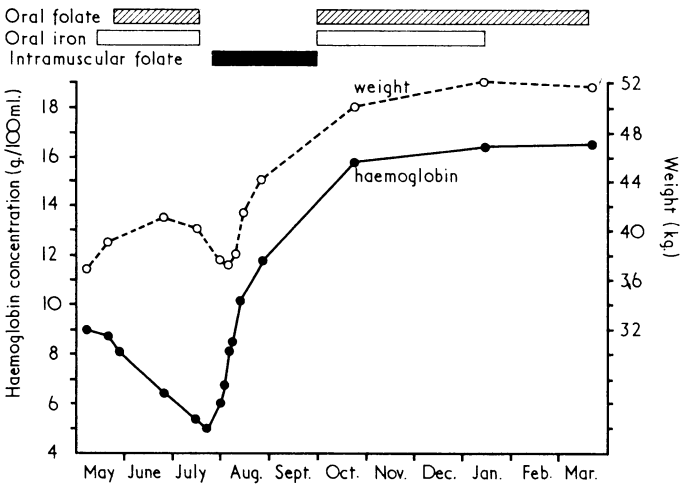

Changes in body weight and haemoglobin concentration, showing specific response to parenteral folate.

She was readmitted on 17 July with severe anaemia, weakness, and pyrexia. The mouth and tongue had numerous aphthous ulcers, the tongue being red and atrophic, and there was a small boil on the face. The motions were bulky and semiformed, two or three times daily, and contained 9 g. of fat a day. The xylose absorption test was again abnormal (five-hour excretion 19%). Oral folic acid and iron were continued under supervision in hospital, in spite of which the haemoglobin fell from 5·1 to 4·8 g., with an M.C.H.C. of 33%, reticulocytes 1%, W.B.C. 3,500, and a partly macrocytic film as before. Bone marrow aspiration on 23 July showed frank megaloblastosis. Serum vitamin B_{12} was 150 pg./ml., folic acid 0·8 ng./ml., and iron 188 µg./100 ml. (40% saturation).

On 19 July she was given a single intravenous infusion of 35 ml. of chelated iron (Imferon). There was no reticulocyte response and no rise in haemoglobin. On 24 July the daily intramuscular injection of 15 mg. of folic acid was started. There was a maximal reticulocyte response of 36% and the haemoglobin rose rapidly (see Chart). A dramatic immediate improvement in her well-being occurred, her appetite improved, and a week after starting the injections she began to gain weight. At the same time the continuous mild pyrexia settled to normal, abdominal discomfort disappeared, and the bowels became regular.

Further recovery was uninterrupted. The patient was discharged in mid-August, twice-weekly injections of folic acid being continued for a month. She was then given a course of oral ferrous sulphate for a month and oral folic acid for six months. All therapy was dicontinued in March 1969, when her haemoglobin was 16·4 g./100 ml. and her weight had risen by 16 kg. In May 1969 the faecal fat averaged 2·2 g./day and the five-hour excretion of xylose was 33·5%. In July 1969 her weight and haemoglobin remained steady and she said "it was lovely to feel so well."

Comment

The traditional diagnostic features of tropical sprue include glossitis and stomatitis, diarrhoea and steatorrhoea, abdominal discomfort, anorexia, wasting, and anaemia. To these in the light of modern investigations may be added folic acid deficiency and a variable degree of jejunal mucosal abnormality which falls short of total atrophy. Unexplained pyrexia is not uncommon. There is a dramatic amelioration of symptoms and of anaemia by parenteral folic acid therapy, with a more gradual and variable improvement in malabsorption, though this also may resolve promptly in the acute case.

On all these counts the above case is a classical one of acute tropical sprue. In view of the fact that the patient had lived all her life in Britain an alternative diagnosis was sought, but the evidence was against gluten-induced enteropathy, abdominal reticulosis, or acute infective enteritis. Further, the patient had no iron deficiency or hypoalbuminaemia to suggest long-standing malnutrition. The complete lack of response to oral folic acid in this case is remarkable, and might be due to biological interference by abnormal flora in the small bowel.

In this general hospital, which includes a regional communicable diseases unit, we have investigated numerous cases of malabsorption following diarrhoea of acute onset that resembled infective enteritis. Most of these cases proved to be either Crohn's disease or gluten-induced enteropathy, but in a few instances no underlying lesion was found, and both the symptoms and the malabsorption resolved spontaneously after several months. Until the aetiology of acute sprue is clarified it is perhaps unjustifiable to claim that sojourn in a known endemic area is a prerequisite for the diagnosis.

