be inclined to ascribe the fall in haemoglobin to a haemolytic crisis. Such a haemolytic crisis must be distinguished from the aplastic crisis described by Singer *et al.* (1950) and from the painful crisis. The latter appears to be due to erythrostasis from sickled red cells, and is commonly observed in bones, joints, and the abdomen (Golding *et al.*, 1959). Diggs (1956) has given good evidence that there is no increased destruction of red cells in the painful crisis, nor in any other acute episode related to sickle-cell anaemia. Our own experience seems to confirm this view: we have never observed a haemolytic crisis, and when we have seen an exacerbation of jaundice this has been accompanied neither by a fall in haemoglobin nor by a rise in reticulocyte count. Only once have we observed an aplastic crisis, and, in Jamaica at least, a "megaloblastic crisis" seems to be the major cause of such severely anaemic episodes in young children with sickle-cell anaemia.

Summary

In a series of 50 cases of megaloblastic anaemia of infancy five cases with associated sickle-cell anaemia were seen.

These cases presented with unusually low haemoglobin and reticulocyte levels for sickle-cell anaemia, and the bone-marrows were megaloblastic. Folic-acid therapy produced a dramatic increase in reticulocytes and a rise in haemoglobin to the level normally seen in sickle-cell anaemia. Some degree of associated iron deficiency was present in three cases.

In one of the cases described it was possible to measure the half-life of transfused erythrocytes with reasonable accuracy. The cell survival was found to be normal.

The question of crises in sickle-cell anaemia is discussed.

ADDENDUM.—Between November, 1959, and February, 1960, we have seen five more cases of sickle-cell disease with aplastic crises. Three of these were in one family in which a child with sickle-cell anaemia was affected. Three weeks later his sister with sickle-cell anaemia also had an aplastic crisis (Hb 1.8 g./100 ml.), and after another two weeks their mother, suffering from sickle-cell/haemoglobin C disease, had to be admitted with a combination of an aplastic and painful crisis.

We are grateful to Dr. E. H. Back, under whose care these infants were, for allowing us to see them and for making the case-notes available to us.

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SPHEROCYTIC ANAEMIA, COMPLICATED BY MEGALOBLASTIC ANAEMIA OF PREGNANCY

BY

H. G. KOHLER, M.D.

M. J. MEYNELL, M.D., M.R.C.P.

AND

W. T. COOKE, M.D., F.R.C.P.

From the United Birmingham Hospitals

The association of congenital spherocytic anaemia (acholuric jaundice) with megaloblastic anaemia during pregnancy has been recorded by Davidson (1952), by Drury and Geoghegan (1957), and by Giles and Shuttleworth (1958). A further case with this association in two successive pregnancies is here reported.

Case History: First Pregnancy

A primipara aged 27 was admitted in labour as an emergency with toxaemia in the 40th week of pregnancy. She had previously enjoyed good health; there was no history of jaundice or any relevant family history. The pregnancy had proceeded normally—under regular medical supervision—until about two weeks before admission, when she became pale, easily tired, and short of breath; oedema of ankles, albuminuria, and an increase in blood-pressure were found.

On the day before admission the membranes had ruptured, discharging meconium-stained liquor. Examination showed pallor of the skin and mucous membranes and marked oedema of face, ankles, and abdomen. Cardiovascular and respiratory systems were normal, with blood-pressure 150/75, pulse 92, and temperature 99° F. (37.2° C.). The urine contained a moderate amount of albumin. A healthy boy, weighing 7 lb. 15 oz. (3,600 g.), was born 12 hours after the onset of labour. The placenta was grossly infarcted; the membranes were complete. Blood loss was less than 1 pint (570 ml.).

A blood count after delivery was as follows: Hb, 4.4 g./100 ml. (30%); red cells 2,370,000; C.I., 0.65; white cells, 22,100 (polymorphonuclears 81%, lymphocytes 15% myelocytes 4%). The red blood cells were microcytic and hypochromic with marked anisocytosis and poikilocytosis; many showed polychromasia and punctate basophilia. There were eight normoblasts to 100 white blood cells.

Cultures of a catheter specimen of urine, and a high vaginal swab yielded a growth of coliform bacilli. After delivery blood-pressure was 130/70, pulse 128, and temperature 99.6° F. (37.6° C.) in the evening, which was not influenced by treatment with penicillin, sulphadimidine, or streptomycin. Three pints (1,700 ml.) of blood was transfused, but one week later a further count showed no great improvement. The white blood cells, however, had fallen to 2,850/c.mm.

