cythaemia vera who, after venesections, developed an anaemia resembling pernicious anaemia and who responded dramatically to liver therapy.

Wellington and Whitcomb (1960), however, reported the case of a patient with polycythaemia vera who, after venesections, developed an anaemia resembling pernicious anaemia and who responded dramatically to liver therapy. This patient died from pyelonephritis following prostatectomy. At necropsy normal red-blood-cell maturation was found in the bone marrow, as was myeloid metaplasia in the spleen. The case reported by Hinz (1957) showed cerebral haemorrhage and necrosis at necropsy, but otherwise the post-mortem findings were generally similar to those in the case we have described.

Summary

A case is described of a woman showing megaloblastic anaemia, who developed features of polycythaemia vera after treatment with liver or vitamin B₁₂. Anaemia recurred on discontinuation of treatment.

Clinical and haematological data over a period of 11 years are recorded. The patient was ultimately kept in satisfactory haematological balance with infrequent small doses of parenteral vitamin B₁₂.

The necropsy findings are summarized.

The occurrence of vitamin-B₁₂ deficiency developing in a patient prone to myeloproliferative disorder is regarded as a coincidence.

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Ageing, its Changes and its Promise is the report of the Tenth National Conference on the Care of the Elderly which was held in Blackpool in the spring of 1960. The conference covered the housing of the elderly; social policies: residential care for the physically and mentally frail; development in hospital care and hospital services; and a forward view of the next two years. There were discussion groups on visiting; clubs; preparation for retirement; training and recruitment; housing; and day centres and workshops. The report costs 5s. from the National Old People's Welfare Council, 26 Bedford Square, London W.C.1.

MEGALOBlastic ANAEMIA IN CONGENITAL SPHEROCYTOSIS

BY

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The purpose of this paper is to report two cases of congenital spherocytic haemolytic anaemia complicated by megaloblastic anaemia. The first case occurred in association with pregnancy. So far as we are aware, the second is unique in that, apart from the congenital spherocytosis, no cause for megaloblastic erythropoiesis could be discovered.

Case 1

The patient became pregnant at the age of 28 while in Germany. She first attended the antenatal clinic when 16 weeks pregnant and was found to have a haemoglobin level of 11.4 g./100 ml. At 22 weeks she began to complain of breathlessness and swelling of the ankles, and was noted to have a definite yellow tint to her skin. The dietary history was satisfactory and there was no abnormality of bowel habit.

She was admitted for investigation and the blood count showed: haemoglobin, 6.5 g./100 ml.; red cells, 1,790,000/c.mm.; white cells, 7,200/c.mm.; packed cell volume, 18%; mean corpuscular haemoglobin concentration, 36%; mean corpuscular volume, 101 cubic microns; reticulocytes, 7%. The red blood cells showed anisocytosis and macrocytosis with some polychromasia and an occasional normoblast. Some of the polymorph leucocytes were noted to be hypersegmented, but the platelets were normal. The bone-marrow showed erythroid hyperplasia and erythropoiesis was megaloblastic; leucopoiesis was normal. Free acid was present in the stomach. The serum bilirubin level was 1 mg./100 ml.

A diagnosis of megaloblastic anaemia of pregnancy was made and the patient was treated with folic acid in a dose of 10 mg. a day. A reticulocyte peak of 20% was reached on about the eighth day, but the haemoglobin level and red-cell count showed little change, and 19 days after her admission the haemoglobin was still 6.2 g./100 ml., and the red-cell count 1,420,000/c.mm. She was transfused with 3 pints (1.7 l.) of compatible blood, which raised her haemoglobin level to 9 g./100 ml. Despite continued folic acid therapy the haemoglobin level six weeks later had fallen to 6.5 g./100 ml. She was transfused with a further 4 pints (2.3 l.) of packed cells and three weeks later was delivered of a baby girl. Her haemoglobin level at this time was 10.4 g./100 ml. After the puerperium folic acid therapy was stopped, and five months after the delivery her haemoglobin level was 11.8 g./100 ml., red-cell count 4,770,000/c.mm., colour index 0.83, and white-cell count 9,200/c.mm.

