FAMILIAL MEDITERRANEAN FEVER

A CAUSE OF PERIODIC FEVER

BY

A. ERIC DORMER, M.D., M.R.C.P.

AND

J. F. HALE, M.A., B.M., M.R.C.P.

*Medical Professorial Unit, St. Bartholomew's Hospital,
London*

In the heterogeneous group of diseases of unknown aetiology described as "periodic disease" (Reimann, 1951) some exhibit recurrent fever. One such is familial Mediterranean fever, which has also been called familial recurring polyserositis, and a case presenting in England is here reported.

Case Report

A man, born in 1900, was admitted to St. Bartholomew's Hospital in 1959 for the investigation of an illness in which periodic fever and proteinuria became dominant features. He had lived in England all his life, and had been at work up to the time of his admission. His father, an Italian of non-Jewish stock, had married an Englishwoman and had died of "Bright's disease" when aged 29. No significant illness had affected his mother, his five siblings, or his two daughters, aged 22 and 21.

In 1939 he had an appendicectomy, and when a haematemesis followed this operation a partial gastrectomy was done. In 1955 he noticed slight slurring of speech, followed two years later by some tremor of the arms and legs. His gall-bladder, removed in 1957, contained calculi. No unusual features were found in hospital records apart from a blotchy skin rash noted during an attack of pain presumed to be due to cholecystitis. His urine had been tested on many occasions, but was normal apart from a single record of slight proteinuria during 1957. He attended a clinic in 1955 with pain in the hands, and in 1956 with painful red swellings of hands, feet, and knees, but no diagnosis was made.

In May, 1959, he was admitted to hospital after a few days' pain in the lower back and in the right side of the chest, unaffected by breathing, and associated with fever and night sweats. Although it was not realized at this time, he had been subject to attacks of fever with scattered pains since childhood, at first every few months but latterly more frequently. He was well in between attacks and would take only a few days off work. He had not complained of these

attacks, and this history was obtained subsequently from his wife.

On examination he had an expressionless facies, was febrile, and looked ill. Scattered over the right side of the chest, back, and right thigh were hot, tender, erythematous areas $\frac{1}{2}$ -1 in. (1.3-2.5 cm.) in diameter. Heart, lungs, and abdomen showed no evidence of disease. Blood-pressure was 135/85. There was slight rigidity of the limbs with tremor of the right hand. The haemoglobin was 9.5 g./100 ml., red cells 3,600,000/c.mm., and reticulocytes 1%. The blood urea was 30 mg./100 ml., serum proteins 6.5 g./100 ml. (albumin 3.8 g., globulin 2.7 g.) with electrophoresis showing slight increase of α_2 -globulin. Negative results were obtained for the following investigations: throat swab; blood and marrow cultures; stool examination; blood film for parasites and on dark-ground illumination; blood W.R. and Kahn; Paul-Bunnell test; agglutinations for typhoid, paratyphoid, and brucella; complement fixation for Q fever; mouse inoculation for *Streptobacillus moniliformis*; L.E. cell test. The urine showed no abnormality of centrifuged deposit. Serial white blood counts varied between 4,700 and 12,000/c.mm. and bore no relation to the level of fever; the corresponding neutrophil polymorph counts ranged from 2,800 to 7,320, the lymphocytes from 550 to 3,120, while the monocytes were elevated to between 750 and 1,560. The E.S.R. varied between 25 and 116 mm./hr. Westergren, the highest readings being associated with febrile episodes.

The sternal-marrow cellularity was increased owing to myeloid activity and there was also an increase of monocytes, which totalled 9% (normal 1.5% or less): erythropoiesis was slightly suppressed. A pre-scalene lymph-node biopsy was histologically normal. Biopsy of one of the tender skin nodules showed a mild subacute inflammatory reaction in the subcutaneous fat, polymorphs and lymphocytes predominating; there were no vascular changes. X-ray examination of the chest, lumbar spine, and sacro-iliac joints and excretion pyelography showed no significant abnormality.

Under observation in hospital his rash faded within a few days, but he continued to complain of ill-defined chest, lower back, and abdominal pains. He ran a periodic fever (see Chart) unaffected by penicillin (weeks 5 and 6), neoarsphenamine (weeks 7 to 10), or aspirin in a dose up to 1.2 g. four-hourly (week 21). The findings at laparotomy on August 28 to exclude abdominal reticulosis were normal, a mesenteric lymph node having normal histology. After operation the fever expected during week 17 did not appear, but thereafter two further episodes were recorded with the usual time interval. At this stage it was decided to see if symptoms could be suppressed by prednisolone, which was started on October 6, in a dose of 15 mg. daily. He remained in hospital, afebrile, for a further 25 days on this drug and was discharged taking the same dose.

