fetal breathing movements; but further control studies will have to be done to exclude the possibility of the degree of inhalation varying with the type of cigarette.

Cigarette smoking in pregnancy is suspected of being detrimental to the fetus. Statistical surveys have shown that the babies are smaller at birth (Butler *et al.*, 1972) and suggested an increase in prematurity and perinatal mortality. It is not easy to relate our observations on the acute effects of smoking two cigarettes to the long-term epidemiological reports. Nevertheless, physiological factors such as hypoxia and hypoglycaemia, which might be expected to have a detrimental effect on the fetus, also reduce the normal incidence of fetal breathing movements in animals and man (Boddy and Dawes, 1975; Boddy *et al.*, 1975). Whether the similar effect of cigarette smoking is to be interpreted in the same way is as yet a matter for conjecture. The size of the transient change observed (see fig.) was less than the normal diurnal variation in the incidence of fetal breathing.

We make this report because clinical physiologists and obstetricians in several countries are beginning to use fetal breathing movements as an index of health. These observations are best made some hours after the last cigarette has been smoked to exclude the acute effects of this variable.

This work was carried out with the aid of a grant from the Medical Research Council. We thank Professors G. S. Dawes and Alec Turnbull for their help, the consulting staff of the department of obstetrics for access to their patients, the nursing staff, and the subjects who volunteered for the study.

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MEDICAL MEMORANDA

Neutral-lipid Storage Disease: A New Disorder of Lipid Metabolism

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In 1953 Jordans described two brothers with progressive muscular dystrophy whose leucocytes and monocytes contained large fat vacuoles. Rozenszajn *et al.* (1966) later reported a similar abnormality in the white blood cells of two sisters who also had ichthyosis but no evidence of myopathy. We report here a similar abnormality of leucocytes, which was, however, part of a generalized accumulation of neutral lipid droplets in most cells of the body and which differed from known lipid-storage disorders in many significant respects.

Case Report

A 22-year-old Ugandan Asian woman presented in the dermatology outpatient department with a scaly generalized skin disorder which had been present all her life and which was associated with itchiness of the skin. It affected the face, trunk, and limbs, including the flexures, and was diagnosed as lamellar ichthyosis. She had no other complaints and coped adequately at work. Her diet was vegetarian with milk daily and occasional eggs.

Examination.—Apart from a generalized skin disorder an examination showed a slightly plump healthy girl (height 157 cm, weight 62 kg) of normal intelligence. There was no lymphadenopathy, and spleen and liver were not palpable. Examination of all systems showed nothing abnormal.

The blood count showed an iron-deficiency anaemia (haemoglobin concentration 8·2 g/dl) due to menorrhagia, which responded fully to oral ferrous sulphate.

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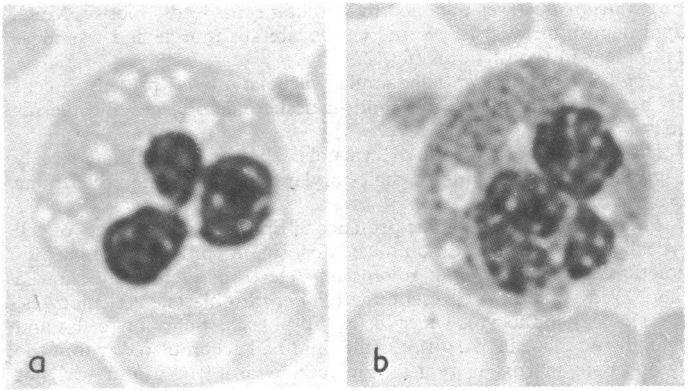

FIG. 1—Neutrophil polymorph leucocyte showing multiple clear lipid vacuoles (a) and eosinophil polymorph leucocyte showing multiple clear lipid vacuoles (b).

The stained blood film, in addition to hypochromia, showed multiple vacuoles up to 1-2 μm in diameter in the cytoplasm of neutrophil, eosinophil, and basophil polymorphs and in monocytes (fig. 1). These were not seen under ordinary microscopy in lymphocytes nor in red cells. These vacuoles took up fat stains, such as oil red-O. There were no acanthocytes. Three siblings and two cousins did not have similar blood abnormalities.

Distribution of Lesions.—All investigations were performed with the patient's informed consent. On the advice of a gynaecologist a curettage was carried out because of her menorrhagia.

Sternal Marrow.—Lipid vacuoles were present in the granulocytic series, in monocytes, but not in erythroblasts or megakaryocytes. Vacuoles were absent in myeloblasts, relatively small and often solitary in promyelocytes, and more prominent in myelocytes and particularly metamyelocytes. Plasma cells showed similar vacuoles.

