RESPONSE OF MEGALOBlastic ANAEMIA OF PREGNANCY TO CRYSTALLINE PENICILLIN G

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The purpose of this paper is to describe a case of megaloblastic anaemia of pregnancy which was successfully treated solely with injections of crystalline penicillin G, 400,000 units daily for 17 days. The reticulocyte, erythrocyte, and haemoglobin responses were maximal for the blood count and conformed to the criteria described by Ungley (1950) for 15th-day responses. The red-cell count and haemoglobin rose from 1,300,000 and 3.5 g.% to 4,300,000 and 12 g.%. The patient appeared to resemble the cases of megaloblastic anaemia of pregnancy which we saw in Macedonia (Fairley, Bromfield, Foy, and Kondi; 1938; Foy and Kondi, 1939) and those which Wills *et al.* (1930-4) have described from India. The women here are mostly apparently well nourished, and have a well-developed layer of subcutaneous fat and a high indirect van den Bergh reaction. It was previously suggested (Foy, Kondi, and Hargreaves, 1950) that their anaemias might be related to a deficiency of first-class protein.

In a previous paper (Foy *et al.*, 1951) we described the treatment of megaloblastic anaemia in a non-pregnant woman with a histamine-fast achlorhydria, who responded similarly to seven injections of penicillin G (2,800,000 units). This woman had had three previous relapses of anaemia, which had been successfully treated with either "marmite" or liver. Apart from the absence of nervous symptoms the case had appeared to be one of pernicious anaemia.

Case History

The patient, a negress six months pregnant, belonged to the Jalu tribe inhabiting the eastern littoral of Lake Victoria. This is a hot, damp area with a heavy rainfall, much malaria, and considerable infestation with hookworm. The tribe itself has a sickling rate of 25%. The woman appeared to be well nourished and of good physique. She entered hospital on January 4, 1951, for weakness and breathlessness. We saw her first on January 6, when she was obviously gravely ill. Her liver was enlarged two fingerbreadths below the costal margin; her spleen was not enlarged; her nails, teeth, and tongue were all normal, as were her reflexes. Her heart and lungs showed nothing that was not compatible with her anaemic condition. She had one other child, aged 3, and she said that during that pregnancy she had been well, and had never had any anaemia. There was no history of miscarriages or abortions. Slight oedema of the ankles was present, and the upper lids were puffy. She said she ate meat three times a week—this may or may not have been so.

Reticulocyte counts were started on January 6, and a full blood examination carried out on the 11th is shown in the Chart. Price-Jones curves were done on January 10, when the reticulocytes were 1.6%, and, during treatment, on January 20, when they were 26%, and on January 27, when they were 10%. The M.C.A.T., mean diameter, macrocytosis, and M.C.V. for the various reticulocyte levels

are all given in the Chart. As will be seen, there is not always a good correlation between these variables, the lack of it being probably due in this case to spherocytosis (Foy and Kondi, 1943; Foy, Kondi, Hargreaves, and Lowry, 1950). A paper on the subject is now in course of preparation.

Before treatment the patient's marrow showed some intermediate megaloblasts and many giant stab-cells. Coombs's test was negative, and there was no sickling. A gastric test on February 5, after histamine, showed normal distribution of both free and combined acid. Schumm's test was positive, and the indirect van den Bergh was 2.8 mg. per 100 ml., indicating that there was some haemolytic process involved as in the Macedonian cases.

The Chart shows that the reticulocytes remained fairly stable at a low figure from January 6 to 12. On the 12th the patient received 200,000 units of crystalline penicillin G (sodium salt) twice daily, and similar amounts were given on the next 16 days. She said that she felt much better 24 hours after the first injection; this may have been merely a psychological reaction to an injection, but it is well known that similar feelings of well-being follow a liver injection. What was remarkable was the dramatic improvement in the patient's appetite.

On the seventh day of penicillin treatment her reticulocytes rose to 26%, and there was an improvement in the red-cell count and haemoglobin. On the sixteenth day after the beginning of treatment the red-cell count was 2,340,000, and the haemoglobin 7.4 g.%; on the twenty-second day the red-cell count was 2,830,000, and the haemoglobin 8.8 g.%.

