rheumatism of childhood cannot be of great importance, since there are many facts that declare it primarily an environmental disorder.

Glover (1930) has called rheumatism an obsolescent disease, and this no doubt depends on the slow removal of the appropriate environmental stresses amongst the poor. Such "gradualness may be inevitable," but it is suggested that the health of the rheumatic child is improved and stabilized by treatment of its nervous instability. This is done by the removal of the grosser environmental stresses, if possible, by the adjustment of the child's reaction to its environment, and, most important of all, by continuous sedation with phenobarbitone.

I am grateful to Lieut.-Col. Paul Wood, R.A.M.C., for much helpful criticism in the revision of this paper.

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MACROCYTIC ANAEMIA OF PREGNANCY AND THE PUERPERIUM

BY

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It is generally believed that the macrocytic anaemia, or so-called "pernicious anaemia," of pregnancy is due to a lack of the anti-pernicious-anaemia principle brought about by one or more of the following causes: (a) a temporary depression of secretion of the specific intrinsic factor of Castle (Strauss and Castle, 1933; *Brit. Ency. med. Pract.*, 1936); (b) a deficient intake of the extrinsic factor (Strauss and Castle, 1933; *Brit. Ency. med. Pract.*, 1936); and (c) a diversion to the foetus of the anti-anaemic principle itself (Vaughan, 1936). The usual conception of treatment is that it is similar to that of Addisonian pernicious anaemia except that in the macrocytic anaemia of pregnancy it may be discontinued after delivery, when the demands of the foetus no longer exist and a return of the secretion of intrinsic factor has been presumed to occur (Strauss and Castle, 1933; Vaughan, 1936). The three cases to be described are of interest because there was little or no improvement in the blood level after liver extracts given parenterally, but rapid regeneration occurred when this treatment was supplemented by the ingestion of whole liver.

Case I

Mrs. A., aged 39, was admitted to hospital in Nov., 1941, during the 36th week of pregnancy. For two weeks before admission she felt tired and breathless and vomited frequently. The pregnancy had until then been uneventful, and she had

taken a diet which was notable in only one respect—namely, that she had never cared for and seldom ate any red meat. She had five children, all alive and well. The last child was born in Nov., 1937, and at that time she was noted to be severely anaemic and was given a blood transfusion after labour. Next day the haemoglobin was 30% and a film was described as showing the features of pernicious anaemia. In the next 13 days 40 c.cm. of campolon was injected. Reticulocyte counts apparently were not done, but it is of interest that 15 days after the first injection the haemoglobin had fallen slightly to 28%. Large doses of campolon were continued, and recovery was then rapid. She was discharged with a haemoglobin of 70%; no further treatment was given. There seems little doubt, therefore, that she had had "pernicious anaemia" of pregnancy in 1937.

When seen in Nov., 1941, she was obviously severely anaemic. Physical examination revealed no notable abnormality. The tongue and nails were normal. Free hydrochloric acid was secreted after the injection of histamine—maximum, 30 units at one hour. The haemoglobin was 20%, and the other findings were compatible with Addisonian pernicious anaemia except that anisocytosis was less than would be expected at this level. A Price-Jones curve gave a mean cell diameter of 8.5 μ .

In the first three days 10 c.cm. of campolon and 8 c.cm. of anaheamin were injected (see Fig. 1). Three days after the

FIG. 1.—Chart of Case I.

first injection there was a reticulocytosis of 9.7%. On this day delivery occurred and a blood transfusion of two pints was given. The blood loss after delivery was estimated at about one pint. The slight improvement produced by the transfusion was transient and the blood count had fallen almost to the initial level on the tenth day. From the eighth day onwards daily injections of anaheamin or neo-hepatex and small doses of campoferron orally were given. On the sixteenth day there was a reticulocyte crisis of 40%, but very little rise in the red cell count occurred. On the fourteenth day treatment with whole liver was begun. The reticulocytes were 29% on the thirtieth day, and the blood count then rose rapidly.

