Drug Treatment of Disease

PREPARATIONS OTHER THAN IRON FOR THE TREATMENT OF ANAEMIA

BY

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The days when megaloblastic and refractory anaemias were treated with liver, whole or proteolysed, with yeast or yeast-concentrates such as "marmite," and with crude or refined liver extracts for parenteral injection are past. These medicaments owed what success they achieved to their content of factors such as cyanocobalamin and folic acid, and since the active principles are now cheaply available they may be directly prescribed with a consequent gain in specificity and in therapeutic efficacy. In this article only those compounds which have proved clinically effective in one or other variety of anaemia are discussed, and for the more controversial of these some references to original articles and reviews are given. Many other substances, ranging from riboflavin and pantothenic acid to copper, manganese, and other trace elements have been shown to be necessary for normal erythropoiesis in laboratory animals, but deficiencies of these substances severe enough to produce anaemia do not occur in man, and they have not therefore been included. I have also excluded further reference to humoral "erythropoietins" and to batyl alcohol, since, despite their experimental interest, they have not yet established a place in clinical therapeutics.

Vitamin B₁₂ (Cyanocobalamin)

This compound was isolated from animal liver in 1948 and identified as the essential anti-pernicious-anaemia factor. Since that time it has become readily available as a product of controlled fermentation by *Streptomyces griseus* and has firmly replaced liver extracts in the treatment of pernicious anaemia, being cheaper, more effective, more concentrated, and much less liable to induce allergic reactions. For initial treatment cyanocobalamin should be given subcutaneously or intramuscularly in a dose of 250 µg. twice weekly for three weeks, the dosage then being reduced to 250 µg. weekly until the haemoglobin has reached a normal level. Maintenance requirements vary in individual patients, but 250 µg. monthly is usually ample for uncomplicated cases, while a similar dose at weekly or fortnightly intervals should be given if there are residual symptoms of subacute combined degeneration of the cord.

Alternatives to parenteral vitamin B₁₂ for the treatment of pernicious anaemia have been proposed. They include cyanocobalamin snuff, mixtures of the vitamin with intrinsic factor, peptides, or sorbitol, and mucosal extracts containing intrinsic factor activity. While these various preparations have sometimes been effective and possess the obvious advantage of avoiding the need for injections, none of them can be recommended for routine use at present. They all appear to exhibit a certain irregularity in action and a tendency to become decreasingly effective after a time. The risk of relapse

is too serious to be neglected, especially since relapse may be heralded by the rapid development of neurological features rather than by gradual fall in the haemoglobin level.

In megaloblastic anaemias other than pernicious anaemia, when deficiency of cyanocobalamin has been shown to exist by measurement of serum levels or by radioactive uptake studies, parenteral cyanocobalamin again provides the only reliable replacement therapy.

Folic Acid (Pteroylglutamic Acid)

Folic acid, like vitamin B₁₂, is an essential haematonic whose absence or deficiency leads to the development of megaloblastic erythropoiesis, with macrocytic anaemia. The two substances are associated, together with ascorbic acid, in the metabolism of purines and pyrimidines in nucleoprotein synthesis. There is evidence that deficiency of one substance may sometimes be made good, partially and for a restricted period, by an excess of the other. Thus, for example, pernicious anaemia in relapse has been found to respond haematologically with a brisk reticulocytosis and satisfactory rise in haemoglobin when folic acid has been given. The neurological features of pernicious anaemia are not improved, however, and subacute combined degeneration of the cord may occur, sometimes with explosive onset, during the course of treatment. Moreover, folic acid is ineffective for maintenance therapy; even when initial haematological response has been good the haemoglobin level begins to fall again after a variable period of weeks or months. For these reasons, and especially because of the grave risk of serious neurological disorder, folic acid is strictly contraindicated in the treatment of pernicious anaemia. The prohibition applies also to the use of proprietary mixtures containing folic acid for inadequately diagnosed anaemias.

Deficiency of folic acid may arise from many causes, ranging from coeliac disease and idiopathic steatorrhoea to pregnancy and the administration of anticonvulsant drugs. Unfortunately many of the conditions leading to deficiency of folic acid may also cause deficiency of cyanocobalamin, and it may be difficult to determine which deficiency predominates. Discussion of these diagnostic problems is beyond the scope of the present article, but when doubt about the cause of a megaloblastic anaemia exists it seems most reasonable to start treatment with cyanocobalamin injections, and, only if response does not occur or is suboptimal, to replace or supplement these with folic acid (10–20 mg. daily) and ascorbic acid.