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Fulminating Hyperpyrexia during Anaesthesia in a Member of a Myopathic Family

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Rapidly rising body temperature resistant to treatment and usually ending fatally has been described on several occasions during the course of surgical anaesthesia (Saidman *et al.*, 1964; Thut and Davenport, 1966; Stephen, 1967; Wilson *et al.*, 1967; *British Medical Journal*, 1968; Hawthorne *et al.*, 1968). It has been called fulminating hyperpyrexia. The cause of the condition is not known, nor has it yet been possible to forecast its development in patients who have been affected. A sensitivity to succinylcholine has been postulated, and myopathy, infection, and enzymatic aberrations have all been suggested as aetiological factors. A further case is reported here with a possible myopathic association.

Case Report

A youth of 16 was admitted to hospital on 10 July 1968 at 2.30 p.m. with a history and signs suggestive of acute appendicitis. On examination he was of full adult stature and strikingly muscular build. His temperature was 100·2°F. (37·9°C.), pulse regular at 84/minute, and blood pressure 130/90. The heart and lungs were clinically normal.

After premedication with atropine 0·6 mg. and pethidine 100 mg. anaesthesia was induced at 10.15 p.m. with thiopentone 400 mg. followed by suxamethonium 50 mg. An unusually pronounced muscular twitching for about 10 seconds occurred after the suxamethonium. It was noted that his mouth did not open easily, though intubation was not difficult. He was ventilated with oxygen and nitrous oxide, and spontaneous respiration returned. Tubocurarine 30 mg. was then given, but relaxation was poor, though no abnormal resistance to intermittent positive-pressure ventilation was noticed. He became cyanosed within 30 seconds of being disconnected from the anaesthetic machine for transfer to the adjacent theatre. After this a high oxygen percentage was needed to

prevent cyanosis. A persistent tachycardia developed. Within 15 minutes of the start of the anaesthetic his axillary temperature was 107°F. (41·7°C.). The rectal temperature taken later was 108°F. (42·2°C.). The appendicectomy was rapidly completed and attempts were made at surface cooling, with ice and a fan, and also intragastric cooling.

When ventilation was instituted with a mark 3 Boyle circle absorber the soda lime went white and became very hot almost at once. An episode of ventricular asystole was converted to ventricular fibrillation with intravenous adrenaline, and external electrical defibrillation re-established normal rhythm.

Physical examination at this time showed muscular rigidity of all limbs with pronounced plantar flexion of the feet and a claw-like position of the fingers, with extension of the wrists and metacarpophalangeal joints. There was also some opisthotonus and adductor spasm of the legs. Tendon reflexes were absent, fundal haemorrhages were present in both eyes, the heart rate was 140, and the rectal temperature was 106°F. (41·1°C.).

The temperature fell to 105°F. (40·6°C.) and a lumbar puncture failed to yield diagnostic information, though the fluid was lightly blood-stained. The temperature gradually fell to subnormal overnight; active cooling was discontinued after one hour. The patient did not regain consciousness or spontaneous respiration and died at 8.15 the following morning. The muscular rigidity persisted until death.

At necropsy the findings were negative apart from generalized signs of venous congestion. Nothing abnormal was found at the site of the appendicectomy, and death was certified as being due to hyperpyrexia.

Patient's Family

In view of the patient's impressive muscular build and the possible association of fulminating hyperpyrexia with myopathies the other members of his immediate family were examined—namely, both parents, two brothers, and one sister. Some family likenesses were at once apparent. The mother, aged 48, one brother, aged 27, and a sister, aged 14, were all of slight build, were completely normal on physical examination, and had not had any appreciable illnesses. The maternal grandmother had been diabetic at the time of her death when aged 72.

The father, aged 56, and the other brother, aged 19, were, however, muscular in build like the patient, the most striking feature being the pronounced development of the bellies of the voluntary muscles. Both had some athletic ability. The father had had a submucous resection under general anaesthesia in another hospital in 1967. The anaesthesia was uncomplicated, though he was given 50 mg. of suxamethonium for intubation. He has suffered from chronic low back pain for 10 years, accompanied recently by some weakness of the right leg. Examination showed pronounced wasting of the adductors of the right thigh and some localized areas of muscle hypertrophy. There was no myotonia or any sensory abnormality. He did not wish any further examination of himself or his family at this stage. Three months later, however, increasing weakness of the right leg, which caused difficulty, mainly in getting upstairs, led him to seek advice once more; he was then admitted to the hospital for further investigation.

His general condition appeared good. There were no gross abnormalities in the respiratory, cardiovascular, or alimentary system. The spine was mobile, there was no scoliosis and straight-leg raising was not limited. The plantar reflexes were flexor. The right ankle jerk was less brisk than the left; the right knee jerk was absent. There was some local hypertrophy of the sternomastoids, deltoids, rhomboids, and biceps. There were asymmetrical areas of hypertrophy and atrophy in the rectus femoris on both sides, the atrophy being most pronounced on the right side (see Figs. 1 and 2). There was no pronounced weakness of the glutei and trunk extensors and no fasciculation or noticeable myotonia.

