, it is unusual to find early granulocytes in the peripheral blood in agranulocytosis except during recovery. Generally the polymorphs drop suddenly without warning, and no precursors reach the peripheral blood until regeneration of the marrow is taking place. In this case, also, only 8 g. of sulphadiazine had been given. The alternative suggestion of acute leukaemia appeared at first to fit the severe anaemia with myeloblasts in the peripheral blood, but sternal puncture did not confirm this. The findings of a definite megaloblastic reaction in the marrow suggested rather a deficiency of the haemopoietic principle, and it seemed probable that this was the primary abnormality and that the high proportion of myeloblasts was due to a coincident failure of maturation of the granulocytes rather than a true leukaemic change.

Although liver therapy was not begun until a late stage in the disease, the poor response to the three preparations used seems to indicate the refractory nature of the anaemia. Defective absorption from the intestine may have been partly responsible for producing the anaemia, since proteolysed liver was even less effective than neohepatex. Nutritional deficiency might also account for the failure in maturation of the granulocytes.

Summary

A case of megaloblastic anaemia of pregnancy is described.

An unusual feature was the marked immaturity of the circulating granulocytes simulating an acute myeloblastic leukaemia.

The case proved refractory to various types of liver therapy and to blood transfusion.

ADDENDUM

Since the completion of this paper, blood and sternal marrow films were referred to one of us (M.G.) from another L.C.C. hospital for diagnosis. The patient, a married woman aged 34, had been treated by her doctor for acute tonsillitis and various other complaints with 70 g. of a sulphonamide over a period of five weeks. On admission she complained of giddiness and faintness of two weeks' duration, and her blood count on Dec. 8, 1947, was: red blood cells, 1,000,000 per c.mm.; haemoglobin (Sahli), 24%; colour index, 1.2; white blood cells, 13,000 per c.mm. (neutrophil polymorphs 9%, promyelocytes 77%, myeloblasts 14%); mean cell diameter 7.8 μ ; nucleated red blood cells, 21 per 100 white blood cells (normoblasts 15, megaloblasts 6); anisocytosis ++, poikilocytosis +, polychromasia ++.

The patient was transfused with 2 pints (1.14 litres) of blood, and on Dec. 10 the sternal marrow films showed the following distribution:

Neutrophil polymorphs	..	..	..	1.5%
Metamyelocytes	..	..	..	0.0%
Myelocytes	..	..	..	0.5%
Promyelocytes	..	..	..	30.0%
Myeloblasts	..	..	..	11.0%
Lymphocytes	..	..	..	4.0%
Normoblasts, late	..	..	..	7.5%
" intermediate	..	..	..	2.5%
" early	..	..	..	0.0%
Megaloblasts, late	..	..	..	11.5%
" intermediate	..	..	..	20.0%
" early	..	..	..	9.5%
Proerythroblasts	..	..	..	2.0%

Myeloid/erythroblast ratio = 1:1.2

Since both the peripheral blood and marrow resembled the case described above the patient was treated with liver and iron but showed no reticulocyte response. After two further transfusions on Dec. 12 and 17 her red blood cells rose to 3,800,000 per c.mm. and haemoglobin to 73%. Although she was given penicillin throughout her stay in hospital she developed pneumonia on Dec. 19 with Friedländer's bacillus and *Ps. pyocyanea* in the sputum. The blood count was maintained without

further transfusion and the white cells, which had dropped to 750 per c.mm. on Dec. 20, rose to 9,000 per c.mm. on the 24th, with a much lower percentage of primitive cells. The patient died on Dec. 25. Post-mortem examination showed bronchopneumonia and an extremely cellular bone marrow. Sections showed the majority of cells to be of the red cell series and apparently megaloblastic.

The similarity between the two cases is striking. Both showed extreme anaemia with megaloblasts and primitive white cells in the peripheral blood and a megaloblastic reaction in the marrow, and both failed to respond to liver. Aetiologically, however, the two cases differed: in the first case pregnancy, and in the second the excessive dosage of sulphonamide, were apparently the main contributory factors.

We are indebted to Dr. R. D. Green, of Paddington Hospital, for the clinical notes of the second case.