Case II

Mrs. B., aged 39, was admitted to hospital in June, 1941, five weeks after giving birth to her sixth child. She insisted that she had no untoward symptoms until three weeks after delivery, when she began to be breathless and tired; but she was inclined to belittle her symptoms, and it is quite possible that their onset was earlier than this. At the same time there developed a burning pain in the tongue, and her appetite, which previously had been excellent, began to fail, so that shortly before admission she had literally to force herself to eat. Her diet appeared to have been satisfactory, and was

distinctly better than that taken by most women of the hospital class.

The tongue showed no papillary atrophy, but there was a superficial ulcer on each margin. The spleen was easily palpable four fingerbreadths below the costal margin. Free hydrochloric acid was secreted after the injection of histamine. The initial blood count was: Hb 27%, R.B.C. 1,400,000, C.I. 0.96, reticulocytes 3.7%, W.B.C. 3,100 (see Fig. 2). The appearances in a film were compatible with Addisonian pernicious

whether this fact is due to its rarity or whether it has been largely overlooked. A study of the literature shows that cases of this type have occurred (Stevenson, 1937-8; Ungley, 1938); but little emphasis has been laid upon them, and in a recent review by Sodeman (1940) they receive no mention. In the discussion which followed a communication based on the cases reported here (meeting of the Association of Physicians of Great Britain and Ireland, April, 1942), L. S. P. Davidson

FIG. 2.—Chart of Case II.

anaemia. Sternal marrow showed 55% of erythroblasts, with 18% of megaloblasts. Following injection of 2 c.cm. of anahaemin there was a small reticulocyte response (maximum 7.6% on the fourth day), but in spite of this the blood count fell slightly. On the seventh day after beginning treatment with whole liver, campoferron, campolon, and anahaemin the reticulocytes reached a peak of 27%, and this was followed by extremely rapid blood regeneration, the haemoglobin rising by 60% and the red cells by 3 millions in the 18 days following the start of this treatment. The patient has been seen at intervals for six months, and has maintained a normal blood count without further treatment.

Case III

Mrs. C., aged 36, was admitted to hospital in Sept., 1941, 6 weeks after giving birth to her ninth child. Immediately after labour she felt weak and tired, and these symptoms gradually became more marked. For about a week before admission there were diarrhoea and pain in the tongue. Her appetite was good until the last two months of pregnancy, and she had always taken a good mixed diet. In this case there was histamine-fast achlorhydria, and the tongue papillae were atrophic. The initial blood count was: Hb 18%, R.B.C. 650,000, C.I. 1.30, W.B.C. 3,600, reticulocytes 14% (see Fig. 3). The film was indistinguishable from that of Addisonian pernicious anaemia. A Price-Jones curve gave a mean cell diameter of 7.88 μ , and the mean cell volume was 92.6 cu. μ . The sternal marrow showed 28% erythroblasts, including 8% megaloblasts.

A reticulocyte response of 27.5% occurred 11 days after the injection of 4 c.cm. of anahaemin and 7 days after 10 c.cm. of campolon. The blood count, however, rose only slightly, and then gradually fell. Seven days after beginning treatment with whole liver and daily injections of neo-hepatex there was a reticulocytosis of 28.6%, and another peak of 20% occurred 6 days later. At the same time the blood count began to rise very rapidly.

Discussion

That the macrocytic anaemia of pregnancy and the puerperium may be refractory to treatment which is efficacious in Addisonian anaemia is not well recognized, and it is not clear

FIG. 3.—Chart of Case III.

described a series of 16 cases of macrocytic anaemia occurring in pregnancy and the puerperium of which 10 were temporarily refractory to treatment with massive doses of liver extract. Details of these cases have been published by Davidson, Davis, and Innes (1942). Now that attention has been drawn to cases of this type it is possible that they will be found to form a considerable proportion of the macrocytic anaemias associated with pregnancy.

