and P.A.S. gave very good results in a large number of cases of endobronchial tuberculosis. The six cases of this condition treated with streptomycin and sulphone, however, produced only one satisfactory result; two showed considerable improvement and two slight improvement; and one patient, whose strain showed reduced sensitivity before treatment, was unimproved.

Complications.—The only serious complication encountered was haemolytic anaemia, which was present in three of the six patients who received a daily dose of 200 mg. or more of D.D.S. One of these showed a drop of over two million red cells per c.mm. in a fortnight. After a short interval (two weeks) treatment was resumed on the reduced dosage scheme, and the haemoglobin slowly improved. In spite of iron administration throughout there was an average drop of 10% haemoglobin in the 22 patients. Methaemalbumin was present in the blood in three of the high-dosage cases, and the violet coloration of the skin associated with this substance was observed in two further cases.

Discussion

The African leper and the European tuberculous patient appear to differ greatly in their tolerance to sulphone. Lowe's cases (Lowe, 1950) received up to 300 mg. of D.D.S. a day, giving blood levels from 0.8 to 1.4 mg. per 100 ml. without showing haemolysis, whereas a smaller dosage scheme in our cases caused severe haemolysis with a much lower blood sulphone level of from 0.2 to 0.6 mg. per 100 ml. It certainly seemed inadvisable to proceed with our original dosage scheme, which was based on the leprosy work, when serious drops in erythrocyte counts occurred with great rapidity.

There is no apparent trend suggesting a correlation between blood sulphone levels and emergence of resistant strains. The only surviving sensitive strain was in a patient whose blood sulphone never exceeded 0.15 mg. per 100 ml.

The emergence of eight resistant strains and only one fully sensitive strain after eight weeks' streptomycin treatment compares very unfavourably with the findings in the streptomycin and P.A.S. group of the M.R.C. (1950) trial, in which 97% showed a resistance ratio of less than 9 at the same stage of treatment. Bernard *et al.* (1950) found 51% resistant strains after 70 days of combined streptomycin and sulphone treatment, compared with 91% in the control group treated with streptomycin alone. This result also is much worse than the M.R.C. streptomycin and P.A.S. group.

Conclusions

D.D.S. is not tolerated in doses of 200 mg. daily by European tuberculous patients.

In the tolerated dosage it does not prevent or delay the emergence of streptomycin-resistant strains of *Mycobacterium tuberculosis*.

The clinical results with combined streptomycin and D.D.S. were not encouraging.

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MEGALOBlastic ANAEMIA OF INFANCY

BY

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Megaloblastic anaemia of infancy was first recognized as a distinct clinical syndrome by Zuelzer and Ogden (1946). The disease occurs predominantly within the first year of life, is characterized by a fairly distinctive clinical pattern, and responds to folic-acid therapy. The response to folic acid is often complete and permanent. Since its original description the disease has often been reported from America, though the only case recorded by British authors is that by Hutchison and MacArthur (1949). A further case is here described and the literature on the subject is briefly reviewed.

Case History

A baby girl aged 8 months was referred by her practitioner for a blood count on August 8, 1951. She was the youngest of a family of three children, her sister and brother being healthy and never having suffered from anaemia. The mother is in good health and has never suffered from anaemia either before or during her recent pregnancy. For the first three months of life the child had been breast-fed, and during this time she was well and there were no feeding difficulties. After the third month she was weaned and put on National dried milk, her diet being supplemented by daily orange juice and cod-liver oil. After about one month on dried milk she first started to show symptoms of feeding difficulty characterized by frequent attacks of diarrhoea and vomiting coupled with a marked reluctance to take her feeds. During the three months before admission increasing pallor had become evident.

Clinical examination revealed a very pale infant weighing 15 lb. (6.8 kg.)—about 3 lb. (1.4 kg.) under her expected weight—with a temperature of 99° F. (37.2° C.), but no other physical abnormality. A blood count at this time showed: Hb, 46% (6.8 g. per 100 ml.); red cells, 1,900,000 per c.mm.; reticulocytes, 0.8%; white cells, 16,000 per c.mm.; the differential count showed one nucleated red cell for every 100 white cells counted, and 63% lymphocytes.

The infant was admitted to hospital during the course of the next few days. A blood count on admission showed little change except for one important feature: nucleated red cells were still present, and a few of these showed a quite distinctive megaloblastic pattern. A diagnosis of megaloblastic anaemia of infancy was suggested on this finding and a tibial puncture was performed. The marrow showed a typical megaloblastic reaction. Not only were the erythroblasts of megaloblastic type, but hypersegmentation of polymorphs and ballooning of metamyelocytes were evident.

Other investigations included a fractional test meal, which showed free acid after histamine stimulation. The faeces were examined for evidence of steatorrhoea, but analysis revealed normal fat content. Tests for occult blood were negative, and no parasites were found in the faeces. The Wassermann reaction and Coombs test were negative. Radiographs of the long bones showed no abnormal features.

Treatment consisted of only one 10-mg. dose of folic acid and one 10-μg. dose of vitamin B₁₂. Within a very short time there was a dramatic clinical and haematological response. On the fifth day the reticulocyte count reached a peak of 26%. The haemoglobin showed a steady rise, and 15 days after treatment it had risen from 46% to 84%. Within 36 hours of treatment bone-marrow films showed a complete reversion to normoblastic erythropoiesis. Marrow

smears obtained 11 days after the starting of treatment again showed a normoblastic pattern. The clinical improvement was steadily maintained and the patient was discharged from hospital three and a half weeks after admission. Five months after discharge she relapsed. A blood count on readmission showed: Hb, 44% (6.5 g.); red cells, 2,400,000 per c.mm.; white cells, 6,000 per c.mm. Folic acid was administered and again dramatically converted the blood picture to normal. Since discharge the patient has been kept on a daily maintenance dose of 10 mg. of folic acid. She has remained well and her blood picture is normal in every way.

