urinary output of folic acid after the 5-mg. subcutaneous dose was 1.31 mg. and after the 5-mg. oral dose 1.1 mg. (excretion index 84%). The faecal excretion of fat (12-day collection on unrestricted diet) averaged 3.3 g./day (normal range 2 to 7.2 g./day, Doig and Girdwood, 1960), and barium follow-through examination was negative. The results of liver-function tests were normal.

When the patient was told that she had again become anaemic she refused to continue with phensuximide but agreed to remain on phenobarbitone. On October 18 2 pints (1,140 ml.) of whole blood were transfused. During the next 10 days further treatment was withheld and there was no evidence of spontaneous haematological improvement. On October 28, 1,000 µg. of cyanocobalamin was given intramuscularly (part of the Schilling test); during the next 72 hours no significant alteration occurred in the serum iron concentration and the marrow remained unchanged; the peripheral blood findings were: Hb, 8.7 g./100 ml.; red cells, 2,590,000/c.mm.; packed cell volume, 25.5%; mean cell volume, 99 cubic microns; mean corpuscular haemoglobin concentration, 34.2%; reticulocytes, 1%; white cells, 3,800/c.mm. On October 31, 5 mg. of folic acid was given subcutaneously, and this was followed, 24 hours later, by an equivalent dose by mouth (part of the folic acid absorption test); thereafter the patient received orally 5 mg. of folic acid twice daily. Within 48 hours of the administration of folic acid there was a significant fall in the serum iron concentration, indicating the occurrence of a haematological response; the values at 0, 24, and 48 hours were 210, 148, and 83 µg./100 ml. respectively. The reticulocyte count on the sixth day of therapy was 20%, and on the thirteenth day the Hb had risen to 9.6 g./100 ml. and red cells to 3,110,000/c.mm.

On December 22, when her peripheral blood findings and sternal marrow were entirely normal, she was persuaded to resume her previous treatment with phensuximide and phenobarbitone; the epilepsy was adequately controlled on this regime, and with the continuance of folic acid therapy her blood findings at regular follow-up visits always remained normal. She committed suicide two years later in a state of reactive depression immediately after unexpected discharge from her employment. A necropsy was not performed.

COMMENT

Detailed investigation of this case failed to reveal a cause for the megaloblastic anaemia other than the anticonvulsant therapy. It is probable that the anaemia was induced by phensuximide either alone or in combination with phenobarbitone; the alternative possibility of phenobarbitone having been solely responsible for the anaemia is regarded as unlikely, as only one example of megaloblastic anaemia complicating phenobarbitone administration has been reported in the literature, and this occurred in a patient receiving large doses of the drug (Chanarin *et al.*, 1960). The absence of previous reports of megaloblastic anaemia occurring during phensuximide therapy may be related to the fact that this drug has been mainly used in the treatment of petit mal in children. In Great Britain megaloblastic anaemia is very rare in this age-group and there have been no reports of this type of anaemia complicating anticonvulsant therapy in children.

The severe anaemia which the patient developed in 1954 while receiving sodium phenytoin, primidone, and phenobarbitone may have been megaloblastic in type, but a more definite opinion cannot be given, as the marrow smears, made elsewhere at that time, were not available for study. None the less it appears that the patient's bone-marrow was unduly sensitive to anticonvulsant drugs. The megaloblastic anaemia which occurred during phensuximide and phenobarbitone therapy was refractory to cyanocobalamin but responded

promptly to folic acid. This finding is in agreement with the hypothesis of Girdwood and Lenman (1956) and Chanarin *et al.* (1958) that megaloblastic anaemia due to anticonvulsant drugs does not result from tissue depletion of folic acid but arises from an interference with folic acid metabolism.

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Diabetic Xanthomatosis in an African

Diabetic xanthomatosis was first described by Addison and Gull (1851). Joslin *et al.* (1959) found only 14 cases among a series of 21,000 diabetic patients. Most recent accounts have been single case reports (McGavack and Shepardson, 1933; Thompson *et al.*, 1935; Combes and Behrman, 1941; Spencer, 1951; Margolin, 1953; Gumpel and Lipton, 1955; Kolb *et al.*, 1955; Bloom and Crowley, 1956; Grollman, 1956; Johnston, 1959).

CASE REPORT

On April 8, 1959, an African boy aged 14 was admitted to hospital. For 10 months he had suffered from polyuria, polydipsia, polyphagia, loss of weight, and lassitude. For nine months he had noticed pain, numbness, paraesthesiae, and weakness of his legs, which had rendered him bed-ridden by the time of his admission. For three months a rash had been present. Of special interest was his diet, which, typical of many rural Africans in these parts, consisted almost entirely of maize meal and meat, with no butter and very little milk.

On admission he was extremely ill—unable to stand and almost too weak to move. He weighed 84 lb. (38.1 kg.) and had many of the stigmata of kwashiorkor: for example, oedema

Photograph showing skin lesions above the left elbow.

of the lower limbs and puffiness of the face; brownish, silky hair which had lost its normal coarse tight black curls; generalized depigmentation; and obvious wasting of the body. There was a papular eruption affecting mainly the

extensor surfaces of the body, superficially resembling pustules, with yellow centres and dark areolae. The individual papules varied in size from 1 to 5 mm. in diameter and were most marked on the knees and elbows (see illustration), but were also present on the shoulders, buttocks, and to a less extent the chest and face. The pulse was 75 and the B.P. 110/70. The only other positive findings were in the nervous system, where there was a peripheral neuritis affecting the lower limbs. The fundi showed lipaemia retinalis.