Creatinine phosphokinase was 690 milli i.u./ml. (normal 5-50) and serum aldolase 675 milli i.u./ml. (normal up to 6). The glucose tolerance test was abnormal, the fasting blood sugar being 122 mg./100 ml., with half-hourly figures after 50 g. of glucose of 183, 177, and 110 mg./100 ml., glycosuria being absent in all specimens. All other routine haematological and biochemical investigations were normal, as was the lumbar myelogram. Neither creatinine nor myoglobin was detected in the urine.

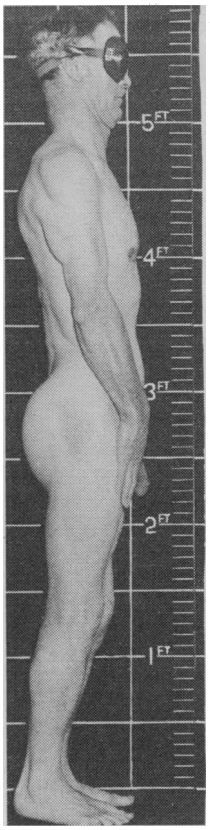

FIG. 1.

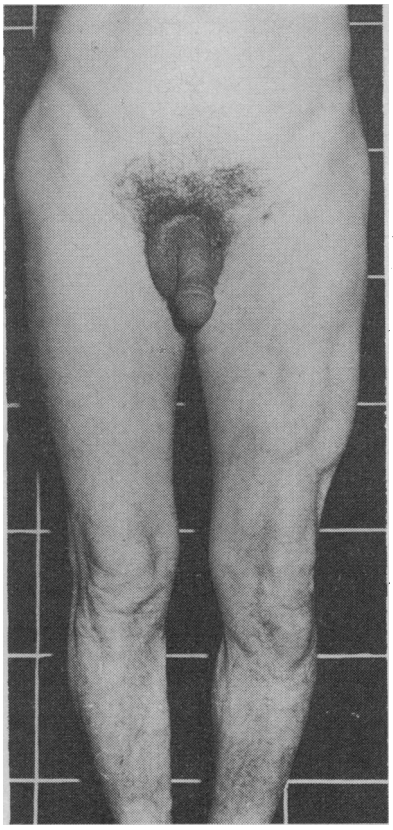

FIG. 2.

Electromyography was performed by Dr. R. G. Willison, at the National Hospital for Nervous Diseases, who reported that sampling of the right tibialis anterior and right vastus medialis showed no spontaneous fibrillation with a full pattern of voluntary activity and sharp polyphasic units up to 3 mV, the appearances being those of primary muscle disease.

A muscle biopsy was performed at the London Hospital, the sample being taken from the right rectus femoris. The histology showed fairly uniform large muscle fibres, with some central displacement of their nuclei, interspersed with scanty necrotic fibres and abundant basophilic regenerating fibres. There was no inflammatory infiltrate, and the appearances were those of a myopathy.

In view of these findings the 19-year-old brother of the patient who died was further examined. Beyond his impressive muscular development no striking abnormality appeared. Biochemical investigations showed a creatinine phosphokinase of 103 milli i.u./ml. and a cholinesterase number of 170 (normal 0-100). Serum aldolase was 1·5 and the glucose tolerance test and routine haematological and biochemical investigations were normal. The results suggest that he might in the course of years develop a myopathy like his father's; the same might have been true of the patient who died.

This family displayed the characteristics of the myopathy described by Barnes (1932). (1) Evidence of myopathy in three generations, obeying the criteria for Mendelian dominance. (2) Three of the four stages were seen in the family—namely, father, stages 2 and 3; son son, stage 1. (3) Histology agrees well with that noted by Barnes, though the diagnosis of Barne's myopathy on purely cytological grounds is not possible.

Comment

It is noteworthy that the reported cases of hyperpyrexia have mostly been those of young people—75% were under 30, the oldest case being 47. It is thus possible that the likelihood of developing fulminating hyperprexia lessens with increasing age. If there is a connexion it might be associated with only one

stage of Barnes's myopathy. If the present patient had Barnes's myopathy it would have been in the hypertrophic stage, whereas the father is now in the atrophic stage. The onset of hyperyrexia was quicker in the present case than in most of those described. A possible explanation is that the patient was pyrexial before induction of anaesthesia was begun.

We had hoped to pursue the family history in the present case to see if there was any connexion with the family described by Barnes. So far it has not been possible to obtain the necessary data. No definite relation between Barnes's myopathy and fulminating hyperpyrexia has been established, but the occurrence of two such rare conditions in the same family is worth recording.