Bone-marrow examination revealed a highly cellular marrow with many megaloblasts. A diagnosis of megaloblastic anaemia of pregnancy was made, and 100 mg. of folic acid was given by mouth for the first three days. Reticulocytes rose to 27% and the general condition improved. She was then transferred to a general hospital for further investigation. Clinical examination confirmed a grade I splenomegaly. Laboratory examinations showed increased corpuscular fragility and bilirubinaemia varying between 1 and 1.6 mg./100 ml.; other liver-function tests were essentially normal. Faecal fat excretion on a 50-g. daily intake over six days was normal, and free HCl was present in the gastric contents. Microspherocytes were

consistently present in the blood films and reticulocyte counts showed marked daily variations (5–23%) unrelated to treatment.

The patient was discharged home feeling well but still with splenomegaly and anaemia, a blood count of 3,200,000, and Hb 9.3 g./100 ml. Further observations over the next 12 months showed no essential change. Splenomegaly, bilirubinaemia, and increased osmotic fragility persisted. Splenectomy was refused and the patient failed to attend for further observation.

Second Pregnancy

The patient was next seen six years later, as an emergency admission to the Birmingham Maternity Hospital in the 29th week of her second pregnancy. In the interval she had been in good health and had remained so during her second pregnancy until two weeks before admission. She then began to look pale and feel increasingly tired, with shortness of breath. Examination was negative apart from a palpable spleen and marked pallor; blood-pressure 130/80, pulse rate 92, and temperature 98.6° F. (37° C.). The urine contained a trace of albumin. The uterus corresponded in size to that of a 26-weeks pregnancy. Foetal movements and heart sounds were present.

Investigations.—Blood count: Hb, 5 g./100 ml. (34%); red cells, 997,000; C.I., 1.7; white cells, 6,800; P.C.V., 11%; M.C.V. 110 cubic microns; M.C.H.C., 45.5%. Stained film: "typical late megaloblasts are present in small numbers." Schumm's test for methaemalbumin was positive and haptoglobin was absent from the electrophoretogram, indicating active haemolysis. Serum iron, 0.265 mg./100 ml.; serum protein, 6.4 g./100 ml. (albumin 3.3 g., globulin 3.1 g.); serum vitamin B_{12} (*Lactobacillus leichmannii* method), 40 $\mu\mu$g./ml.

Treatment

Folic acid, 20 mg. daily, was given by intramuscular injection for nine days. On the day after admission the patient's haemoglobin fell to 4.4 g./100 ml. (30%), and next morning her temperature rose to 102° F. (38.9° C.). She collapsed, and 2 pints (1,140 ml.) of cross-matched blood was transfused. Foetal heart sounds were now no longer perceptible. The serum-iron level had fallen to 0.111 mg./100 ml., suggesting a therapeutic response to folic acid, while the reticulocytes reached a peak of 15% four days after the start of treatment.

In view of the low serum level of vitamin B_{12}, a dose of 100 μg. of cyanocobalamin was given on two separate occasions. On the ninth day the haemoglobin level was 10 g./100 ml. (68%).

Progress

A red-cell fragility test showed diminished osmotic resistance. At her own request the patient was discharged to continue to take folic acid by mouth. Improvement was maintained at home until the 32nd week of pregnancy, when it was noted that the uterus corresponded in size to a 24-week pregnancy. A positive Spoulding sign confirmed the death of the foetus. Repeated examinations of the fibrinogen levels were made, but at no time did the level fall below 200 mg./100 ml. A mild but definite jaundice was noted clinically for the first time, while the serum bilirubin varied between 2 and 2.5 mg./100 ml. A reticulocytosis of 12% was also noted, which could not be accounted for as a therapeutic response. Repeated examinations confirmed the abnormal osmotic fragility of the red cells. The serum vitamin B_{12} level had fallen to 75 $\mu\mu$g./ml.

In the 34th week of pregnancy the patient was delivered at home of a macerated stillbirth. The post-mortem appearance of both foetus and placenta was consistent with intrauterine death at the 28th to 30th week of pregnancy, that is, the period of severest anaemia of the mother.

Ten days post-partum, the patient was seen at the out-patient department, feeling very well, though blood counts were still abnormal (R.B.C., 3,450,000; Hb, 10 g./100 ml.) and a blood film indicated excessive erythropoietic activity. The serum bilirubin was still elevated at 1.4 mg./100 ml. The patient remained steadfast in her refusal of splenectomy and declined further blood examinations. She was visited a year later by a health visitor, who found her in good condition, but failed to persuade her to attend at the follow-up clinic, nor was it possible to check the patient's relatives for the presence of spherocytosis.