Chart showing temperature, pulse, and urinary protein.

An important facet of this long illness was the presence of proteinuria (see Chart), which was absent on admission when he was febrile, but tended gradually to increase with time and to be worse during fever. At the time of discharge proteinuria was persistent.

He continued without fever as an out-patient but never felt robust enough to return to work. From time to time red nodular lesions appeared in the skin, chiefly of the legs. Proteinuria was massive, and, despite diuretics, increasing oedema appeared, necessitating return to hospital on May 17, 1960, seven months after the start of steroid treatment. On readmission his blood count was little changed and both blood urea and electrolytes were normal, but moderate numbers of granular casts were present in the urine. The serum cholesterol was 422 mg., serum albumin 2.7 g., and serum globulin 1.5 g./100 ml.

There was a diuresis in response to treatment, and on August 22 a renal biopsy (Dr. A. M. Joekes) was performed. All the glomeruli were much enlarged and showed uniform deposits of amyloid in relation to the capillary wall. There were patches of tubular atrophy; the majority of tubules, however, were fairly well preserved but showed early flattening of the epithelium. There was striking amyloid deposition in relation to the tubular basement membrane. No particular involvement of the vessels was seen. In the interstitial tissue there was some cellular infiltration in relation to areas of atrophic tubules.

With the presence of amyloid confirmed, it was decided to stop prednisolone treatment, but the appearance of tender red nodules on the backs of fingers and overlying the right scapula, and the recurrence of slight fever, finally resulted in its continuance at a dose of 2.5 mg. b.d. Gross proteinuria continued, and in due course, despite diuretics, oedema returned. He complained much of abdominal pain which appeared to have no relation to musculo-skeletal or visceral activity, and a barium-meal examination showed no ulcer. Uraemia developed and he died on October 14, 1960.

At post-mortem examination (Dr. G. W. Marsh) there was anasarca and terminal bronchopneumonia. The spleen, kidneys, and liver were smoothly enlarged; histology showed infiltration with amyloid, widespread in the spleen, kidneys, and adrenals, and to a much less extent in the liver.

Discussion

Early descriptions of cases of familial Mediterranean fever occur in articles by Alt and Barker (1930) and Althausen *et al.* (1937), discussing pyrexia of unknown origin and the "false" acute abdomen respectively; but recently a more extensive literature of case reports has been built up, especially by French authors (Mamou and Cattani, 1952; Siguier *et al.*, 1953). The criteria for diagnosis are recurrent attacks of fever, often over the course of many years, associated with pain in the abdomen, chest, joints, or skin, without a known causative factor. The fever may recur at varying intervals, often 7 to 21 days, although sometimes much longer. There may be remissions, especially during pregnancy (Heller *et al.*, 1958). The onset is often before the age of 10, and in almost all cases by the age of 20.

Sohar *et al.* (1960) concluded that in the majority of cases the disease is inherited through a recessive autosomal gene. Bouroncle and Doan (1957) published a pedigree in which five generations were involved, thus showing that dominant inheritance also occurs. Males are affected slightly more often than females. Almost all patients have been of Mediterranean stock, 85% being Armenians or Jews, the latter mostly non-Ashkenazi, indicating origin from Mediterranean regions. That the disease can occur in other races has been shown by Fox and Morrelli (1960).

The abdominal pain can be persistent or it may be confined to the febrile attacks, when it may be severe and associated with abdominal distension, lack of bowel movement, and vomiting. At such time fluid levels and delay in passage and discontinuity of barium associated with dilatation of the bowel have been demonstrated by radiology, appearances in between attacks being normal (Eyler *et al.*, 1960). Peritoneal inflammation has been seen at laparotomy and necropsy (Siegal, 1945; Tuqan, 1958). Chest pain is usually of pleuritic nature and small pleural effusions and basal atelectasis have been found during attacks. Inflammatory signs in one or several joints usually, but not always, remit between attacks. Synovial biopsy has shown only non-specific chronic inflammation. Shakin *et al.* (1960) noted that the joints most often involved radiologically were the knees, hips, and sacro-iliacs. The latter may show sclerosis, but the common finding is of subperiosteal osteoporosis and erosions of the inner aspect of the cortex, sometimes associated with narrowing of the joint space. The skin rash usually takes the form of irregular, tender areas of erythema, sometimes with obvious swelling or nodularity.