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HEREDITARY OEDEMA (MILROY'S DISEASE)

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Reports on a heredo-familial variety of oedema of the lower limbs were published almost simultaneously by Nonne (1891) and Milroy (1892). A few years later Meige (1899) reported a further series of cases. The condition described as hereditary oedema, or eponymously as Milroy-Nonne-Meige disease, has since been recognized as a distinct clinical entity, having been recorded by many physicians in various countries. References in British literature have, however, been relatively scanty, the only one in recent years being that of Weber and Schlüter (1937). The main features of Milroy's disease are here summarized.

Aetiology.—The disease is hereditary. Milroy's original family of 97 persons in six generations presented 22 cases. Meige reported eight cases in four generations, Hope and French (1907) 13 cases in five generations of 42 persons. Gates (1946), analysing the family described by Hope and French, considers the hereditary trait to be a Mendelian dominant, but notes that in one affected person it was transmitted through an apparently normal mother. Two unaffected mothers in the third generation of Milroy's family passed the tendency on to some of their offspring. Such a skipping of a generation is common in human dominant pedigrees. Both sexes are affected. The cause of the oedema is not known; it is not related to the usual general or local causes of oedema, such as cardiac or renal disease, venous or lymphatic obstruction. Meige postulated a "congenital malformation of trophic centres in the spinal cord," though this has never been proved. Hope and French compare the disease with other heredo-familial disorders of the vasomotor system, such as angioneurotic oedema, Raynaud's phenomenon, and urticaria, and suggest that it may be a "vasomotor neurosis." Milroy (1928), in a review of the condition.

agrees with this point of view, favouring a local cause, such as an abnormality of function of veins or lymphatics, of neurogenic origin.

Pathology.—A necropsy has not yet been recorded on a case of Milroy's disease, and the only microscopical study which appears in the literature is that of McGuire and Zeek (1932), who report the results of biopsy in a typical case. Microscopy of a portion of the skin and subcutaneous tissue showed a normal epidermis but a marked condensation of the superficial portion of the dermal papillary layer composed of fine collagen fibrils which in some places were undergoing hyalinization; oedema was more pronounced in the dermis, and this, together with an increase of collagen fibres, produced a great increase in the proportion of dermis to epidermis. There was a considerable sprinkling of lymphocytes related to the capillaries and venules. The subcutaneous tissue was also thickened, consisting of masses of oedematous fatty tissue and pools of colourless fluid not contained within definite limiting boundaries. The appearance contrasted with that of fresh necropsy material obtained from cases of cardiac and renal dropsy; in these the dermal papillae were flattened and much less obvious.

Clinical Features.—The age of onset varies in the different families recorded. In Milroy's series all but two showed oedema at birth. In one of these two the oedema started at the age of 12; in the other, one swollen foot was present at birth, the other limb being normal until the age of 20, when, following an injury, it became rapidly and permanently swollen. All of Meige's cases had their onset at puberty. In the family recorded by Hope and French (1907) oedema began in infancy, childhood, or adolescence. As each author has described a single family, differences in age of onset and other features may, as Milroy (1928) pointed out, be considered to be familial variations of an essentially identical disorder.

The oedema begins in the toes, gradually spreads up the limb, but never extends above the level of the inguinal ligament, where it is sharply demarcated; it may remain at lower levels, especially joints, for long periods. At first the oedema pits readily on pressure, though later the tissues become more indurated and thickened, and is reduced by rest with elevation of the limb. One or both limbs may be affected. There are no constitutional disturbances and the disorder is compatible with long life. Another remarkable feature of the condition is the absence of disability; in spite of grossly swollen limbs affected persons may be quite capable of a normal existence. One of Milroy's (1928) patients was a Burma missionary who wrote that he found no difficulty in tramping distances of 30 miles a day over rough mountain track. The oedema appears to be permanent, with the remarkable exception of another of the cases mentioned by Milroy (1892) (unfortunately not seen by Milroy himself). This patient was born with oedema of one foot, and at puberty developed swelling of the testicles which became sufficiently great to necessitate orchidectomy, and at the same time the swelling of the foot disappeared.