Gastrointestinal Tract.—There was a striking vacuolation of the columnar epithelial cells beginning about one-sixth of the way up the villi and increasing until maximal in cells of the villus tip. Within a single cell vacuoles were multiple and dispersed through the cytoplasm. Goblet cells showed scanty vacuolation as did Paneth cells at the base of the crypts. Scanty foamy macrophages were found in the lamina propria.

Similar vacuolation was found in the rectal epithelium, most marked in a subnuclear distribution. Foamy macrophages and free lipid were prominent in the lamina propria. A biopsy specimen from the body of the stomach showed vacuolation and lipid deposition in the glandular cells, but this was lacking in gastric pits and the surface mucosa.

Skin.—There was hyperkeratosis with some parakeratosis and focal spongiosis. There was a mild perivascular chronic inflammatory

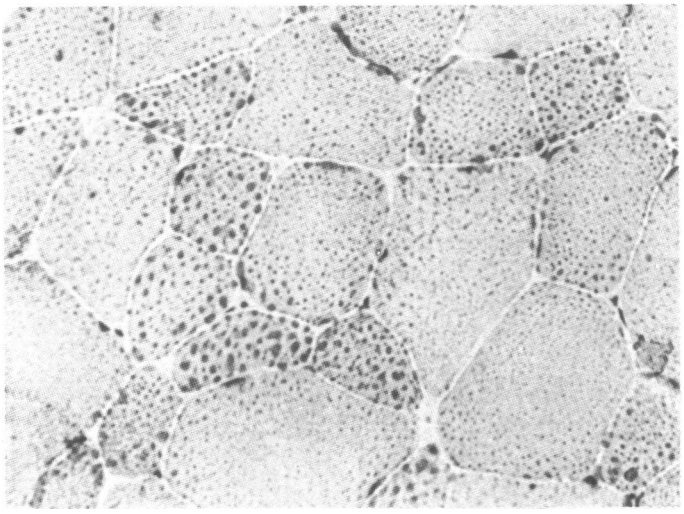

FIG. 2—Section of vastus lateralis showing lipid deposition most marked in type 1 fibres. (Oil red-O. × 315.)

infiltrate in the upper dermis. Sections stained with oil red-O showed an excess of lipid in the keratinizing zone and a marked lipid vacuolation of the stratum basale but lipid vacuoles in the prickle zone were of minor degree only.

Striated muscle was obtained by percutaneous needle biopsy. Much lipid deposition was seen in the vastus lateralis muscle and was more prominent in type 1 fibres (fig. 2).

Other Tissues.—Essentially similar vacuolation was present in cells of the endometrium and liver and in tissue macrophages and plasma cells.

Histochemical analysis of the vacuoles showed neutral fat, largely triglyceride but with a minor cholesteryl ester component in the lamina propria of rectum.

Electron Microscopy.—The presence of lipid in a wide variety of cell types was shown. In addition to the deposits in epithelial and haemopoietic cells seen by light microscopy electron microscopy showed that lipid was also present within erythroblasts, reticulocytes, occasional lymphocytes, mast cells, fibroblasts, Schwann cells, and smooth-muscle cells. In all cells the lipid had accumulated within the cytoplasmic matrix as typical triglyceride droplets. Lipid was not associated with any of the membrane-limited organelles. There was no evidence of endocytic uptake or lysosomal breakdown of lipid.

CLINICAL INVESTIGATIONS

A chest *x*-ray film and electrocardiogram were normal. An *electroencephalogram* showed mildly abnormal changes in both frontotemporal and temporoparietal areas and suggested the possibility of diffuse cortical involvement with the lipid storage process.

Electromyography of the right deltoid showed no fibrillation, but voluntary contraction produced a pattern of small, noticeably polyphasic units consistent with a neuromyopathy.

Chromosome analysis of peripheral blood lymphocytes showed a normal female karyotype with no evidence of mosaicism.

GENERAL BIOCHEMISTRY

The results of routine investigations were within normal limits.

Faecal fat excretion was less than 17·6 mmol/24 h (5 g/24 h) on a 100-g fat intake, and the uptake and excretion of oral xylose was normal. There were increases in serum aspartate aminotransferase to between 38 and 44 IU (normal 10-35 IU) and serum creatine phosphokinase to 121 IU/l (normal 5-80 IU/l). There were persistent slight increases in serum globulins; β-globulin 18 g/l (1·8 g/100 ml), γ-globulin 18 g/l (1·8 g/100 ml); and some increase in immunoglobulins; IgG 21 g/l (2·1 g/100 ml); IgA 3 l/g (0·3 g/100 ml). Urinalysis was normal and myoglobinuria was not present.

LIPID STUDIES

Fasting plasma cholesterol, non-esterified fatty acids, triglycerides and lipoproteins determined by nephelometry were within normal limits (see table). Serum lipoprotein analysis showed raised triglyceride in low-density lipoprotein (cholesterol: triglyceride ratio 1·8, normal value 5·0) associated with a marked increase in the B-peptide in this fraction (184 and 140 units, normal mean value 71). There was a reduction in the A-peptide in high density lipoprotein (59·2 and 74 units, mean normal 138).