Second Pregnancy.—The patient returned to this country and reported to the Haematology Clinic of the Royal Infirmary, Edinburgh, in the 14th week of her second pregnancy. She was complaining of severe lethargy, but was otherwise well and physical examination was negative.

Investigations.—The blood counts were as follows: haemoglobin, 9.9 g./100 ml.; red-cell count, 3,630,000/c.mm.; colour index, 0.92; white-cell count, 5,800/c.mm. The blood film showed some anisocytosis of the red blood cells, with the presence of both macrocytes and microspherocytes. The serum vitamin B₁₂ level was 80 µg./100

ml. (*Lactobacillus leichmannii* method without the addition of cyanide). Normal range, 110 to 810 $\mu\text{g.}/100$ ml. according to Girdwood, 1960).

Treatment.—Folic acid in a dose of 15 mg. daily was given by mouth and continued until the end of the puerperium.

Progress

Two months after starting folic-acid therapy the haemoglobin level was 9.8 g./100 ml., red blood count 3,230,000/c.mm., colour index 1.0, and reticulocyte count still 5.5%; two months later her haemoglobin level was 12 g./100 ml., red blood count 4,350,000/c.mm., colour index 0.93, and reticulocytes 7.7%. There was a slight excess of urobilinogen in the urine. Both the direct and the indirect Coombs test were negative and there was no evidence of any specific blood-group antibodies. On November 17, 1959, the patient was delivered of a live male child who was free of anaemia.

A red-cell survival test carried out by means of labelling the patient's own cells with radioactive chromium five months after delivery showed significant shortening of the red-cell survival time, the half-life of radioactivity in the patient's blood being 19 days (normal, 25–32 days). The reticulocyte count at this time was 3.4%, but there were no significant numbers of microspherocytes in the patient's blood nor in the blood of her two children and her mother.

Comment.—A case of haemolytic anaemia probably due to mild congenital spherocytosis presenting with megaloblastic anaemia in her first pregnancy. Folic acid was begun early in the second pregnancy, which was uneventful.

Case 2

This patient, a man aged 43, was perfectly well until one month before he was seen as an out-patient. He then developed a febrile illness, with generalized muscular pains and frontal headaches. The fever subsided, but he remained weak and lethargic. There was no previous history of jaundice.

Splenectomy had been performed on his brother in 1949 and on his sister in 1957 for congenital spherocytosis. All five of the sister's children have spherocytosis. The patient's father was considered for splenectomy in 1926 during an illness characterized by anaemia and jaundice, but he died at the age of 73, the operation not having been performed.

On examination the skin and mucous membranes were pale and there was an icteric tinge in the sclerae. The tip of the spleen was just palpable at the left costal margin.

Investigations.—Haemoglobin level, 6.7 g./100 ml.; red-cell count, 2,000,000/c.mm.; colour index, 1.12; white-cell count, 6,400/c.mm.; reticulocytes, 2.2%. The blood film showed the presence of microspherocytes and an occasional polychromatic cell. The serum bilirubin was 1.5 mg./100 ml., and urobilinogen was present in excess in the urine. The direct Coombs test was negative and no platelet antibodies could be detected. The blood urea nitrogen was 19 mg./100 ml.

Progress

The patient was admitted to hospital about one month later, when he was noted to have leucopenia of 800/c.mm. Blood transfusion with 4 pints (2.3 l.) of blood was carried out, and one week later the haemoglobin level was 8.9 g./100 ml. The leucopenia persisted, the white-cell count being 1,000/c.mm. (neutrophils 42%, lymphocytes 43%, monocytes 3%, eosinophils 10%, basophils 2%), and the patient was now found to be thrombocytopenic with only 15,000 platelets/c.mm. The leucopenia gradually improved, rising to a maximum of 3,800/c.mm. after a further week, but the platelet count fluctuated between 15,000 and 83,000/c.mm. The bone-marrow showed normoblastic hyperplasia, but some of the red-cell precursors had undergone megaloblastic change. Myeloid and platelet precursors were normal.

