The existence of congenital spherocytosis was suspected only when a persistent irregular reticulocyte response was observed after treatment with folic acid.

We are grateful to Professor H. C. McLaren for permission to publish details from the case notes of the first pregnancy, and to Mr. A. L. Deason from those of the second pregnancy. The haematological investigation after our patient's first confinement was carried out by the late Dr. A. L. Peeney. We are further indebted to Dr. Eileen Shuttleworth for detailed clinical and haematological information on a similar case.

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MYELOMATOSIS WITH LIPAEMIA AND XANTHOMATA

BY

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When a patient develops two rare disorders at the same time it is natural to look for a common factor between them, especially when one hears that they have occurred together in other patients. A patient simultaneously developed extensive xanthomatosis and myelomatosis. The association of myelomatosis with hyperlipaemia seems to be a real one, but I have failed to explain it. This paper presents the results of investigations and a brief review of other cases.

Case Report

A woman of 65 who had previously been healthy began, in 1955, to experience shortness of breath and pain in the chest on exertion. Six months later she suffered a prolonged attack of chest pain typical of myocardial infarction. During convalescence she noticed a yellow discoloration around her eyes and later in the palmar creases. Both she and her husband were certain there had been no trace of yellowness before. From that time the slightest exertion caused severe pain in the chest, and a year after the beginning of her symptoms a second severe attack of cardiac pain occurred, for which she was admitted to hospital. During the preceding weeks she had noticed increasing pallor and some

loss of weight. None of her family had a history suggesting xanthomatosis or early coronary artery disease.

On admission she was strikingly pale, with arresting bright-yellow plaques round her eyes. The whole skin surface was infiltrated with this yellow material, which condensed into soft impalpable plaques over the extensor surface of joints and in the palmar creases as well as round her eyes. The thickest plaques were bright orange; when the skin was stretched over them skin markings could still be seen. Small tuberosus yellow swellings were present on the abdomen and buttocks. There were no xanthomata of the tendons.

Except for a pericardial friction rub, heard on the day after admission, there were no other abnormal findings. An electrocardiogram confirmed the clinical diagnosis of myocardial infarction.

Cause of the Anaemia

On admission the patient's haemoglobin was 6.5 g./100 ml. with a mean cell haemoglobin concentration of 31%. The normal Hb content of the cells and the fact that her stools contained no occult blood made bleeding as a cause of the anaemia unlikely. The sedimentation rate was 160 mm. in the first hour (Westergren) and blood films showed excessive rouleaux formation. Marrow smears from both sternum and iliac crest showed a diffuse infiltration with abnormal plasma cells—mostly primitive nucleolated forms—some binucleate and some showing mitotic abnormalities. A representative nucleated-cell count contained 36% of plasma cells. Repeated marrow studies over the next two years gave similar appearances.

An attempt was made to stain the plasma cells in the marrow smear with an aqueous fat stain. It was necessary to wash freshly aspirated marrow in saline to remove the lipaemic plasma. Bovine albumin was used to stick the washed cells to a slide. The smear was then stained with a saturated solution of scharlach R III and counterstained with 1% aqueous methylene blue. A few fat droplets accidentally deposited on the slide were stained red, but no droplets of fat were seen in the plasma cells.

During her first admission neither x-ray nor biochemical findings suggested bone disease, but films taken two and a half years later showed typical punched-out areas of bone destruction in the skull and the sixth left rib. There was no protein or Bence Jones proteose in the urine. No cryoglobulins were present in the blood. At first a diagnosis of myelomatosis as a cause of the anaemia could only be tentative; as the course of the illness unfolded the diagnosis became certain.

Lipids in the Blood and Skin Nodules

The fasting serum was turbid with many chylomicra; heparin, 5,000 I.U. intravenously, did not alter this turbidity. All the lipid fractions of fasting-serum were increased (total

FIG. 1.—Fractionation of the serum lipids, showing that all fractions were increased. (Analysis kindly performed by Mr. N. Bell.) Hatched columns represent the normal upper limit.