Ascorbic Acid

Scurvy is an uncommon disease among civilized populations to-day, and though anaemia may be

prominent among the features of severe scurvy there has been much difference of opinion on whether the anaemia is directly due to lack of ascorbic acid or is secondary to haemorrhage or dietary deficiency of B vitamins. Animal experiments have given rather equivocal answers, and indeed scorbutic states induced in the laboratory have often not been accompanied by anaemia. During the past 10 years, however, a complex relationship has been found to exist between ascorbic acid, the pteroylglutamate complex, and cyanocobalamin which helps to explain the confusing experimental results. It appears likely that all these substances are essential for erythropoiesis, but that partial deficiencies of one may be compensated for by increased utilization of others. Combined deficiencies of moderate degree may readily produce anaemia in laboratory animals, but deficiency of ascorbic acid alone is unlikely to do so unless a severe degree of depletion is achieved and maintained for some weeks. Perhaps the chief function of ascorbic acid in erythropoiesis is as a hydrogen donor in the conversion of folic acid to the active folinic acid (Nichol and Welch, 1950).

As for the clinical importance of ascorbic acid in erythropoiesis in man, the study of Bronte-Stewart (1953) may be taken to establish firmly that anaemia frequently occurs in severe adult scurvy, that it responds specifically to ascorbic acid, and that it has no important element of iron deficiency. The high doses of ascorbic acid, up to 1,000 mg. intravenously each day, given in severe scurvy lead to rapid improvement in the anaemia. Thus ascorbic acid must be regarded as an essential haematinic. Whether less severe deficiencies of ascorbic acid play a part in the genesis of anaemias secondary to intestinal malabsorption in man is less certain; probably ascorbic acid is important in some cases in facilitating the therapeutic action of folic acid and cyanocobalamin (Boscott and Cooke, 1954).

Pyridoxine

In experimental animals diets deficient in pyridoxine have long been known to induce an anaemia characterized by hypochromia and microcytosis but with a high serum iron. A similar anaemia in man, responsive to pyridoxine, was first recognized by Harris and his colleagues (1956), and since that time several more examples of the condition have been reported. Recent case reports with reviews of the literature and discussions of pathogenetic mechanisms include those of Verloop and Rademaker (1960), and Erslev and his associates (1960). Pyridoxine plays an essential part, after phosphorylation, in the earliest stages of haem synthesis, and impaired formation of haem might be expected to result from dietary deficiency of pyridoxine, from inadequate absorption, from faulty intermediary metabolism, or from excessive demand. Whether an individual patient has indeed pyridoxine-deficiency anaemia and which mechanism is at fault is not easy to establish by currently available diagnostic methods, but fortunately a therapeutic trial of pyridoxine, given orally or by subcutaneous injection, is easily carried out, and reticulocytosis with rise in haemoglobin level rapidly ensues in responsive patients. Although the condition is rare, treatment is so effective that pyridoxine should be given a trial in every case of non-thalassaemic hypochromic microcytic anaemia with high serum iron. Appropriate initial dosage of pyridoxine is 50–100 mg. subcutaneously for 4–7 days, followed by oral

maintenance treatment of 25 mg. daily or less according to the haemoglobin response.

Cobalt

Although a syndrome characterized by anaemia, anorexia, and wasting is known to occur in ruminants in Australia and Denmark as a result of cobalt deficiency, there is no convincing evidence that dietary deficiency of cobalt ever occurs in man. Nevertheless, cobalt has been used, sometimes successfully, in the treatment of refractory anaemias of various kinds, including anaemias of chronic infection and chronic renal disease, and primary red-cell aplasias (Gardner, 1953; Coles, 1955; Seaman and Koler, 1953). The occasional success of this treatment is not due to the repair of cobalt deficiency but to a stimulation of erythropoiesis, which cobalt has long been known to produce. The mechanism of this action, earlier thought to involve inhibition of oxygen-transporting enzymes and consequent anoxia of the marrow, is now believed to be an indirect one. Goldwasser and his colleagues (1958) have shown that injection of cobalt in experimental animals leads to an increase in circulating plasma erythropoietin, probably as a result of anoxia in the kidneys rather than in the bone-marrow.

The use of cobalt for anaemia is not devoid of hazards. Oral doses of 20–100 mg. of cobaltous chloride daily seem to be necessary, and such large doses may produce nausea, vomiting, and severe tinnitus, while there is a slight risk of inducing goitre and hypothyroidism. There is as yet no reliable method of forecasting whether cobalt is likely to be effective in a given case of refractory anaemia, and unfortunately a therapeutic trial needs to be continued for some four weeks before failure to respond can be assumed. Erythropoietin assays may prove helpful in selecting patients for cobalt therapy, since low levels of plasma erythropoietin might be expected to show improvement after administration of cobalt.

Thyroxine

The majority of patients with myxoedema develop a mild anaemia, frequently macrocytic, which slowly responds to administration of thyroxine in doses sufficient to control the myxoedema. Experimental studies have shown that thyroidectomized animals develop a similar anaemia with decreased erythropoietic activity in the bone-marrow. The mildness of the anaemia, the failure of thyroxine to induce polycythaemia in normal animals, and the normal response to hypoxia shown by thyroidectomized animals all suggest that the influence of the thyroid gland on erythropoiesis is not a specific one, but a manifestation of general metabolic stimulation (Van Dyke *et al.*, 1954). Clinically, severe anaemia in myxoedema is unlikely to be due to thyroid deficiency alone, but to a combination with iron deficiency or even, uncommonly, with pernicious anaemia. In such cases, treatment with iron or cyanocobalamin needs to be supplemented with thyroxine if an adequate response is to be achieved.