Investigations produced the following results:

	8/4/59	14/4/59	3/6/59	6/8/59
Blood:				
Haemoglobin (g./100 ml.)	13.0			
W.B.C. (per c.mm.)	8,300			
E.S.R. (Wintrobe)	53 mm.			
Fasting blood sugar (mg./100 ml.)		330		175
Blood urea (mg./100 ml.)	48		40	35
Serum proteins:				
Total (g./100 ml.)	9.8		11.8	7.6
Albumin "	0.8		1.4	3.3
Globulin "	9		10.4	4.3
Alpha 1 (g./100 ml.)			0.7	0.7
Alpha 2 "			2.1	0.9
Beta "			4.9	1.0
Gamma "			2.7	1.7
A/G ratio	0.09		0.1	0.7
Serum lipids (g./100 ml.)	16.0			
Serum cholesterol (mg./100 ml.)			277	230
Phospholipids	1.000			
Lipoproteins	Results mislaid			
Urine:				
Chemistry:				
Albumin	Nil	Nil		
Glucose (g./100 ml.)	2 or more	0.25		
Ketones		Nil		
Microscopy	N.A.D.			
Concentration and dilution test		Normal		

Histology of the papule from the knees: "Lipoid-laden histiocytes (foam cells) are present with some extracellular lipid in the dermis."

For the first week soluble insulin was given six-hourly according to the amount of glucose in the urine, and potassium chloride 5 g. daily. Thereafter soluble insulin 60 units was given half an hour before meals. For the first month tab. aneurin. co. forte, 2 tablets t.d.s., were given. The diet chosen was one we felt the patient would be able to continue once he returned home; it consisted of three more or less equal meals, each composed of meat, soup, maize meal, and a few green vegetables.

Within 24 hours of admission the urine was free of ketones. In three days the milkiness of the serum cleared and the lipaemia retinalis disappeared. After three weeks the minute papules on the face and chest were no longer visible, while the larger papules had decreased in size and lost their yellow centres. However, even when the patient was discharged after four months, the larger papules were still visible as small shiny keloid scars. After one month the puffiness of the face had gone, but the minimal oedema of the feet and ankles was still present after two months. A month after admission the patient was able to walk, the sensory abnormalities having improved, but the foot-drop was still present at the time of discharge. In spite of losing the oedema his gain in weight was spectacular, being 84 lb. (38.1 kg.) on admission, then 93, 100, 110, and 115 lb. (42.2, 45.4, 49.9, and 52.2 kg.) on successive weeks. After two months he weighed 130 lb. (59 kg.) and 132 lb. (59.9 kg.) when discharged four months after admission.

COMMENT

In Thannhauser's (1949) classification diabetic xanthomatosis falls into the group of secondary xanthomatoses in the course of diabetes mellitus due to hyperlipaemia. Insulin acts at various levels in carbohydrate and fat metabolism (Chernick and Chaikoff, 1951; Stadie, 1957). Characteristically the diabetic state is associated with the frequent occurrence of lipaemia and hypercholesterolaemia. In diabetic

lipaemia the emphasis is on the neutral fat fraction while the cholesterol and phospholipid fractions are increased less or not at all (Hirsch *et al.*, 1953). Hirsch *et al.* (1953) have found that the hyperlipaemia bears a parallel relationship to the blood-sugar levels, while Tuller *et al.* (1954) and Johnston (1959) have shown no precise relationship between the hyperglycaemia and hyperlipaemia. Tuller *et al.* (1954), however, have shown a general relationship between the serum lipid deviation and the degree of acidosis.

Probably, in simple terms, the hyperlipaemia represents an increased mobilization of fats from the tissue depots in an attempt to supply the energy requirements of the body from fatty acid and ketone body oxidation.

This case is of particular interest for several reasons:

(a) it supports the predominant male incidence (Combes and Behrman, 1941); (b) it shows the condition in its extreme form, as could be seen only in a primitive person seeking attention at the last moment; (c) it demonstrates that the fat content of the diet is not important in the causation of the entity or its treatment; (d) it illustrates the progress of the skin lesions in Africans who are prone to keloid formations; (e) it shows xanthomatosis in association with peripheral neuritis, which was thought to be diabetic rather than due to malnutrition, owing to its slow and incomplete response to vitamin therapy; (f) it was associated with oedema, which was thought to be due to hypo-albuminaemia and a kwashiorkor-like state, and possibly to a less extent a trophic change due to the peripheral neuritis; (g) it showed gross abnormalities of the serum proteins, especially the alpha-2 and beta-globulin fractions, the more detailed analysis of which was lost, but which probably represented lipoproteins as previously shown by Bloom and Crowley (1956); and (h) it shows that this rare complication does also affect Africans in whom diabetes itself is considered rare (Gelfand, 1957).

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