FIG. 2.—Electrophoresis of patient's serum, showing heavy staining for protein, fat, and carbohydrate in the β_2 -globulin zone. The fat-staining zone migrated a little faster than the zone staining for protein and carbohydrate.

4.5 g./100 ml. instead of the normal 1.2 g./100 ml.) (see Fig. 1). Biopsy showed that the skin nodules stained strongly for neutral fat and were composed of aggregations of foam cells. The serum bilirubin, fasting blood sugar, and radio-iodine studies of thyroid function were normal. No studies were made on the rate of lipid clearance from the blood.

Serum Proteins

Paper electrophoretic strips (Fig. 2) stained for protein with lissamine green (Discombe *et al.*, 1954) showed an abnormal β_2 -globulin band, and this zone also stained for carbohydrate with periodic acid Schiff reagent (Köiw and Grönwall, 1952). Just in front of this band was a zone which stained heavily for fat with Sudan black (Swahn, 1953). Dr. C. B. Laurell kindly estimated the different serum-protein fractions by paper electrophoresis as follows: total protein, 11 g./100 ml. (albumin 4 g., α_1 -globulin 0.3 g., α_2 -globulin 0.4 g., β_1 -globulin 0.3 g., β_2 -globulin 5.7 g., γ -globulin 0.3 g.). He found that the abnormal β_2 -globulin contained about 6% of polysaccharides, half of which was hexose. The presence of carbohydrate in abnormal myeloma proteins has been noted previously (Sachs *et al.*, 1954; Osserman and Lawlor, 1954). Dr.

FIG. 3.—Immuno-electrophoresis showing an abnormal precipitation line (marked with arrow) in the β -globulin position. (Reproduced by courtesy of Dr. Ch. Wunderly.)

K. W. Walton measured the cholesterol content of the α and β zones (Nury and Smith, 1957) and found that only 30 mg. (normal 30–70 mg./100 ml.) of the total serum cholesterol of 830 mg./100 ml. was in α -lipoprotein while the remaining 800 mg. (normal 150–230 mg./100 ml.) was in β -lipoprotein. Thus paper electrophoresis revealed an abnormal β_2 -globulin in high concentration and nearly four times the normal β -lipoprotein concentration.

These findings were extended by immunological methods. Using a gel-diffusion technique (Gell, 1957) and a specific antiserum for human β -lipoprotein, Dr. J. F. Soothill found that the serum contained qualitatively normal β -lipoprotein in about double the usual concentration. Immuno-electrophoresis, kindly performed by Dr. Ch. Wunderly and Dr. J. F. Soothill, showed an abnormal precipitation line in the β -globulin position (Fig. 3).

TABLE I.—Analysis of Low-Intensity Lipoprotein Fractions Separated at Density 1.063. Normal Values Obtained from Gofman *et al.* (1954a). (Analysis Kindly Performed by Dr. J. W. Gofman)

Fraction	Patient	Upper Limit of Normal
Sf ⁰ 0–12	576 mg./100 ml.	642 mg./100 ml.
Sf ⁰ 12–200	427 „ /100 „	202 „ /100 „
Sf ⁰ 20–100	1,241 „ /100 „	237 „ /100 „
Sf ⁰ 100–400	165 „ /100 „	111 „ /100 „

TABLE II.—Concentration of Serum Protein Components Separated in the Ultracentrifuge (60,000 r.p.m. in Barbitone Buffer, pH 8.6, I=0.05+0.2 M NaCl). There is an increased S₇ Component Which is Not Altered by Removing Low-density Lipoprotein. (Analysis kindly performed by Dr. D. R. Stanworth)

Component	Whole Serum	Serum Fraction Freed from Low-density Lipoprotein
S19	Trace	—
S9	0.47 g./100 ml.	0.42 g./100 ml.
S7	4.23 „ /100 „	4.62 „ /100 „
S4.5	3.54 „ /100 „	2.62 „ /100 „
Total	8.25 „ /100 „	7.66 „ /100 „

