

Megaloblastic Anaemia associated with Adult Scurvy: Report of a case which responded to Synthetic Ascorbic Acid alone

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THE purpose of this report is to discuss, in the light of recent work, the case of a man, known to have hepatic cirrhosis, who developed clinical scurvy and a megaloblastic anaemia. Both the scurvy and the anaemia responded to the administration of synthetic ascorbic acid alone.

CASE REPORT

Philip McP., a labourer aged 57, had been in good health until April 1952 when he developed a respiratory infection for which he was admitted to hospital. Resolution was slow and, when he was discharged on June 21st, 1952, it was evident that residual fibrotic changes were present.

On this first admission to hospital, it was observed that he had hepatomegaly associated with slight disturbance of blood chemistry suggestive of hepatic dysfunction (serum albumin, 3.0 g. per 100 ml.; serum globulin, 3.5 g. per 100 ml.; thymol turbidity, 11.5 Maclagan units). Alkaline phosphatase and prothrombin were normal. The urine contained excess urobilinogen and a trace of bile. Liver puncture biopsy revealed some bile pigment retention and increased fibrosis. The blood picture was normal (red cells, 4,700,000 per c.mm.; haemoglobin, 13.7 g. per 100 ml.; leucocytes, 4000 per c.mm.). Bone-marrow examination showed nothing abnormal; erythropoiesis was normoblastic.

The patient was discharged from hospital on June 21st, 1952. By November the liver appeared to have increased in size, the edge being felt about 7.5 cm. below the costal margin.

The patient was not seen again until his admission in May 1953, when he complained of progressively increasing dyspnoea, anorexia and weakness, and loss of weight of about 5 months' duration.

CLINICAL FINDINGS

On readmission on May 22nd, 1953, he presented the typical picture of scurvy, with massive ecchymoses and petechiae on the lower limbs. General nutrition was poor and he admitted to having subsisted on a very poor diet since leaving hospital 11 months previously.

The liver was enlarged about 7.5 cm. below the costal margin. No splenomegaly was detected. Capillary fragility (Hess's Test) was moderately increased.

LABORATORY FINDINGS

A severe macrocytic anaemia with normal leucocyte count and slight thrombocytopenia was present (red cells, 1,850,000 per c.mm.; haemoglobin, 6.5 g. per 100 ml.; leucocytes, 5600 per c.mm.; platelets, 170,000 per c.mm.; reticulocytes, 3 per cent). Examination of bone marrow obtained by sternal puncture revealed that erythropoiesis was frankly megaloblastic (Fig. 1).

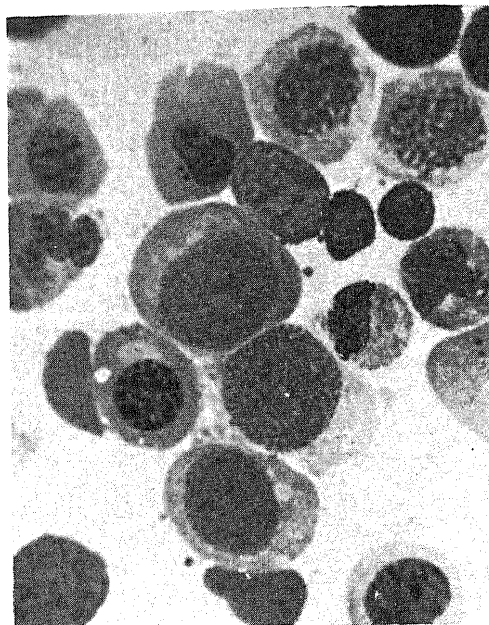


FIG. 1. Bone-marrow film before administration of ascorbic acid. Erythropoiesis is megaloblastic. $\times 900$.

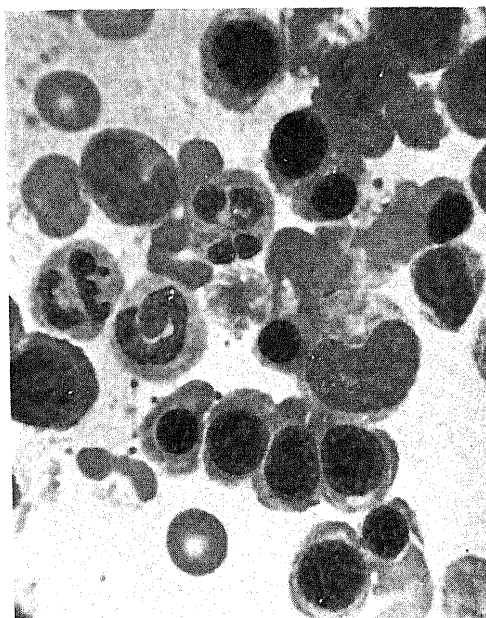


FIG. 2. Bone-marrow film on nineteenth day of treatment. Erythropoiesis is normoblastic. $\times 900$.