Comment

Our purpose in reporting this case is to emphasize the possibility of two types of anaemia occurring in the same patient and the need for full investigation in all instances of severe anaemia in pregnancy. It may not be sufficient to arrive at a diagnosis, but the response to treatment should be watched also. This case and the one reported by Drury and Geoghegan (1957) presented as megaloblastic anaemia of pregnancy. The spherocytosis was discovered when treatment with folic acid resulted in considerable improvement but failed to bring about the usual return to normality.

The cases described by Davidson (1952) and by Shuttleworth and Giles (1958, personal communication), on the other hand, were diagnosed as cases of haemolytic anaemia before any pregnancy anaemia had developed. In both instances the observers were particularly interested in the study of megaloblastic anaemia, and thus diagnosed the complication promptly.

It is, however, quite possible that a number of such combinations are missed. A patient diagnosed as suffering from megaloblastic anaemia of pregnancy and improving on folic acid therapy may well be lost sight of after delivery. Conversely, a woman with known congenital haemolytic anaemia has a convenient explanation for any exacerbation that may occur in pregnancy, and consequently further investigation is shelved.

The close causal association between the congenital haemolytic anaemia and the complicating megaloblastosis is demonstrated by Drury and Geoghegan (1957). Their patient had developed megaloblastic anaemia in two consecutive pregnancies prior to splenectomy, but not in a third pregnancy which occurred afterwards. Our patient, by refusing splenectomy, did not give us an opportunity of confirming these observations. Two patients, however, have been observed in this centre who had had previous splenectomies for congenital haemolytic anaemia. Neither showed any tendency to develop a megaloblastic anaemia when pregnant.

The nature of the deficient factor in megaloblastic anaemia of pregnancy is still uncertain. The response to folic acid therapy and the low serum levels of vitamin B_{12} in our patient suggest that these vitamins were subject to increased demands. Davidson considered that "it is reasonable to suppose that the additional strain of pregnancy led to the development of megaloblastic anaemia by increasing the needs for haemopoietic factors in a patient whose requirements were already greater than normal because of pre-existing haemolytic anaemia."

Summary

A further case is reported of complication of congenital haemolytic anaemia by megaloblastic anaemia. This happened in two consecutive pregnancies more than six years apart. The patient had no symptoms of haemolytic anaemia when not pregnant or puerperal.

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

J. E. LENNARD-JONES, M.A., M.B., M.R.C.P.
Registrar, University College Hospital, London; late Medical Registrar, Central Middlesex Hospital, London

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 tuberous 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

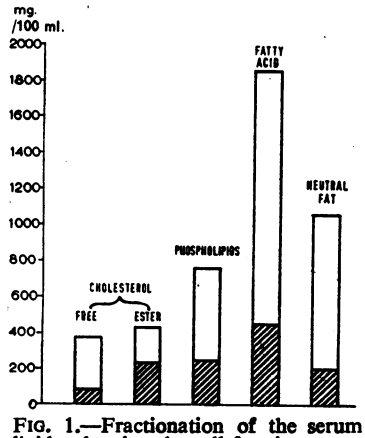

FIG. 1.—Fractionation of the serum lipids, showing that all fractions were increased. (Analysis kindly performed by Mr. N. Bell.) Hatched columns represent the normal upper limit.

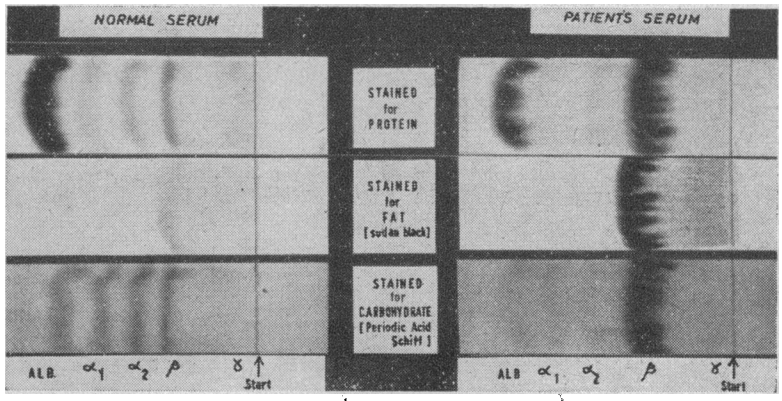

FIG. 2.—Electrophoresis of patient's serum, showing heavy staining for protein, fat, and carbohydrate in the β_2-globulin zone. The fat-staining zone migrated a little faster than the zone staining for protein and carbohydrate.