By adjusting the density of the medium, lipoproteins can be made to float in the ultracentrifuge while other proteins sediment. Dr. J. W. Gofman and Dr. K. W. Walton kindly undertook this study (Table I), and found a great increase of low-density β -lipoproteins (two to four times normal) but no increase of high-density (HDL-2 and HDL-3 of Gofman) α -lipoprotein. Dr. D. R. Stanworth analysed in the ultracentrifuge whole serum and serum freed from low-density lipoprotein. He found that the S₂₀4.5 component (mainly serum albumin) was reduced and that there was an increased S₂₀7 component which was apparently not affected by first removing the low-density lipoprotein (Table II). Only traces of S19 (macroglobulins) components were present. Similar results were found by Dr. J. W. Gofman, who also observed an appreciable and unusual S₂₀9–15 component.

Investigation of Family.—The patient had only two close relations: her daughter's serum cholesterol was 213 and her sister's 279 mg./100 ml. Paper electrophoresis showed a normal protein pattern in both of them.

Course and Treatment

She recovered uneventfully from her acute illness and her haemoglobin level was then maintained at about 8 g./100 ml. by blood transfusions every few months. Attempts to reduce the lipaemia were unsuccessful. A diet containing only 30 g. of fat daily had no effect. Treatment with sunflower-seed-oil emulsion (iodine number 122) produced a fall in the serum cholesterol from 800–900 mg./100 ml. to about 600 mg./100 ml. This emulsion was unpalatable, it did not affect her xanthomata, and it increased her weight, so it was stopped after three months. Treatment with triiodothyroacetic acid did not affect the serum cholesterol level or cause angina.

After two years of freedom from symptoms she developed incapacitating anginal pain and continuous back pain; x-ray films now showed the areas of bone destruction described above. Despite further blood transfusions and treatment with diamidinodiphenylamine dihydrochloride (M & B 938), her condition steadily deteriorated, and she died three and a half years after her symptoms began.

Post-mortem Findings (Dr. A. Pomerance)

The internal organs showed no fatty infiltration, and the atheromatous plaques in the aorta and great vessels were not unusually extensive for a patient of her age. The left coronary artery showed a local occlusion by a calcified plaque, but the coronary arteries were otherwise little affected by atheroma. The heart muscle showed no obvious fibrosis. A mass, 4 cm. in diameter, projected into the pleural cavity from the sixth left rib and in two places the skull was completely eroded by tumour tissue; the tumours were composed of typical myeloma cells. The bone-marrow contained numerous abnormal plasma cells. The immediate cause of death appeared to be purulent bronchitis.

Discussion

Waldenström (1952) described the case of a woman with myeloma, lipaemic serum, and large increase of β_2 -globulin on electrophoresis. Her fasting serum lipid was 1.9 g./100 ml. and serum cholesterol 580 mg./100 ml. She did not have xanthomata or coronary artery disease. Waldenström reviewed the literature and found only two similar, but poorly documented, cases. One of these had marked lipaemia (7.3 g./100 ml.), myocardial infarction, and myeloma, but no skin lesions (Brehmer and Lübbers, 1950). No analysis of the serum proteins was given. Hollan (1958) mentioned a patient who had myelomatosis, "with all the serum lipid fractions increased," and whose blood contained "an abnormal lipoprotein moving with the β_2 -globulin

fraction." This patient's plasma cells stained for fat, unlike those of our patient. Frame (1960) describes the case of a patient with a history of repeated episodes of pneumonia who presented with xanthomatosis and anaemia. He was found to have hyperlipaemia (1.48 g./100 ml.), a raised serum cholesterol (550 mg./100 ml.), a total serum protein of 9.5 g./100 ml. with 5.5 g. of γ -globulin, and 70% of myeloma cells in the bone-marrow. Thannhauser's (1958) patient, who died of multiple myeloma at the age of 57, nearly 20 years after developing widespread yellow-orange "xanthomatosis" of the skin, differs in that his serum cholesterol and phospholipid concentration were normal.