Gastric test-meal revealed a histamine-fast achlorhydria. A vitamin-C saturation test (Harris, 1943) revealed a very marked deficiency. Liver biopsy showed the picture of cirrhosis with interlobular fibrosis and bile-duct proliferation. Stainable iron was present in the liver tissue. Liver function tests revealed a slightly increased thymol turbidity (8.5 Maclagan units) and alkaline phosphatase (7.8 Bodansky units). The serum albumin was 2.3 g. per 100 ml. and serum globulin 5.3 g. per 100 ml.

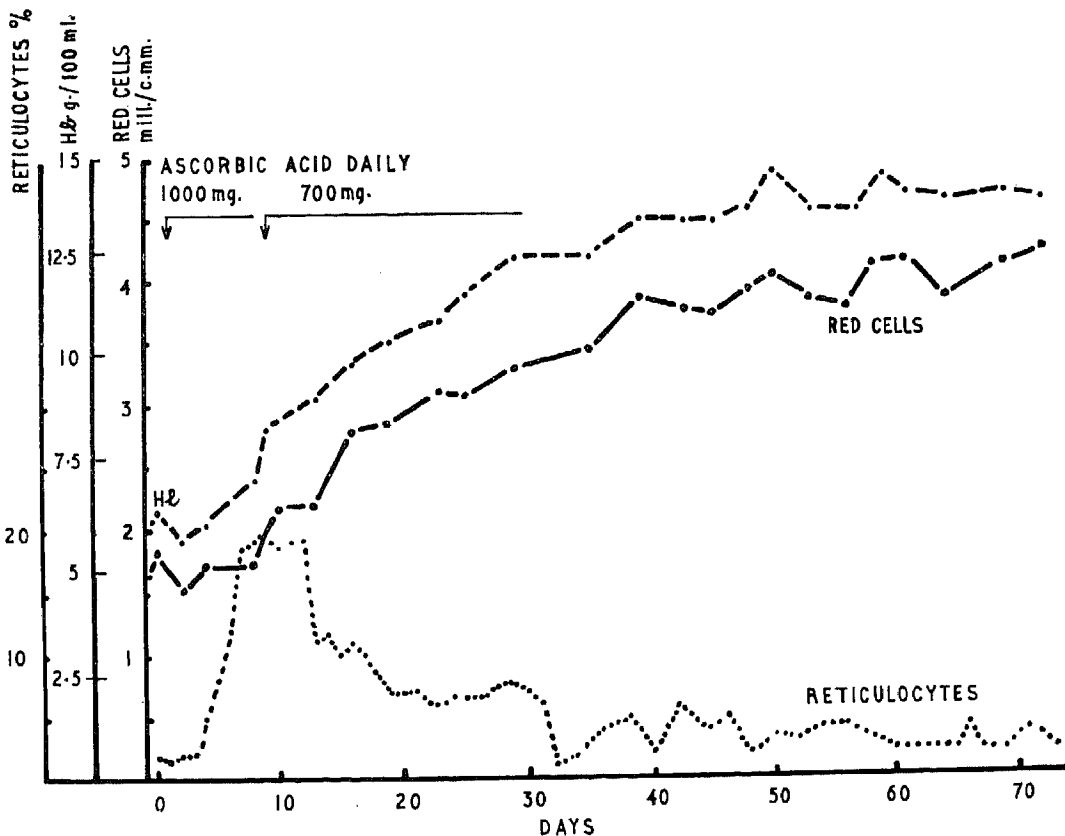


FIG. 3 Peripheral-blood response to the administration of ascorbic acid alone.

TREATMENT AND COURSE

It was established that no haematinic treatment had been given before admission to hospital and from May 22nd, 1953, he was put on a diet low in vitamin C and animal protein. Meat was later (June 15th, 1953) entirely eliminated from the diet. A vitamin-C saturation test was begun on May 23rd, and saturation did not occur until 7.9 g. of ascorbic acid had been given over a period of 10 days. Thereafter he was given 700 mg. of ascorbic acid daily for a further 21 days.