Testosterone

The red-cell count and haemoglobin concentration is generally higher in men than in women, and this difference is thought to be due to contrary actions of

testosterone and oestrogens on erythropoiesis, the former providing a mild stimulus and the latter mild inhibition. Mild anaemia may follow orchidectomy both in man and in experimental animals, and this responds to testosterone, but the anaemia is never severe and it is hard to believe that testosterone normally exerts more than a slight and probably non-specific action on erythropoiesis. Nevertheless, occasional examples of dramatic response to testosterone have been observed in patients, especially children, with idiopathic aplastic anaemia (Shahidi and Diamond, 1959), and a therapeutic trial in such patients is certainly justified. The hormone is best given intramuscularly as testosterone propionate 5 to 50 mg. daily, though methyl testosterone, 20 to 100 mg. daily, may be dissolved under the tongue when injections are to be avoided.

A.C.T.H. and Adrenocortical Steroids

These compounds have at least two important contributions to make in the treatment of anaemias. The first results from their effectiveness in suppressing antibody formation and in minimizing the deleterious consequences of antigen-antibody union at cell surfaces, and has its chief application in the treatment of auto-immune acquired haemolytic anaemia. Initial doses as high as 100 mg. daily of prednisone may be necessary to control a serious haemolytic state, but satisfactory maintenance can often be achieved with as little as 5 to 10 mg. daily, and treatment can sometimes be discontinued without relapse after a variable period. Occasional patients who are apparently refractory to prednisone or cortisone respond well to A.C.T.H., but generally there is little to choose between A.C.T.H. and the cortical steroids in therapeutic efficiency, and the latter are most often used because they can be taken orally. The second major use of these steroids in anaemia is the treatment of aplastic and pancytopenic states, when their marrow-stimulating properties may expedite the return of marrow function. Unfortunately their use is successful only in a small minority of cases, but a trial should invariably be made.

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"The number of cases referred to the solicitors during the year shows a tendency to increase, but the amount paid in damages, at £2,384, is less than the amount paid out for some years. The law charges, however, at £5,037, indicate how much it costs to protect the interests of members against claims which cannot be justified." (*57th Annual Report, Medical and Dental Defence Union of Scotland Limited.*)

MEDICAL ELECTRONICS

DOCTORS AND ENGINEERS IN CONFERENCE

Some 180 papers, lectures, and contributions were presented at the Third International Conference on Medical Electronics, held in London from July 21 to 27. The conference was organized by the Electronics and Communications Section of the Institution of Electrical Engineers in association with the International Federation for Medical Electronics. The chairman at the opening session was Sir WILLIS JACKSON, F.R.S., president of the Institution of Electrical Engineers, and he was supported by Dr. V. K. ZWORYKIN (U.S.A.), president of the International Federation for Medical Electronics, who said that the conference was concerned with the application of the most recent accomplishments in technology, and more particularly electronics, in the medical field.

Among the subjects discussed at the various sessions were instrumentation for medicine and biology, the motor and nervous systems, medical electronics in aviation and space flight, efficiency, reliability, and safety of hospital and medical electronics equipment, instrumentation for physiology and neurophysiology, the circulatory system, electronic aspects of sight, hearing, and locomotion, the respiratory system, ultrasonics and microwave radiation, telemetering, the digestive system, isotopes, radiology, and obstetrics. It is possible to report here only a few out of the large number of papers read at the conference.

Instrumentation in Medical Practice and Research

In his opening address Professor J. McMICAL, F.R.S. (London), said that electronic instrumentation must be welded with medical engineering and with the use of automation in the laboratory. For dealing with the quantitative data which were being accumulated electronic computers would soon come into their own, but he pointed to a real danger of entering on an era of press-button research in the biological field. It was so easy once the apparatus was available to proceed to collect quantitative data, and the application of a few statistics made the whole thing look like a profound contribution to knowledge. "Your instruments extend enormously our powers of observation," he continued, "but this does not necessarily improve our powers of thinking. Our journals are full of ill-digested data rather than research. Often too little effort is made to fit the findings to existing knowledge or to consider how current hypotheses may have to be modified, or even to consider whether the data are really established and acceptable."

The exceptional and the unexpected in research were often the keys to new knowledge. The stimulus to thought arose in the laboratory itself and in the making of observations at first hand by the observer. The joy of research lay in creative activity. While electronics, electronics technicians, electronics engineers, physicists, and physical chemists would be required in increasing numbers and with increasing responsibilities in medical research, the ultimate interpretation of the data would always depend on the biologists, physiologists, and physicians trained to the appreciation of the complex biological variables likely to be at work in the particular experimental circumstances.

Ultrasonics

A session devoted to ultrasonics and microwave radiation evoked particular interest. In a survey of the diagnostic use of ultrasound, Dr. D. H. HOWRY, of the United States, explained that ultrasound was composed of mechanical waves which were generated by the instruments in the form