Discussion

Megaloblastic anaemia of infancy was first recognized by Zuelzer and Ogden in 1946, although Amato (1946) in the same year described several cases in Italian infants. Zuelzer and Ogden originally described 25 cases of the disease occurring in infants under 18 months of age. In their series of cases the outstanding clinical feature was extreme pallor. They described the disease as having an insidious onset, usually associated with symptoms of upper respiratory or gastro-intestinal infection. Of their 25 cases 6 showed evidence of clinical scurvy. All the infants responded well to treatment with pteroylglutamic acid (folic acid).

Since the above original report many other cases have been recorded (Aldrich and Nelson, 1947; Siebenthal, 1948; Hutchison and MacArthur, 1949; Luhby and Wheeler, 1949; Woodruff *et al.*, 1949; Taylor and Hettig, 1949; McPherson *et al.*, 1949; Sturgeon and Carpenter, 1950). The cases reported by these authors have served to confirm the clinical and pathological features originally described by Zuelzer and Ogden.

Reisner *et al.* (1951) have described four new cases of a megaloblastic anaemia in infants which they term "juvenile pernicious anaemia." The existence of pernicious anaemia in children is largely doubted, though several cases have been reported as true pernicious anaemia (Faber, 1928; Bachman, 1936; Langmead and Doniach, 1937; Davis, 1944; Petersen and Dunn, 1946). The last-named authors laid down the criteria for the diagnosis of pernicious anaemia in the following terms: the anaemia should be macrocytic; histamine-fast achlorhydria should be present; the marrow should show megaloblastic erythropoiesis; the anaemia should respond to liver therapy; and continuous treatment should be necessary to maintain a continued remission.

If these criteria be accepted, almost all of the previously reported cases of juvenile pernicious anaemia become unacceptable. In one case only, that described by Peterson and Dunn, does there seem to be any justification for naming the disease juvenile pernicious anaemia, and even in this case it may well be argued that enough time has not yet elapsed to satisfy the last requirement. It is not yet known whether these cases will need liver therapy into adult life.

Reisner *et al.* have gone even further, and have separated juvenile pernicious anaemia from megaloblastic anaemia of infancy on the response to vitamin B₁₂. Those children relapsing after vitamin-B₁₂ therapy are regarded as cases of juvenile pernicious anaemia, while those responding to it and not needing maintenance therapy are classified as megaloblastic anaemia of infancy. This classification has been adopted notwithstanding the fact that most cases of megaloblastic anaemia of infancy do not respond satisfactorily to vitamin-B₁₂ therapy. Moreover, of the four cases reported by Reisner and his associates three had free acid in the gastric juice. The very term pernicious anaemia has long since lost its descriptive value, and it is clearly wrong to extend the term to embrace other types of megaloblastic anaemia. The presence of a histamine-fast achlorhydria should be regarded as a *sine qua non* before a diagnosis of pernicious anaemia is established.

Aetiology

In view of the frequently reported association of scurvy in megaloblastic anaemia of infancy May *et al.* (1950) placed monkeys on various diets which resembled those reported for different infants who have developed the anaemia. The animals used were of a species known to be susceptible to vitamin-C deficiency and also capable of developing megaloblastic anaemia. The monkeys varied in age from newly born to nearly mature. Each diet was fed to the animals with or without vitamin C. The results were remarkable in that no monkey given vitamin C developed the anaemia and all monkeys deprived of ascorbic acid regularly developed megaloblastic anaemia. Administration of pteroylglutamic acid was promptly effective in relieving the anaemia. Ascorbic acid was also effective, but took much longer to cure the disease, whilst vitamin B₁₂ was without effect unless given in conjunction with ascorbic acid, when it produced prompt relief. It has been suggested that ascorbic acid does not have a direct haemopoietic effect but acts by sparing folic acid. Luhby and Wheeler (1949) regard the disease as essentially a folic-acid-deficiency state.

The possibility of maternal deficiency in folic acid has received some support since Jones and Smith (1950) demonstrated that pteroylglutamic acid could cross the placenta of the pregnant rat and affect embryonic haemopoiesis. This finding may well have some bearing on the aetiology of the disease.

Although folic acid is the drug of choice in the treatment of megaloblastic anaemia of infancy, McPherson *et al.* (1949) and Sturgeon and Carpenter (1950) have reported good results following the administration of vitamin B₁₂. Several cases, however, have shown little or no response to vitamin B₁₂.

It seems not unlikely that folic-acid deficiency is the most important factor predisposing to the development of the anaemia, but that ascorbic acid and vitamin B₁₂ are also important and may affect the degree of folic-acid deficiency.

Summary

A case of megaloblastic anaemia of infancy is described.

There was a dramatic response to folic-acid therapy.

Other cases of megaloblastic anaemia of infancy and so-called juvenile pernicious anaemia are briefly reviewed.

It is suggested that the term juvenile pernicious anaemia should not be used in describing megaloblastic anaemias in infancy and childhood.

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