Under this treatment a reticulocyte response rising to 19 per cent occurred and a steady increase of red-cell count and haemoglobin followed (Fig. 3). Repeated marrow examinations revealed a progressive reversion of erythropoiesis towards the normoblastic type which was complete by the nineteenth day (Fig. 2).

Vitamin-B₁₂ and Folic-acid Estimation

Serum B₁₂ levels on June 6th and 9th (fourteenth and seventeenth day of treatment) were normal (325 and 250 µg. per ml. respectively) and the folic-acid content of the serum (on June 9th) was also normal (0.33 mµg. per ml.). These assays were repeated on July 29th with closely similar normal results (B₁₂, 160 µg. per ml.; folic acid 0.30 mµg. per ml.).

The patient was discharged from hospital on August 24th, 1953, with a normal blood picture. He attended from time to time for review as an out-patient and a year later he had only minor symptoms referable to the pulmonary fibrosis which had resulted from his respiratory infection in 1952. The hepatomegaly was unchanged; no splenomegaly was detected. There was no anaemia.

DISCUSSION

Although clinical scurvy is frequently associated with anaemia the aetiological relationship between the latter and the deficiency of ascorbic acid has never been established on a very secure foundation. Anaemia is not always present, even in severe scurvy (Mettier, Minot and Townsend, 1930; McMillan and Inglis, 1944; Brown, 1951; Bronte-Stewart, 1953), and when it does occur, it does not always conform to any particular type; it is usually normocytic, but it may be macrocytic or occasionally hypochromic (Brown, 1951; Bronte-Stewart, 1953). In addition, although there is some evidence that synthetic ascorbic acid is capable, under carefully controlled conditions, of inducing a haematological response (Vilter, Woolford and Spies, 1946; Brown, 1951; Bronte-Stewart, 1953), it has not yet been found possible to induce anaemia in man as a result of experimental vitamin-C deficiency (Crandon, Lund and Dill, 1940; Medical Research Council, 1948). Of course, even if ascorbic acid does play a part in haemopoiesis, deficiency of this substance may not be the only factor involved in the production of anaemia in scurvy. Associated dietary defects may be responsible in some cases. The haemorrhagic tendency has also been suggested as a factor, but no correlation exists between the extent of the ecchymoses or of external blood loss and the severity of the anaemia (McMillan and Inglis, 1944; Vilter, Woolford and Spies, 1946; Brown, 1951). The frequent finding of reticulocytosis in the peripheral blood, and the presence of icterus and increased urobilinogen excretion, are compatible with haemolysis; and there is evidence that the survival time of red cells transfused to scorbutic patients is reduced (Merskey, 1953). Nevertheless, there is really no acceptable evidence that there exists any haemolytic mechanism other than the destruction of red cells extravasated into the tissues (Proehle and May, 1952; Bronte-Stewart, 1953).

There seems to be a fairly wide and loosely held opinion that megaloblastic erythropoiesis is not uncommonly found in the anaemia of scurvy, and some authors have accepted this opinion as an established truth (May, *et al.*, 1950). There is no justification for this view. Anaemia in adult scurvy is almost invariably normoblastic even when it is macrocytic. The references to the finding of megaloblastosis by Jennings and Glazebrook (1938) and Vilter, Woolford and Spies (1946) are not convincing, and even if the statements of McMillan and Inglis (1944) and Bronte-Stewart (1953) are accepted, the rarity of its occurrence serves merely to suggest that some factor other than vitamin-C deficiency was responsible. Furthermore, a search of the literature has failed to reveal any well-authenticated instance of an adult megaloblastic anaemia which responded to synthetic ascorbic acid alone.

An accessory role has been ascribed to ascorbic acid in adult megaloblastic anaemias by several workers. In 1942, Dyke, Della Vida and Delikat produced some evidence that otherwise typical cases of Addisonian pernicious anaemia may be refractory to liver extract as a result of vitamin-C deficiency. In 1951, Holly stated that ascorbic acid was of therapeutic value in certain cases of megaloblastic anaemia of pregnancy. There does not appear to have been any definite confirmation of these reports, and in my own experience administration of ascorbic acid has contributed little if anything to the treatment of such cases. More recently, Boscott and Cooke (1954) have claimed that there is a disturbance of vitamin-C metabolism in patients with steatorrhoea, and that administration of vitamin C may be of value in the treatment of the megaloblastic anaemia associated with this condition. Unfortunately, the evidence presented in support of this view is not convincing. Similar results might equally well have been obtained had ascorbic-acid treatment been withheld.