One serious aspect of the disease is renal involvement to which attention was first drawn by Mamou and Cattani (1952). Shwayri and Tutunji (1955) described transient gross haematuria occurring during the febrile attacks, but the commonest finding is proteinuria. Such proteinuria, which is usually worse during the attacks, may be present over many years and tends to increase with time. Some patients develop a nephrotic syndrome and die within a year or so of renal failure. Amyloidosis, which has been revealed by renal and by rectal (Gafni and Sohar, 1960) biopsy and at necropsy, is the cause of the nephropathy. Heller *et al.* (1961) reported urinary abnormality in a third of their 141 patients, most of these already being affected by the age of 30. Most deaths due to renal failure have been recorded in the second and third decades, with one (Camatte *et al.*, 1953) at the age of 52. Two of Heller's cases are of importance: in one of them renal biopsy revealed amyloid before any urinary abnormality had been detected, while renal amyloid without clinical familial Mediterranean fever was found in the brother of a patient suffering from the latter disease.

No investigations are as yet diagnostic of familial Mediterranean fever, but the E.S.R. tends to be persistently raised; it is associated with increase of fibrinogen. The white blood count is not consistently altered although often elevated when fever is present: slight normochromic anaemia is usual. Red-cell and plasma changes have been reported by de Vries *et al.* (1957), but their significance has been questioned (Lawrence and Mellinkoff, 1959). No specific histological patterns have been found on biopsy.

Aetiology and Treatment

Little is known of the aetiology of this disease although presumably some metabolic defect is present. At the height of fever no transferable pyrogen has been detected (Bouroncle and Doan, 1957) and the pyrogenic steroid aetiocholanolone, a cause of some cases of periodic fever, does not appear to be important (Cohn *et al.*, 1961).

Although E.E.G. abnormalities have been reported (Eliakim and Bental, 1961), anti-epileptic drugs are of no value. Aspirin has been reported as modifying the

fever, but in other reports and our own case it was without effect. In some reports cortisone has not helped (Lawrence and Mellinkoff, 1959). In our case corticosteroids controlled the fever, and others report similar experience, some patients being treated with interrupted courses of steroids to coincide with and modify attacks (Bouroncle and Doan, 1957). It may be of significance that use of A.C.T.H. may precipitate a severe attack (Mamou and Cattani, 1952). However, special consideration must be given to the use of steroids in view of the uncertainty of their effect on the course of amyloidosis (see Teilum, 1952; West and Newns, 1952; Grayzel *et al.*, 1956; Squire, 1960).

Case I of Reimann (1949) failed to show improvement when elimination diets were tried, but a probable case described separately by Janeway and Mosenthal (1908) and Cooke (1933) remitted when milk was excluded from her diet, and Mellinkoff *et al.* (1961) obtained dramatic improvement by restricting dietary fat. This latter approach, which may have an important bearing on aetiology, and the use of chloroquine (D'Eshougues *et al.*, 1960) appear at present to be the best treatment in preventing attacks, but the effect on the amyloidosis is unknown.

Summary

A case of familial Mediterranean fever presenting in England is described and our knowledge of this disease discussed.

Our thanks are due to Professor E. F. Scowen for permission to publish the case history of this patient admitted under his care, and to Dr. R. A. Shaddick for providing some details of the patient's past history.