As will be seen from the Chart, the penicillin was stopped on January 29 until February 7, and during this period the blood count remained unchanged or fell slightly, with the reticulocytes at about 3%. This stationary state occurred in our pregnant Macedonian cases with liver treatment, in which it was found that unless the liver was continued until the termination of pregnancy, or until the red-cell count had risen to between four and five millions, the patient either remained in a stationary condition or relapsed (Fairley *et al.*, 1938; Foy and Kondi, 1939). In the non-pregnant and in males it is necessary to continue the liver for only a few days after the attainment of the maximal reticulocyte response to ensure complete remission. In our previous case, that of a non-pregnant woman treated with penicillin, only seven days' administration was necessary to bring about a complete cure (Foy *et al.*, 1951). It seems that in pregnancy the extra drain on the haemopoietic system necessitates a continuation of treatment, or perhaps higher doses.

On February 7 the penicillin was again started in the same dosage. The reticulocytes rose to 7% on February 12, and on the 14th the red cells numbered 3,000,000 and the haemoglobin was 9 g.%. By February 17 the red cells numbered 3,500,000. At this stage the patient could be kept in hospital only with the greatest difficulty, and on February 26 she finally insisted on leaving. A complete blood examination done on this day showed that her blood count had risen to 4,300,000 and her haemoglobin to 12 g.%. The rest of the data appear in the Chart.

As a contrast to this case a non-pregnant negress entered the hospital with a megaloblastic anaemia, the red-cell count being 1,630,000 and the haemoglobin 4.2 g.%, and was given 80 µg. of vitamin B₁₂ ("cytamen"). After two months her red-cell count was 3,470,000 and her haemoglobin 8.5 g.%. On February 19, three months after the last dose of vitamin B₁₂, the red cells numbered 3,600,000 and the haemoglobin was 10 g.%.
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Discussion

This is the second case of dyshaemopoietic anaemia that we have treated with crystalline penicillin G. The response, as in the first case, was rapid, complete, and in every way similar to that obtained with liver, folic acid, and vitamin B₁₂. Crystalline penicillin (sodium

salt) contains no vitamin B₁₂ (Dr. Macrae, personal communication), and the mechanism by which the haemopoietic response is brought about cannot at present be stated with certainty. It is possible that the penicillin preparation contains some as yet unknown haemopoietic factor, or it may be acting as the so-called animal protein factor (when penicillin improves the growth of animals on certain diets). It is known that penicillin usually clears up cases of infantile diarrhoea, and penicillin, streptomycin, and chloramphenicol are all known to affect the flora of the gut both qualitatively and quantitatively, penicillin being the least radical in its effect. "Aureomycin" is stated to clear the gut almost completely of its flora, and unless vitamins are given with it vitamin deficiency may result. Whether all these antibiotics are affecting the same organism in the gut is unknown; it is likely, however, that some of them deal with one organism and some with another.

Rominger (1950) has claimed that in infants treated with streptomycin there is no change in the intestinal flora, and that the effects of this drug are in his opinion due to the elimination of toxins the origin of which are unknown. From work on baboons with megaloblastic anaemia we believe that the elimination of "toxins" produced by intestinal organisms may be an important factor in the results that we have been obtaining.

Cameron and his colleagues (1949) have suggested that in the megaloblastic anaemia occurring with intestinal stricture there may be a change in the flora of the gut that leads to the loss of an organism that synthesizes haemopoietic factors, or to the production of an organism that competes for haemopoietic factors, or to the production of antagonists. Aureomycin has been found to prevent the development of this kind of anaemia.

It has generally been assumed that the lack of first-class protein, or some factor contained therein, is important in the genesis of the megaloblastic anaemias of pregnancy and the so-called nutritional megaloblastic anaemias. We wonder, however, whether deficiency of protein is as important as other items in the diet, such as high intake of bulky carbohydrates, as has been found to be the case with rats. A deficiency of the first and an overabundance of the latter may produce an intestinal environment that is unsuitable for the synthesis and absorption of haemopoietic substances, or affect the liver. In most countries where we have worked, and where these megaloblastic anaemias are prevalent, the diet of large sections of the peasants consists predominantly of bulky carbohydrates (Greece, South Africa, Bechuanaland, Mozambique, East Africa). The line of demarcation between these megaloblastic anaemias of pregnancy, those of nutritional origin and pernicious, seems to become less and less clearly defined as knowledge progresses, and the terms "extrinsic" and "intrinsic" factors would seem to us to need revision.

It is not impossible that the relapses and remissions that occur in pernicious anaemia may be associated with changes in the intestinal flora, leading to the destruction or formation of haemopoietic substances such as vitamin B₁₂ or folic acid (Hunter, 1909; Noer, 1950). If bacterial synthesis is an important source of haemopoietic factors, then it might be possible by means of aureomycin to produce relapses, as it is known that both aureomycin and terramycin "antagonize" penicillin (Gunnison *et al.*, 1950).