In addition to the above clinical features Hope and French (1907) described acute attacks in many of their patients in which the affected limbs suddenly became red, painful, tender, and much more swollen; there was no obvious cause for the onset or remissions of these attacks.

Treatment.—Because of the minimal symptoms there is usually no indication of any treatment other than bandaging to control the size of the limb. Among patients with oedema of the limb treated by the Kondoleon operation Sistrunk (1918) records two cases with oedema of the lower limb in which the clinical histories suggest a diagnosis of Milroy's disease; good results were obtained, and this suggests that surgery may be useful if there is serious disability.

Case Report

An apprentice engineer aged 19 was referred by Dr. Hugh Garland from his out-patient clinic at the General Infirmary at Leeds and admitted to St. James's Hospital, Leeds, complaining of swelling of his right leg and his scrotum. He had had no previous major illness. There was no history of "allergic" disease or of infection in the legs. He had never been out of this country.

Family History.—The patient was the youngest of three children. His parents were not blood relatives. His elder sister, a housewife aged 24, had noticed swelling of her right leg when she was 14. Up to the age of 20 she had worked in a factory and the swelling was then severe at the end of the day, and at its worst had extended from ankle to knee. When seen by us the left leg appeared normal; the right leg showed a pitting oedema involving the ankle and the lower third of the right calf. There was no other evidence of disease of any kind. She had had no children. The younger sister, a housewife aged 22, had no history of oedema and no abnormality on examination. She had one child, a boy aged 2, with no abnormality. The father, aged 52, had no abnormality on examination. The mother, aged 45, one of twelve siblings, though showing no abnormality of the lower limbs on examination, herself asserted that since puberty she had noticed her ankles to be swollen at the end of a day's work. No history was obtained of any oedema of the limbs in preceding generations on either side, nor was there any history of familial disease.

History of Illness.—The patient first noticed swelling of his right ankle at the age of 17, which was painless and decreased at night after rest. It had gradually and steadily increased, spreading upwards to involve the whole of the leg. He had also noticed swelling of the scrotum, which he thought had begun at about the time the leg swelling had reached the groin. He thought the condition had been stationary for the four months before admission. Despite the size of the leg there had been little interference with function and he led a normal life. He had had no acute exacerbation of the condition, nor anything suggestive of infection in the leg. It seems that puberty had not been reached until the age of 17 and had roughly coincided with the onset of the oedema. He was shaving only once a week at 19.

On examination he was a slimly built youth who looked younger than his age. There was little facial, axillary, or pubic hair. The left leg was normal. There was massive pitting oedema of the right leg, sharply limited above by the inguinal ligament and fading towards the toes, which appeared normal when first seen. The colour and temperature of the limb were normal. There were no trophic disturbances of the skin and no enlarged veins. After he had worn slippers for two days the oedema spread into the toes. The scrotum was not oedematous. There was bilateral hydrocele, left larger than right. After the hydroceles were tapped the testicles were found to be bilaterally and symmetrically enlarged, and testicular sensation was much diminished. After complete rest in bed the oedema decreased steadily, the minimum size being reached in five days; it increased to its maximum in three days when the patient was allowed up again. (See illustration.)

Measurements

	On Admission				After 5 Days at Rest			
	Right		Left		Right		Left	
Mid-foot	in. 10	cm. 25.4	in. 9	cm. 22.8	in. 8½	cm. 22.3	in. 9	cm. 22.8
Ankle	12½	31.75	9	22.8	9	22.8	9	22.8
Calf 4 in. (10 cm.) below patella	16½	41.9	12	30.5	13½	34.5	12	30.5
Mid-thigh	20½	52.0	16	40.6	17½	44.5	16	40.6

Laboratory Tests.—Haemoglobin, 108%; leucocytes, 6,500 per c.mm. (44% polymorphs, 52% lymphocytes, 4% monocytes). Blood potassium, 21.2 mg. per 100 ml.; blood urea, 19 mg. per 100 ml.; serum protein, 7.7%; chlorides (as NaCl), 0.57%; creatinine, 1.7 mg. per 100 ml.; uric acid, 4 mg. per 100 ml. Glucose-tolerance test normal. Urine: S.G. 1026, acid; no albumin, sugar, casts, or cells. Urinary chlorides, 7.4 g. in 24 hours. Fractional test meal, normal curve. Histamine

skin sensitivity test, no reaction. Radiograph of bones normal. Wassermann reaction negative.