It is unfortunate that in each of the cases reported above the degree of anaemia was so severe that the separate trial of different therapeutic agents was not justified. Accordingly, massive treatment with parenteral liver extracts, campoferron (oral liver extract with iron, Bayer Products Ltd.), and whole liver was instituted in each case after the effect of parenteral liver extract had been found to be slight or absent. This makes interpretation of the results more difficult than would have been the case if the different forms of therapy had been used separately, but analysis of the results appears to justify certain conclusions.

In Cases I and III large doses of campolon (Bayer Products Ltd.) and anahaemin (British Drug Houses Ltd.) produced reticulocyte responses but little or no rise in the blood count, while in Case II 2 c.cm. of anahaemin brought about a small reticulocyte response but no improvement in the anaemia. All the liver extracts used were potent; for example, the same dose of the same batch of anahaemin as was used in Case II produced an optimal reticulocyte response and rapid blood regeneration in a case of Addisonian pernicious anaemia. Moreover, there was no evidence of sepsis or other condition that might have had an inhibitory effect, and the rapid blood regeneration which followed massive therapy makes it clear that marrow hypoplasia was not present. It may be concluded, therefore, that a deficiency of factors other than the anti-pernicious-anaemia principle was concerned in the production of the anaemia. The evidence suggests that the ingestion of whole liver provided these factors. It might be argued that they were present in low concentration in the parenteral extracts

used, and that these extracts in the very large doses given were responsible for the ultimately satisfactory blood regeneration. This possibility seems unlikely, since Cases I and III showed little or no rise in the blood count after quite large initial doses of campolon and anahaemin. Moreover, the concentration of such additional factors in liver extract is likely to be much greater in crude preparations like campolon than in the refined extracts anahaemin and neo-hepatex (Evans Sons Lescher and Webb), and it is seen from Figs. 1 and 3 that campolon was not given during the period of massive therapy which produced rapid blood regeneration. The effect of campoferron can probably be discounted, since the dose given was small, and when used alone for 11 days in Case III this preparation produced a small reticulocytosis but no rise in the blood count.

Attention is drawn to the double reticulocyte response which occurred during the period of massive therapy in Cases I and III. The phenomenon was not discernible in Case II, perhaps because of the infrequency of the observations during this period. The time relationships of these reticulocyte crises suggest that the first was due to parenteral therapy, and the second to the ingestion of whole liver. The occurrence of this second reticulocytosis, and the fact that it was accompanied and followed by rapid blood regeneration, are further evidence that whole liver provided essential factors which were not present in the parenteral extracts.

The characteristics of the responses shown by the cases under discussion suggest an analogy with the macrocytic anaemia of sprue and other steatorrheas, in which it has been noted that in some cases blood regeneration does not follow the reticulocytosis produced by parenteral liver extracts unless a high protein diet is also given. Davidson (1939) has described a case of this type and suggested that the high intake of protein might be necessary for the formation of red cell stroma. Of particular interest is the fact that one of the constituents of the diet used in his case was 1/2 lb. of liver daily. Moreover, I have recently studied 3 cases of macrocytic anaemia associated with steatorrhea which were refractory to parenteral extracts but responded rapidly when whole liver was given without any other alteration in the diet. It is hoped to publish these cases at an early date. These observations suggest that in cases of macrocytic anaemia of pregnancy and the puerperium of the type here described there may exist a deficiency of factors present in whole liver similar to those which are lacking in some cases of macrocytic anaemia associated with steatorrhea. The nature of these factors and the causes which produced deficiency in the cases described are quite obscure. Certainly the histories do not point to direct dietary deficiency, and although a temporary depression of absorption from the intestine brought about by the pregnancy would explain the findings, there is no direct evidence that such a condition existed.