Treatment with folic acid, in a dose of 5 mg. three times a day, was instituted, and after an interval of two days the haemoglobin level was 9.6 g./100 ml., the white-cell count 7,000/c.mm., and platelets 140,000/c.mm.

Splenectomy was performed, and during the next few days the platelets rose, reaching a level of 660,000/c.mm. ten days after operation. The white-cell count was maintained at about 4,500/c.mm. Repeat bone-marrow examination showed that the cytology had returned to normal and erythropoiesis was normoblastic. Platelets were abundant.

Post-operative Vitamin B₁₂ and Folic Acid Studies

Serum vitamin B₁₂ (*L. leichmannii* method with added cyanide)—126 $\mu\text{g.}/\text{ml.}$ normal level, 140 to 1,000 $\mu\text{g.}/\text{ml.}$: Girdwood, 1960). Vitamin-B₁₂-absorption test, normal (20% faecal recovery of radio-activity). Folic acid excretion test, normal (the urinary output after a 5-mg. injection of folic acid was 1.95 mg. and the output of 5-mg. oral dose was 2.3 mg. Excretion index, 117.9%) (Girdwood, 1960). Maximal histamine secretion test (Kay, 1953), 0.9 mEq in the post-histamine hour.

Comment.—A case of congenital spherocytosis complicated by pancytopenia and megaloblastic anaemia.

Discussion

Megaloblastic erythropoiesis is occasionally observed when there is a prolonged increase in blood-cell production from a variety of causes—for example, leukaemia, erythraemic myelosis, haemolytic disease. The reason for the appearance of megaloblasts in the marrow in these conditions, while not definitely known, is thought to be due to deficiency of folic acid (Girdwood, 1956). Chanarin *et al.* (1959a) have been able to show that the clearance rate of an injected dose of folic acid from the plasma is increased in patients with haemolytic disorders compared with normal subjects, and this may indicate an increased requirement of folic acid and perhaps of other haemopoietic factors when marrow turnover is accelerated; it follows that a deficiency of these factors in varying degrees of severity could conceivably arise. Although the utilization of iron is also increased in these circumstances, iron falls into a different category because of the substantial body stores of this element and because the iron which is released from haemoglobin katabolism is almost all available for re-use.

Megaloblastic blood formation has been more often observed in association with the haemolytic anaemias than in the myeloproliferative syndrome, but this may merely reflect a tendency to longer survival in the former and hence deficiency of haemopoietic factors. Megaloblastic anaemia has been reported as a complication of acquired haemolytic anaemia (Baikie and Pirrie, 1956; Chanarin *et al.*, 1959a), thalassaemia (Crosby and Sacks, 1949; Goldberg and Schwartz, 1954; Jandl and Greenberg, 1958), and sickle-cell anaemia (Jonsson, 1958). There have also been instances of megaloblastic anaemia as a complication of congenital spherocytosis (Davidson, 1952; Drury and Geoghegan, 1957; Giles and Shuttleworth, 1958; Kohler *et al.*, 1960); however, so far as we are aware, all such cases have been associated with pregnancy.

The fact that pregnancy has often been implicated when haemolytic disease has been complicated by megaloblastic blood formation is worthy of comment. It has been known for some time that pregnancy may lead to an exacerbation of haemolytic anaemia, and McElin *et al.* (1950) think that this is particularly likely to occur from the third month of gestation onwards. Baker *et al.* (1958) showed that the levels of vitamin B₁₂ and folic acid were higher in the serum of newborn infants than those found simultaneously in their mothers. Other studies have shown that maternal serum

vitamin-B₁₂ levels decline through pregnancy, and after delivery infant levels are approximately twice those of the mother (Okuda *et al.*, 1956; Boger *et al.*, 1957; Dumont, 1957), and the low levels of serum vitamin-B₁₂ reported in the case of Kohler *et al.* (1960) and in the case recorded above are interesting in this respect. More recently, observations made in normal subjects indicate that in pregnancy there may often be an increased clearance of intravenously injected folic acid from the blood (Chanarin *et al.*, 1959b; Girdwood and Delamore, 1960).