Since 1952 several studies of serum lipids in myeloma have been published. Sachs *et al.* (1954) found that the total serum lipid was raised in 3 out of 11 patients (highest value 1.4 g./100 ml.) but none of these had an abnormal β -globulin in the blood. The total serum cholesterol in the two patients with an abnormal β -globulin was actually lower than normal. Lewis and Page (1954) found that the serum cholesterol of 24 patients with myeloma was lower than normal. Very low concentrations of lipoprotein were found by ultracentrifuge studies in four of the patients who showed an abnormal β -globulin. The lipoprotein concentration in all the patients was normal or low. Magalini *et al.* (1956) found a normal cholesterol level in four cases of myeloma with normal distribution of the cholesterol among the serum globulins. Nikkilä (1953) observed that two out of four patients with myeloma had raised γ -globulin levels in the blood and also high serum cholesterol (395 and 448 mg./100 ml.). A high proportion of β - to α_1 -lipoprotein was found in three of the patients.

Snapper (Spain *et al.*, 1956) found no case of coronary occlusion among his extensive series of patients with myelomatosis. He and his colleagues compared the post-mortem coronary and aortic atherosclerosis in 104 cases of multiple myeloma with two control groups, one dying a violent death and the other dying from cancer. Those with multiple myeloma had less atherosclerosis than the other groups. Two of the few patients with advanced sclerosis had a high serum cholesterol level (300 and 314 mg./100 ml.). The serum cholesterol level in the other 15 patients in whom it was known was below 200 mg./100 ml. Some of these patients even had an abnormally low serum cholesterol—for example, 36 mg./100 ml.

It is possible that our patient had two diseases—"idiopathic hyperlipaemia" and multiple myeloma—both of which developed independently. Yet, because the two conditions came on within six months of each other, it seems more than likely they were associated, especially as it is unusual for "idiopathic hyperlipaemia" first to show itself after the age of 60 (Lever *et al.*, 1954; Malmros *et al.*, 1954). Her blood contained a high concentration of immunologically normal β -lipoprotein just as Gofman *et al.* (1954b) have found in other patients with xanthomata of skin and tendons. If the myeloma cells produced the lipoprotein, as they presumably produced the abnormal globulin, this might explain the association of the two disorders; I cannot offer any evidence either for or against this hypothesis.

Summary

A patient developed xanthomatosis and myelomatosis at the same time.

Her blood was lipaemic, containing a high concentration of β -lipoprotein.

An abnormal globulin was found. It migrated in the β_2 -globulin position on electrophoresis, moved with the S7 component in the ultracentrifuge, and stained heavily for carbohydrate.

A possible association between hyperlipaemia and myeloma is discussed.

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[Another salmonella sent to Colindale was identified as an organism called *Salmonella abony*.] "It so happened that our local medical officer of health remembered having read that this organism occurred in the alimentary tract of tortoises. So he visited the patient's home, and there, sure enough in the garden, he found a tortoise. It was hibernating, and the family readily agreed to the admission of this tortoise to hospital, and it is now asleep in the hospital laboratory. They are waiting for it to wake up, and I suppose one may say, 'be a good tortoise.' Then a specimen will be available from which they expect to discover *Salmonella abony*. The alimentary tract of the tortoise is alive with a whole tribe of these things that have caused quite a lot of human infection. One pathologist in the Public Health Laboratory Service runs a tortoise farm to collect them. It is a strange episode in human disease, but it is a very important one. Moreover, it is exceedingly difficult to get rid of, because the alimentary tract of the tortoise is exceedingly sluggish. It is necessary to put a tortoise into a thing called a tortorium, where it is kept for four or five years while it clears itself and frees itself from salmonella." (Speech by Lord Taylor, Public Health Laboratory Service Bill, February 4.)