Treatment.—The patient suffered very little disability from his oedema and was quite able to enjoy a normal life. He complained of some "tiredness" of the affected limb at the

end of the day, but despite this he would voluntarily indulge in gymnastic exercises after a full day's work. No surgical intervention was therefore advised. Firm bandaging had some effect in controlling the oedema and also gave him a feeling of support.

Discussion

Examples of unilateral or bilateral oedema of the extremities for which no obvious cause can be discovered are not infrequently encountered; cases with a clear hereditary or family history are, however, much less common, and few have been recorded in British medical literature. The question arises whether patients who display the typical oedema of one or both lower limbs as described above, but who lack the appropriate family history, should be regarded as suffering from Milroy's disease. In this connexion we note that Parkes Weber, discussing at a meeting of the Royal Society of Medicine a family of four sisters in whom oedema of the legs began between the ages of 20 and 23 (Weber and Schlüter, 1937), considered that if the other features were present a family history was not essential for the diagnosis, and for that reason preferred the eponym Nonne-Milroy's disease to the term hereditary oedema. However, the heredo-familial factor in the classical descriptions quoted above is so striking that it seems to justify a separate nomenclature for the hereditary and non-hereditary forms. In describing the aetiological factors it was noted that one unaffected person in the family reported by Hope and French (1907) and two unaffected persons in the family reported by Milroy (1892) produced affected offspring. Apart from these gaps, however, the line of inheritance is direct. It appears, therefore, that the responsible gene is transmitted as a Mendelian dominant with occa-

sional skipping of a generation. In view of this possibility of skipping, the fact that the disease has been recognized for the first time in members of a particular generation does not rule out the likelihood that it has been handed down from earlier generations, especially when it is remembered that the manifestations may be minimal, easily missed by patient and doctor. (In the families described above there was considerable case variation in the degree of oedema, and this was also found in the family reported by us.) Alternatively the condition may arise as a mutation, though this is impossible to establish.

Apart from the description by Milroy (1892) of the patient with testicular enlargement and subsequent disappearance of the oedema, we have not discovered any record of a patient who, like the one we have reported, suffered also from hydrocele and testicular abnormality. While there seemed to be definite evidence of diminished testicular function, it is not clear that there was any relation between this and the oedema, nor would it justify in itself any suggestion that an endocrine factor plays a part in the production of the oedema. Although the disorder has been recognized for over fifty years, the ultimate mechanisms responsible for the chief symptoms remain obscure.

Summary

Milroy described a hereditary form of oedema of the lower limbs for which there was no obvious cause.

This condition produces little or no disability.

A typical case, with bilateral hydrocele and delayed puberty, is described.

We wish to acknowledge our thanks to Dr. Hugh Garland, consulting physician to St. James's Hospital, and to Dr. J. A. Fraser Roberts for much helpful advice and criticism. Dr. W. McIntosh, Medical Director of Leeds Municipal General Hospitals, kindly granted permission to publish this case. Our thanks are also due to Miss C. E. Campbell for the photograph.

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TWO CASES OF PERIARTERITIS NODOSA WITH OBSERVATIONS ON AETIOLOGY, DIAGNOSIS, AND TREATMENT

BY

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Periarteritis nodosa was first described by Rokitsansky in 1852. Kussmaul in 1866 related symptomatology to clinical findings, and during the next 76 years some 350 cases of the disease were reported. Here are recorded two further cases.

Case 1

This patient, a Merchant Navy man, aged 43, was admitted to the Western Infirmary, Glasgow, on Oct. 20, 1946. He complained of an aching pain in the muscles of his back and legs, epigastric discomfort, anorexia, and loss of weight for four weeks. This had been associated with a low-grade pyrexia. He had had malaria in 1938, and in 1939 was treated for staphylococcal empyema by rib-resection and with sulphapyridine over a long period. Sulphonamides had also been administered three weeks and again three days before admission to the infirmary.

On admission the abdomen showed slight generalized distension. It was "doughy," and on palpation the epigastrium and