Fasting Serum Lipid Values in Patient Studied Compared to Normal Ranges

	Values in Patient Studied	Normal Range
Cholesterol (mmol/l)	3·9	4·0–7·5
Non-esterified fatty acids (μmol/l)	480	300–700
Triglyceride (mmol/l)	0·576	0·339–2·03
Lipoprotein (g/l):		
L particle	0·04	0–0·28
M particle	1·65	0·1–2·4
S particle	2·76	2·34–5·5
Plasma carnitine (mmol/l)	0·35	0·324–0·356

Conversion: SI to Traditional Units
Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.
Non-esterified fatty acids: 1 μmol/l ≈ 0·3 g/l.
Triglyceride: 1 mmol/l ≈ 88·5 mg/100 ml.
Carnitine: 1 mmol/l ≈ 16 mg/100 ml.

Analysis of lipids extracted from peripheral blood granulocytes showed the neutral triglyceride content to be two to three times greater than that of normal controls with no excessive accumulation of cholesterol or non-esterified fatty acids.

Total serum bile acids were not significantly raised at 17·3 μmol/l (approx. 8·65 mg/l) (normal range 0-16 μmol/l (approx. 0-8 mg/l)). Granulocyte acid lipase activity was normal.

Abdominal subcutaneous fat obtained by percutaneous needle biopsy was microscopically normal and showed normal basal rates of lipogenesis and lipolysis in vitro as measured by incorporation of ^{14}C-glucose into lipid and release of glycerol respectively.

The plasma carnitine level did not differ from that of six controls matched for age and sex measured at the same time.

FIBROBLAST CULTURES

Fibroblasts were grown from a skin biopsy specimen (2 mm in diameter) in 10% fetal calf serum and 90% minimal Eagle's medium with penicillin and streptomycin. From their first appearance the cells contained large cytoplasmic lipid inclusions which became more numerous with time and persisted after subculture (fig. 3). No such inclusions were seen in two control cultures. Mixed cultures of abnormal with normal fibroblasts retained their differences, and the abundance of lipid inclusions was not altered by growing the patient's fibroblasts in medium in which normal cells had previously been grown.

Thin-layer chromatography (T.L.C.) on silica gel (Merck prepared plates) in a variety of solvents showed a gross excess of a substance with the mobility of a triglyceride. This was confirmed by mass spectrometry, and the compound was identified as a triglyceride containing palmitate, stearate, oleate, myristate, palmitoleate, and linoleate but no unusual fatty acid.

Accumulation of triglyceride was measured by incubating the abnormal fibroblasts with ^{14}C-palmitate (Radiochemical Centre, Amersham; specific activity of 200 μCi/l). Labelled palmitate was incorporated into lipid in a linear fashion with respect to time, but while the proportion appearing in the phospholipid fractions was similar in control and abnormal cells the triglyceride fraction (identified

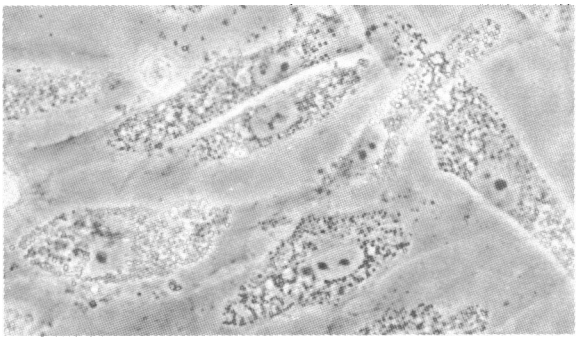

FIG. 3—Fibroblast culture of skin biopsy specimen taken from patient 10 hours after third subdivision, photographed by phase-contrast illumination (× 650), showing numerous refractile lipid droplets.

by T.L.C.) from abnormal cells contained about six times as much ^{14}C-palmitate after five days in culture as did that from control cells.

Addition of L-carnitine to the cultures (0·2 g/l of medium) did not modify the enhanced rate of incorporation of ^{14}C-palmitate into triglyceride by the abnormal cells.

Comment

The principal clinical features in this patient, ichthyosis and electromyograph abnormalities, may both be related to a defect of lipid metabolism which has led to excessive accumulation of intracellular triglyceride.

Lipids probably play an important part in normal keratinization, and excessive lipid deposition was seen in the keratinizing zone in our case. Furthermore, our patient showed abnormal amounts of lipid droplets in most of the tissues examined, suggesting a generalized defect of lipid metabolism.