The first patient described above presented in her first pregnancy with a megaloblastic anaemia that was unresponsive to folic acid therapy and with haemolytic anaemia in the second. It is possible that the prophylactic administration of folic acid in the second pregnancy may have prevented the development of megaloblastic erythropoiesis. Apart from the time of pregnancy the health of this patient has been entirely normal. In addition to this case, we have recently observed two other patients who were similar in that congenital spherocytosis was first suspected in pregnancy because on routine examination of the blood they were found to have anaemia and unusual reticulocytosis. In all of these patients the red-cell defect may well have remained unrecognized except for the advent of pregnancy.

The second patient is unusual in that we have not found records of any others in whom congenital spherocytosis produced megaloblastic anaemia in the absence of some other conditioning factor. Although the patient had a low level of vitamin B₁₂ in the serum he had hydrochloric acid in his gastric juice and normal absorption of vitamin B₁₂. He had a sudden crisis after an infection, and his blood picture was later characterized by leucopenia and thrombocytopenia. In the short period available for observation before operation, the administration of folic acid seemed to improve the white-cell and platelet counts.

It would appear that when haemolytic anaemia exists conditioned depletion of folic acid and perhaps also of vitamin B₁₂, as may occur in pregnancy, may aggravate the anaemia and lead to megaloblastic erythropoiesis; and that when a megaloblastic anaemia is discovered in pregnancy with an unusual reticulocytosis and is unresponsive to the usual therapy haemolytic anaemia should be considered. Moreover, as stated by Chanarin *et al.* (1959a), "a sudden increase in severity of anaemia or the onset of reticulocytopenia in a patient who is known to have a long-standing haemolytic anaemia should suggest the possibility that megaloblastic change is developing." We would add that in view of the appearance of leucopenia and thrombocytopenia in Case 2, sudden reduction in the white-cell and platelet counts may also indicate the need for examination of the marrow.

Summary

The cases of two patients in whom congenital spherocytosis is complicated by megaloblastic anaemia are described. In one patient it occurred in association with pregnancy, but in the other there appeared to be no complicating factor. It is suggested that if a patient suffering from chronic haemolytic anaemia suddenly becomes more anaemic, or develops leucopenia or thrombocytopenia, megaloblastic change should be suspected.

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CONGENITAL PYLORIC STENOSIS IN THE AFRICAN INFANT

BY

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In Europe and America congenital pyloric stenosis is regarded as the commonest condition requiring surgical treatment in infancy, and in Britain the incidence of the disease is usually estimated at three or four cases per thousand births. No case of this condition occurring in an African infant had been reported in the English literature until Petcher (1953) described two cases in Northern Nigeria. Since then, further cases have been reported from East, Central, and South Africa (Shepherd-Wilson and Gelfand, 1955; Luder, 1956; Griffiths, 1956; Hamilton, 1957; Menezes and Thethravusamy, 1957; Scragg, 1958; Boroda, 1960). A total of 11 cases of congenital pyloric stenosis affecting African infants have now been described, and their clinical details are summarized in Table I. In addition, Griffiths (1956) mentioned one and Scragg (1958) noted two further cases as having been diagnosed at their hospitals, but the cases were not described.

During the past three years six cases of congenital pyloric stenosis affecting Nigerian infants have been diagnosed and treated surgically in Ibadan, two cases in Lagos, and two cases in Enugu. They are reported briefly in Table II. In all these cases the typical pyloric tumour was found at operation and the standard Fredet-Rammstedt pyloromyotomy was carried out. Pre- and post-operative routines corresponded with the generally accepted techniques, and need no further consideration here.

Clinical Aspects.—A study of the case reports in Tables I and II shows that, with the exception of a rather late onset of vomiting in some cases, congenital pyloric stenosis, as so far reported in African infants, does not differ in its clinical aspects from the condition as it occurs in other races. The point is worth making, as cosmopolitan diseases do not always manifest themselves identically in different peoples. Two instances of

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