We would like to thank Mr. W. D. Park, consultant surgeon, and Mr. Bernard Fairburn, consultant neurosurgeon, for permission to publish details of cases under their care. We are indebted to Mr. Sheppard for the photographs, and to the neurological department of the London Hospital for their assistance in the diagnosis of Barnes's myopathy.

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Reversible Renal Tubular Defects in Gluten Enteropathy with Osteomalacia

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A patient with severe osteomalacia was found to have a gluten-sensitive enteropathy with hyperphosphaturia, aminoaciduria, renal tubular acidosis, and glycosuria. The renal tubular defects were corrected after treatment with vitamin D.

CASE REPORT

A single woman aged 34 was admitted to hospital for investigation in April 1968. Since 1963 she had complained of progressive painless weakness in the lower limbs of such severity that by 1965 she was forced to stop working as a waitress. During the next three years she became increasingly incapacitated and was unable to walk without a stick. She developed weakness of the arms and complained of aching pains in the lower lumbar region, the left shoulder girdle, and both hips.

She had been repeatedly investigated in hospital with no firm conclusion being reached, though a birth injury, Marfan's syndrome, and multiple sclerosis had in turn been tentatively diagnosed. The family history was unhelpful, the dietary history was normal, and she denied any abnormality in bowel habit.

On examination she walked with a pronounced waddling gait and there was noticeable weakness and wasting of the thigh muscles, with less severe changes in the shoulder girdle muscles. She was moderately myopic and her fingers were long and slim but not abnormal. Further examination was negative.

Haematological investigations all gave normal results. Skeletal survey showed multiple pseudofractures and Looser zones. Trephine biopsy of the iliac crest was diagnostic of severe osteomalacia. Further investigations were performed to determine the underlying cause.

Renal Investigations.— Random urine analysis 0·25% glucose; 24-hour specimen contained 2g. of glucose; no proteinuria; specific gravity 1025 (after overnight fluid deprivation) creatinine clearance 88 ml./min.; electrolytes normal; calcium 70 mg./24 hours (free diet). Heavy phosphaturia was present (phosphate excretion index +0·28), but the urine was virtually freed of phosphate by a standard calcium infusion, the phosphate excretion index falling to −0·06. One-way amino-acid chromatogram showed significant aminoaciduria, with increased excretion of glycine, alanine, and glutamine. The "short" urinary acidification test of Wrong and Davies showed renal tubular acidosis with a minimum urine *p*H of 6·0 and maximum ammonia excretion 141 μEq/min.

Alimentary Investigations.—Barium meal and follow through was normal, as were xylose absorption test, serum B_{12} and Schilling test, daily faecal fat excretion, and a ^{51}Cr test for possible protein loss. The serum folate was 2·3μg./ml. and jejunal biopsy showed the classical appearances of subtotal villous atrophy.

She was given a gluten-free diet and treated with calciferol and supplements of calcium and folic acid by mouth. Within five weeks there was clinical and biochemical evidence of improvement, the serum calcium rising to 10·1 mg. and phosphate to 2·9 mg./100 ml., the alkaline phosphatase falling to 16 K.A. units/100 ml., and the muscle weakness remitting. Six months later she felt entirely well, had normal muscle power with no evidence of wasting and walked normally. She returned to work and there was no radiological evidence of osteomalacia. She required vitamin D by injection, as the alkaline phosphatase showed a tendency to rise on oral therapy, and at the time of this report 50,000 units of calciferol was being given monthly.

Six weeks after starting treatment the glycosuria and abnormal aminoaciduria were abolished. The phosphate excretion index had returned to normal (+0·04). Repeat urinary acidification test was normal, the minimum *p*H attained being 5·13 and maximum ammonia excretion 52 μEq/min. After 10 months of therapy these tests remained normal. A further biopsy with the Crosby capsule showed a normal jejunal mucosa.

COMMENT

It is well recognized that a wide variety of irreversible inherited and acquired renal tubular defects can cause osteomalacia (Wade, 1969). Less commonly osteomalacia can itself cause specific tubular defects which are reversible with appropriate treatment. It has been suggested that they may be due to secondary hyperparathyroidism (Muldowney *et al.*, 1968).

The patient described here is the first with a gluten-sensitive enteropathy in whom a number of reversible tubular defects have been shown to coexist. There was no clinical reason for suspecting malabsorption, the only evidence being a low serum folate and a jejunal biopsy specimen showing gross abnormalities, which were corrected by treatment with a gluten-free diet. Had these investigations not been performed this case might have been regarded as one of Fanconi syndrome (Fanconi, 1936) or type 4 renal tubular osteomalacia on Dent's classification (Dent, 1952).