The accumulation of apparently normal triglyceride in her cells without a gross excess of cholesterol, the normal serum bile acid concentration, and the absence of hepatomegaly make it unlikely that this patient had cholesterol ester storage disease. Similarly, the absence of lysosomal membranes surrounding the lipid droplets and the presence of normal acid-lipase activity in granulocytes excluded a variant form of Wolman's disease, an inherited disorder of lysosomal lipase activity usually fatal in childhood and rarely seen in adults.

The β-lipoprotein abnormality found in this patient is probably secondary to a defect of intracellular lipid metabolism since fibroblasts continue to show abnormal lipid inclusions when subcultured repeatedly in medium containing normal lipoproteins. Fibroblasts are not known themselves to synthesize β-lipoprotein. A specific defect of triglyceride or fatty acid metabolism at the cytoplasmic level is likely in this patient, and our initial findings suggest impairment either of cytoplasmic lipase activity or of fatty acid transport into mitochondria.

A lipid storage myopathy due to carnitine deficiency was described by Engel and Angelini in 1973. The patient we studied was a vegetarian obtaining little or no carnitine from her diet, so the possibility of defective carnitine biosynthesis leading to impaired transport of fatty acids into mitochondria was considered. This diagnosis was not supported because plasma levels of carnitine were normal and there was no effect on lipid accumulation when L-carnitine was added to fibroblasts in vitro.

Defective carnitine-palmityl-transferase activity could explain our preliminary findings with cultured fibroblasts. Such a lesion was recently shown in a patient with episodic muscle cramps and myoglobinuria (Di Mauro and Di Mauro, 1973), and if confirmed in our case would make a trial of dietary therapy with medium-chain triglyceride worthwhile.

We thank the many colleagues both at Northwick Park Hospital and other hospitals, including Mrs. J. E. Richmond, Dr. G. W. Fenton, Dr. D. S. Smith, Dr. A. Smithies, Dr. B. Lewis, Dr. A. C. Onitiri, Dr. R. D. Cohen, Dr. S. Barnes, Dr. D. Patrick, Dr. M. Ashwell, Dr. P. K. Tubbs, and Dr. A. Lawson who helped us to investigate this patient.

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Syncopal Attacks as Symptom of Severe Coronary Artery Disease

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Syncope is well recognized as a symptom in cardiac disease in association with various arrhythmias (ventricular fibrillation, atrioventricular block, and sinoatrial block), aortic stenosis, hypertrophic obstructive cardiomyopathy, and myocardial infarction. Its association with angina is less well recognized but was noted in original descriptions of angina by Herberden. Gallavardin (1922) and more recently Chiche (1972) described several patients with "syncope anginosa," some with valvular heart disease but also a few with ischaemic heart disease. We report two cases in which syncopal attacks were associated with severe coronary artery disease as shown by coronary arteriography.

Case 1

A 53-year-old bricklayer was admitted to hospital as an emergency case, having collapsed on his way to work. He was unconscious for a short period. On admission the E.C.G. showed sinus rhythm. He remembered that he had stopped walking up a hill on account of chest tightness immediately before falling unconscious. Further questioning disclosed that he had suffered from typical angina pectoris for some two months before this event. The chest discomfort was always related to exertion, such as walking up a steep hill. While in hospital he had a further syncopal episode. This occurred when he stood up suddenly, having been sitting in a warm room in direct sunlight. Initially no pulse was noted but a

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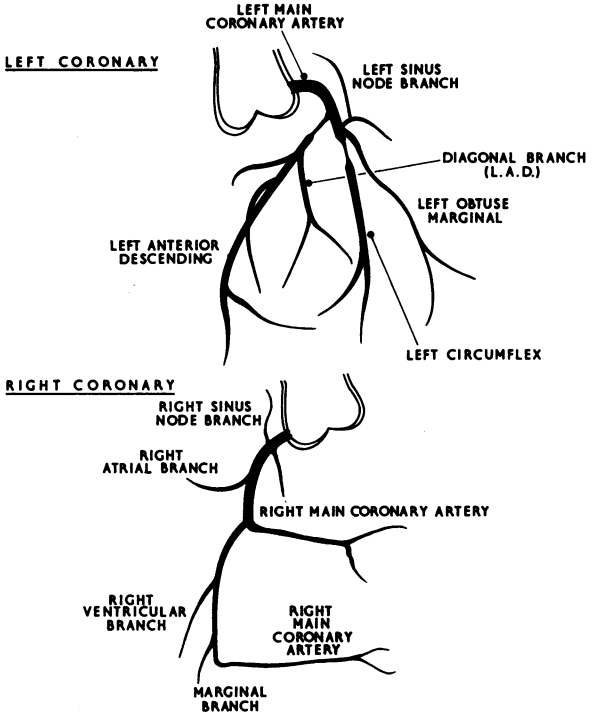

FIG. 1.—Case 1. Left antero-oblique projection of coronary arteries showing major stenoses in proximal parts of left anterior descending and circumflex arteries. Right coronary artery is small in calibre.