Penicillin may bring about its effects by preventing bacteria utilizing essential substances that the body needs for synthesis of haemopoietic substances or nucleo-proteins; it may do this by modifying the flora of the gut (Krampitz and Werkman, 1947) or by interfering with the absorption of glutamic acid or other substances by bacteria in the gut (Gale and Taylor, 1946).

Work is continuing on further cases and by the use of additional methods; we therefore propose to defer further discussion until we can deal with the matter more extensively.

Summary

After the successful treatment of histamine-fast achlorhydric megaloblastic anaemia with crystalline penicillin G (sodium), this substance has been used without other treatment in the megaloblastic anaemia of pregnancy with the same striking results.

A maximum reticulocyte response was observed within five to eight days after the first injection. On the fifteenth day the expected red-cell count and haemoglobin level were reached. The patient was discharged with a red-cell count of 4,300,000 and a haemoglobin level of 12 g. %.

In both these types of megaloblastic anaemia the response to penicillin was similar to that which we have obtained with crude or refined liver, vitamin B₁₂, or folic acid. The marrow reverts to the normal picture, the megaloblasts disappearing rapidly and the giant stab-cells more slowly.

It is suggested that this response to penicillin may be due to any or all of the following: (1) changes in the flora of the gut, which may lead to the destruction of antagonists or competitors, or other factors which may be interfering with the synthesis, absorption, or utilization of haemopoietic factors; (2) interference with bacterial metabolism, thus releasing haemopoietic factors for the use of the body; (3) an effect on protein metabolism and the synthesis of nucleo-proteins from basic amino-acids; (4) the presence of hitherto unknown haemopoietic factors; and (5) the destruction of toxins produced by bacteria.

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A survey has been conducted for the Ministry of Health on the use of hearing-aids. A small proportion only of patients use their aids for the maximum period of 15 hours a day, and about half do not use them for more than five hours. Only one in five uses his aid for more than 10 hours a day. Several ways of economizing in battery consumption have been suggested as a result.

THE CLINICAL SIGNIFICANCE OF VITAMIN-A DEFICIENCY*

BY

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During recent years my colleagues and I have been working on different aspects of vitamin-A deficiency in man. I propose to outline here briefly some of our results, together with a critical review of the literature.

General Considerations

The sequels of vitamin-A deficiency have been studied extensively on experimental animals during the past 25 years. Most impressive changes were observed in the epithelial tissues: atrophy of the epithelial layer followed by reparative proliferation of the basal cells, with growth and differentiation into a stratified keratinizing epithelium (Wolbach and Howe, 1925). These changes occur presumably in all vertebrates, including the foetal stage (Wilson and Warkany, 1947). Epithelial cells with secretory function are predominantly affected (salivary glands, respiratory tract, eyes, skin, genito-urinary tract); keratinization in the secretory cells may produce severe obstruction with cystic dilatation of the gland ducts and accumulation of debris leading to secondary infection (Wolbach and Bessey, 1942). On the other hand, epithelial cells with chemical function—for example, liver cells—do not exhibit marked atrophy or keratinizing metaplasia. Further important tissue changes were observed in the skeleton.

In rats vitamin-A deficiency established at an early stage retarded the enchondral and stimulated the periosteal bone formation. In puppies and rabbits reared on a vitamin-A-deficient diet bony overgrowth of the labyrinth and thickening of the cranial bones (Mellanby, 1938, 1941) was observed, whilst the soft tissues continued to grow normally. Owing to this disproportion between growth of bone and nerve tissues an overcrowding of the cranial cavity, with multiple herniation of the cerebrum and cerebellum into the dural sinuses and compression of the cranial nerves, occurred. For the same reasons spinal-nerve roots herniated into the intervertebral foramina, and thus the mechanical pressure led to degeneration of various cerebral tracts and peripheral nerves (Mellanby, 1939, 1943). However, some degenerating influence of vitamin-A deficiency on the nerve tissue seems to persist (Irving and Richards, 1940).

The normal human organism has the tendency to maintain a more or less constant individually characteristic blood vitamin-A level which is only temporarily affected by the transitory fluctuations of vitamin-A intake. Under the same nutritional conditions healthy male adults seem on the average to have 10–20% higher vitamin-A values than females. Children up to the age of 16–17 have somewhat lower values than adults. The vitamin-A levels in pregnant women are lower than in non-pregnant women; the diminution is most pronounced during the last trimester of pregnancy. Within 24–48 hours after delivery, without any change

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