Summary

Three cases of macrocytic anaemia of pregnancy and the puerperium are described. The results of treatment showed that deficiency of the anti-pernicious-anaemia principle was not the only factor concerned in the production of the anaemia. Reticulocytosis after injection of liver extract may not be followed by remission in the macrocytic anaemia of pregnancy. The administration of whole liver appeared to provide other factors necessary for blood regeneration. An analogy is drawn between these cases and the macrocytic anaemia associated with steatorrhea.

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Taking advantage of the investigation by bronchoscopy of patients suffering from various pulmonary lesions, L. Tuft and N. M. Levin (*Amer. J. med. Sci.*, 1942, **203**, 717) took samples of bronchial secretion before and after the intravenous injection of sodium iodide. The iodide was detected in the bronchial secretion within 15 to 20 minutes after intravenous injection. The authors believe that the excretion of iodides into the bronchial tree accounts for their expectorant action.

ECONOMY IN FATS AND OILS IN TREATMENT OF SKIN DISEASES

BY

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In September, 1939, it was realized that the shortage of fats and oils which would inevitably occur might in time seriously affect the treatment of diseases of the skin. It was then recommended that wet dressings and varnishes should be used whenever possible in place of ointment and paste preparations. Such substitution is not, however, universally applicable. Just as some types of inflammatory skin diseases, particularly inflammatory processes of the eczematous type, are intolerant to greasy applications of all descriptions in certain phases of their course, so other inflammatory conditions, including most cases presenting the eczema type of inflammation, demand grease in some form if a response to treatment is to be achieved. These well-known facts can only be interpreted as showing that processes or reactions which occur at the point of contact between the epidermal surface on the one hand and the opposing surface of the vehicle containing the therapeutic agent on the other have a profound influence on the course of the disease, and this quite apart from any known pharmacological action of substances incorporated in the vehicle. Greasy bases are therefore essential and irreplaceable in dermatological therapy.

A substantial quantity of a greasy base must be used in the treatment of a case. For example, 2 lb. of a paste containing 15% zinc oxide in paraff. moll. is necessary for a single adequate dressing of an eczematous eruption involving the entire body, 6 oz. for an arm and hand only, and 3 oz. for a hand and fingers only. Less is required if zinc oxide or other inert powder employed to give the paste consistence is omitted; but it has been pointed out that the nature of the base may be all-important and determine success or failure with an incorporated drug, and it frequently happens that the paste consistence is essential. To remove a paste from the inflamed skin a preliminary softening and cleansing with a mineral or vegetable oil is necessary, followed by washing with soap and water. The oil and soap add to the total amount of fats and oils used in the treatment of the disease.

As there is no substitute for grease, economy in its use can only be achieved by some procedure or manipulation that eliminates the necessity for using oil and soap in conjunction with it, and this can be done.

Skin-cleansing Substances

The following substances can be added to a bath in small amounts or used in the same way as liquid soap; they will remove from the skin a paste containing 15% zinc oxide without a preliminary cleansing of the skin with oil:

- Sodium salt of highly sulphonated oleic acid (M 1337)*
- Polyethenoxy-ether of cetyl alcohol (M 1344)
- The sodium salt of the sulphuric ester of sperm oil alcohol (M 1773)
- Cetyltrimethyl ammonium bromide

These substances have been used as cleansing agents with no deleterious effect on acutely eczematous skin. They are not primary irritants and, except in the rarest instances, are not substances to which idiosyncrasy may be expected. The latter statement can of course be applied to any widely used skin application or skin contact substance, either therapeutic or cosmetic, or to wearing apparel.

The removal of a pomade with a soft paraffin base which has been thoroughly rubbed into the hair and scalp in the female is an extremely arduous and frequently disappointing procedure when soap preparations are used, but these substances can completely and easily cleanse such a scalp.

* These substances are standardized mixtures to which it would be difficult to assign a precise chemical definition, and for this reason a number is appended to a general descriptive nomenclature.