REFERENCES

- Alt, H. C., and Barker, M. H. (1930). *J. Amer. med. Ass.*, **94**, 1457.
 Althausen, T. L., Deamer, W. C., and Kerr, W. J. (1937). *Ann. Surg.*, **106**, 242.
 Bouroncle, B. A., and Doan, C. A. (1957). *Amer. J. Med.*, **23**, 502.
 Camatte, G., Rouquette, M., and Ruiz, M. (1953). *Bull. Soc. méd. Hôp. Paris*, **69**, 60.
 Cohn, G. L., Bondy, P. K., and Castiglione, C. (1961). *J. clin. Invest.*, **40**, 400.
 Cooke, R. A. (1933). *Bull. N.Y. Acad. Med.*, **9**, 15.
 D'Eshougues, J. R., Griguer, P., and Gille, C. (1960). *Algérie méd.*, **64**, 319.
 Eliakim, M., and Bental, E. (1961). *Arch. intern. Med.*, **108**, 91.
 Eyler, W. R., Nixon, R. K., and Priest, R. J. (1960). *Amer. J. Roentgenol.*, **84**, 262.
 Fox, M., and Morrelli, H. (1960). *New Engl. J. Med.*, **263**, 669.
 Gafni, J., and Sohar, E. (1960). *Amer. J. med. Sci.*, **240**, 332.
 Grayzel, H. G., Grayzel, D. M., Heimer, R., and Saremsky, I. (1956). *Exp. Med. Surg.*, **14**, 332.
 Heller, H., Sohar, E., Gafni, J., and Heller, J. (1961). *Arch. intern. Med.*, **107**, 539.
 ——— and Sherf, L. (1958). *Ibid.*, **102**, 50.
 Janeway, T. C., and Mosenthal, H. O. (1908). *Trans. Ass. Amer. Physns*, **23**, 504.
 Lawrence, J. S., and Mellinkoff, S. M. (1959). *Ibid.*, **72**, 111.
 Mamou, H., and Cattani, R. (1952). *Sém. Hôp. Paris*, **28**, 1062.
 Mellinkoff, S. M., Schwabe, A. D., and Lawrence, J. S. (1961). *Arch. intern. Med.*, **108**, 80.
 Reimann, H. A. (1949). *J. Amer. med. Ass.*, **141**, 175.
 ——— (1951). *Medicine (Baltimore)*, **30**, 219.
 Shahin, N., Sohar, E., and Dalith, F. (1960). *Amer. J. Roentgenol.*, **84**, 269.
 Shwayri, E., and Tutunji, N. (1955). *Arch. intern. Med.*, **95**, 337.
 Siegal, S. (1945). *Ann. intern. Med.*, **23**, 1.
 Siguier, F., Zara, M., Funck-Brentano, J.-L., and Lagrue, G. (1953). *Bull. Soc. méd. Hôp. Paris*, **69**, 679.
 Sohar, E., Pras, M., Heller, J., Gafni, J., and Heller, H. (1960). *Acta Genet. med. (Roma)*, **9**, 344.
 Squire, J. R. (1960). In *Recent Advances in Renal Disease*, edited by M. D. Milne, p. 110. Pitman, London.
 Teilum, G. (1952). *Ann. rheum. Dis.*, **11**, 119.
 Tuqan, N. A. (1958). *Ann. intern. Med.*, **49**, 885.
 de Vries, A., Danon, D., Nelken, D., and Henig, E. (1957). *Harefuah*, **52**, 1.
 West, H. F., and Newns, G. R. (1952). *Lancet*, **2**, 515.

DISTRIBUTION OF ABO BLOOD GROUPS IN CHILDREN WITH EMBRYONIC TUMOURS

BY

J. D. ATWELL,* M.B., F.R.C.S.

Senior Surgical Registrar, the Hospital for Sick Children, Great Ormond Street, London

Since Aird, Bentall, and Fraser Roberts (1953) demonstrated a higher incidence of blood group A among patients with carcinoma of the stomach the distribution of the ABO blood groups has been determined in many other diseases.

The determination of the distribution of the ABO blood groups in childhood malignancies had been neglected until the report by Campbell, Gaisford, Paterson, and Steward (1961) of a survey of tumours from the Manchester region. They found a significant preponderance of group O in a series of gliomas in childhood.

It is possible that there may be a higher incidence of genetic factors concerned in the aetiology of embryonic tumours compared with the commoner acquired tumours of adult tissues because environmental factors would have had less time to exert their effect.

The purpose of this paper is to determine the distribution of the ABO blood groups in a series of the commoner embryonic tumours.

Method

The five commonest embryonic tumours were studied—namely, neuroblastoma (including ganglioneuroma), nephroblastoma, medulloblastoma, hepatoblastoma, and embryonic sarcomas of the urogenital sinus. The cases had been seen at the Hospital for Sick Children, Great Ormond Street, between January, 1938, and April, 1961. Cases are included in the series only if there is a reliable record of the ABO blood group available and if the diagnosis has been confirmed by histological examination of material removed at operation or post-mortem examination. The series has been limited to patients living in London and Suffolk, Essex, Kent, Hertfordshire, Middlesex, Gloucestershire, Oxfordshire, Buckinghamshire, Berkshire, Wiltshire, Hampshire, Dorset, Somerset, Devon, and Cornwall.

It was discovered that the area of England drained by the hospital varied with the type of tumour—for example, approximately 50% of nephroblastomas came from London whereas only 10% of medulloblastomas came from the same area. Although the ABO blood-group distribution fluctuates from county to county in southern England the difference is slight and is unlikely to affect the statistical analysis of the results in any small series.

The selection of a control series for comparison is not easy. Table I shows the percentage distribution of the ABO blood groups in the United Kingdom, London, and the Southern Counties of England (series quoted by Mourant, Kopeć, and Domaniewska-Sobczak, 1958). Fisher and Taylor (1940), in a very large series, quoted the distribution of group A as 43.16%. This agrees closely with the mean between the figures of Discombe

*Now Lecturer in Surgery, the General Infirmary at Leeds.