Deficiency of ascorbic acid has been claimed to be an aetiological factor in certain cases of megaloblastic anaemia occurring in the first 12 months of life. In 1946, reports by Zuelzer and Ogden in America and by Amato in Italy established the existence of a genuine megaloblastic anaemia in infants. The cause of this anaemia was uncertain, but Zuelzer and Ogden and later Aldrich and Nelson (1947) observed that a high proportion of these patients were scorbutic. For the most part they had been reared on a proprietary milk food which was low in vitamin C. According to May and co-workers (1950) enrichment of this same food with vitamin C was, over a period of two and a half years, associated with the disappearance of this anaemia from their clinic.

This apparent association between ascorbic-acid deficiency and the development of megaloblastic anaemia in infancy led May and his colleagues (1950) to attempt to induce megaloblastic anaemia in immature monkeys with a diet deficient in vitamin C. They found that such an anaemia was readily produced if the diet were also low in folic acid, and that administration of ascorbic acid, folic acid, or folinic acid was followed by reversion of the marrow to normal, and by recovery from anaemia. They found also that the anaemia did not develop unless the liver's content of folinic acid was low. Effective treatment was followed by a rise in the folic- and folinic-acid levels in the liver. It was concluded that, in the immature monkey at least, ascorbic-acid deficiency in some way interfered with the metabolism of folic acid and related substances. The report by Nichol and Welch (1950) that ascorbic acid augmented the transformation of folic to folinic acid in liver cells seemed to provide a probable explanation for the observations of May and his associates; and the report by the latter workers (1951) of an instance in which their experimental megaloblastic anaemia was more responsive to folinic than to folic acid was accepted by them as favouring the view that their experimental anaemia was due to folinic-acid deficiency. It seemed probable that this deficiency had been precipitated by lack of vitamin C in animals whose folic-acid intake was low.

Although there is some evidence that ascorbic acid may be concerned in the metabolism of folic and folinic acids in man (Broquist, Stokstad and Jukes, 1951), it must be admitted that most of the work in the experimental field requires confirmation, and its application to the problems of human scurvy has still to be assessed. If, however, the conclusions of May and his associates are accepted, it is evident that the postulated role of vitamin C in erythropoiesis is indirect, and that deficiency of ascorbic acid tends to be associated with megaloblastic erythropoiesis only when accompanied by some additional disturbance of folic-acid metabolism such as defective intake of this substance.

The nature of the metabolic defect in the present patient remains to be considered. That

ascorbic acid was responsible for the haematological recovery is reasonably certain, and therefore it seems that on this occasion vitamin-C deficiency was responsible for the megaloblastosis. In the light of the previous discussion it would seem highly probable that a further factor, such as diminished folic-acid intake or some other defect of folic-acid metabolism, must have co-existed. The intake of folic acid is impossible to estimate, nor is it known if the tissues were low in folic acid prior to treatment. It is evident, however, from the assay studies carried out shortly after commencement of ascorbic-acid administration, that there was no evidence of folic-acid deficiency at this stage. The intake of folic-acid substances may have been below normal but there was nothing to suggest that the patient differed in this respect from other scorbutics. There was, however, one respect in which he differed from others. He had associated hepatic disease. Multilobular cirrhosis of the liver was demonstrated by repeated biopsy, and there was laboratory evidence of defective liver function.

It is now generally believed that the active principle of the folic-acid group of substances is folinic acid, and transformation of folic to folinic acid seems to be a function of liver tissue and one which is potentiated or augmented by ascorbic acid. It might, therefore, be expected that hepatic disease alone would occasionally be associated with megaloblastic anaemia as a result of interference with folic-acid metabolism. There is, however, no good evidence of this association (Davis and Brown, 1953). Nevertheless, it is conceivable that a defect in liver function combined with ascorbic-acid deficiency might result in folinic-acid deficiency and a megaloblastic anaemia analogous to that produced experimentally by May and his associates.

SUMMARY

The case is described of a man known to have hepatic cirrhosis who developed a megaloblastic anaemia in association with clinical scurvy.

The megaloblastic anaemia responded completely to synthetic ascorbic acid alone, as shown by reversal of erythropoiesis from the megaloblastic to the normoblastic type, reticulocytosis, and return of the peripheral-blood values to normal.

The rarity of megaloblastic anaemia in uncomplicated scurvy is stressed and arguments are advanced in favour of its presence in the patient described being due only in part to the vitamin-C deficiency, a predisposing factor being abnormal folic-acid metabolism due to the presence of liver disease.

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