Part III.—The an hæmatopoietic anæmias (deficiency diseases of the erythron): nutritional anæmia, and the anæmias of prematurity, scurvy and coeliac disease

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The widespread prevalence in infancy of hypochromic anæmia, the result of a deficiency of iron in the diet, has been stressed within recent years by Helen Mackay, and in their experimental work on nutritional anæmia in rats Hart, Steenbock, Waddell and Elvehjem have shown that small amounts of copper as supplements to iron are essential for the cure of this condition. The question whether iron alone can produce a cure of experimental nutritional anæmia or if other metals can replace copper as a supplement has been referred to in a preceding paper (Part II). Absence of certain metals from the diet is not the only dietetic deficiency associated with the development of hypochromic anæmia; for instance, the anæmia of scurvy cannot be cured unless adequate amounts of vitamin C are consumed, and the anæmia occasionally found with hypothyroidism or cretinism is said to react specifically to thyroxin. According to Witts¹ iron, copper, vitamin C and thyroxin are necessary for the maturation of normoblast to erythrocyte, and in adults the failure of this change results in the development of a microcytic anæmia. We have been able to demonstrate by means of the hæmatocrit and by Price-Jones curves (Fig. 1) that the nutritional anæmia of infants is also of the microcytic type.

From the recent work of Strauss and Castle² the interaction of two factors would appear to be essential for the maturation of megaloblast into normoblast and the consequent prevention of megalocytic anæmia. These factors are:—(a) an intrinsic factor present in normal gastric juice, and (b) an extrinsic factor which they believe to be vitamin B₁₂. Megalocytic anæmia may also result if there is a failure of absorption or of utilization of the product of the interaction of these two factors.

Deficiency anæmias of the megalocytic type are extremely rare in childhood, but they have been recorded in association with coeliac disease, and even pernicious anæmia itself has been described. The megalocytic anæmia

of coeliac disease, the megalocytic anæmia of the tropics, and that of some cases of sprue, are due to the absence of the extrinsic factor; pernicious anæmia to the absence of the intrinsic factor; and the anæmia associated with *dibothriocephalus latus*, in all probability, to lack of absorption of the product of the interaction of the two factors.

There are two methods of proving that a disease is due to the absence or inadequate supply of some dietetic factor:—(a) the experimental method of excluding the factor from the diet and thereby inducing the disease; and (b) the therapeutic method, of supplying the missing factor to the individual suffering from the disease and effecting a cure. It is obvious that the therapeutic method is the only one applicable to the child, although in times of warfare or economic stress the experimental method may be forced upon the children of the nation affected.

1. Nutritional anæmia of infants.

For many years some pædiatricians have recognized the existence of a nutritional or alimentary anæmia of infants, but it is only recently that the condition has aroused general interest. The investigations of Helen Mackay have demonstrated that nutritional anæmia of a mild degree is almost universal in both breast-fed and artificially-fed babies; that not infrequently a considerable degree of anæmia develops; that it is most marked in babies who are small at birth, and who, relative to their initial weight, increase in size rapidly; and that it is due to iron deficiency which can be remedied by the addition of a medicinal salt of iron to the dietary, although the beneficial therapeutic effect is diminished by the presence of an infection. In her report to the Medical Research Council Mackay³ has not only summarized the literature so adequately that it is only necessary to refer to a few of the more important contributions, but she has also given the results of her investigation of the hæmoglobin of some thousands of children, the great majority of whom were regarded by their parents as healthy. We have studied by comparison a small number of cases, but they have all been sick children, and the hæmatological investigations have been more extensive than were necessary or possible in her series.

In the infant, nutritional anæmia resulting from iron deficiency may occur either from deficient storage of iron in intra-uterine life, or from an inadequate supply of iron in the diet, or from a combination of both factors. As far back as 1889 Bunge demonstrated that in certain animals the ashed residue of the foetus and of its mother's milk contained the same percentage of all minerals with the exception of iron, which was six times more concentrated in the foetal than in the milk ash. He also found that the amounts of iron per kilogramme of body weight, and of iron in the liver and spleen, were highest at birth and progressively fell, reaching a minimum at the end of the suckling period. Ten years later Hugounenq showed that in the human foetus two-thirds of the iron present in the body of the full-term infant is laid down during the last three months of pregnancy. The progressive diminution of the iron stored in the liver during the lactation period has been confirmed

by later workers. Copper is stored in like manner to iron: thus, McHargue and his colleagues found that the liver of calves contained more copper than those of older animals, and that the copper content of infantile liver is about 20 mgrm. per cent. of its dried weight. We have been able to demonstrate that the fall in the copper stores of the liver in the infant during lactation is a continuous one similar to that of iron. Observations made by us and reported elsewhere⁵ on the amounts of copper and iron present in the carcasses of rats from birth to the end of the weaning period, showed that although the absolute amount of both these elements rose during this time, copper, like iron, when expressed as amounts per kilogramme of body weight, showed a progressive diminution.

As far as essential minerals are concerned, and taking iron as the example, the shortage causing anæmia may therefore occur as follows:—

1. Deficient ante-natal storage.
 - (a) Iron deficiency in the mother.
 - (b) Deficient transference of iron to foetus.
 - (c) Prematurity of foetus resulting in insufficient storage.
 - (d) Twins, the iron stores obtainable from the mother being insufficient for both children.
2. Deficient post-natal supply.
 - (a) Insufficient supply of iron in breast milk, possibly due to iron deficiency in mother's diet.
 - (b) Artificial feeding with cows milk which contains less iron than human milk, and gives an iron retention only one-fifth of that in a breast-fed baby (Blauberg).
 - (c) Prolongation of milk feeding beyond the normal lactation period.
3. Deficient ante-natal storage and post-natal supply.

The most recent contribution on the question of iron storage is by Gladstone⁶. He finds that the iron contents of the liver and spleen of the infant do not reach their maximum at birth, but at the age of one to ten weeks; that there is no evidence of large or progressive deposits of iron in the liver and spleen during the last four months of intra-uterine life; and that the large amount of iron present in those organs results from the physiological hæmolysis which occurs at birth. Our observations on the livers of premature and new-born infants are not sufficiently numerous to enable us to criticize Gladstone's findings, but H. Ramage, J. H. Sheldon and W. Sheldon⁷ have carried out spectrographic examinations of a large series of human livers, and find that copper and iron are the only metals stored as reserve material in the liver during foetal life and reach their peak at birth 'when figures as high as 0.06 per cent. (dry) for copper and 0.4 per cent. (dry) for iron may be obtained. After birth these figures drop steadily until the stable value is reached at the age of 12 to 18 months.' In a personal communication J. H. Sheldon has informed us that there may be a rise in the iron content of the liver in the early weeks and that this, as Gladstone suggests, is probably

due to iron derived from hæmolysis. Gladstone's arguments do not appear to us to furnish a satisfactory explanation of the frequent occurrence of nutritional anæmia in the premature infant or in twins, whereas those based on the pre-natal storage of iron do afford, as will be obvious later in this paper, a reasonable solution of this problem.

Congenital nutritional anæmia.—Anæmia due to deficient ante-natal storage may be present at or shortly after birth, and forms one variety of congenital anæmia or anæmia of the new born.

Congenital nutritional anæmia differs from nutritional anæmia of later infancy only in the fact that the child may come under observation shortly after birth, or that there is a history of pallor from birth. The subject of anæmia of the new born is discussed at greater length in the paper on the hæmolytic (erythronoclastic) anæmias of the neonatal period (Part IV of this series) because it is probable that in the majority of instances the anæmia is hæmolytic in character. Nevertheless, we maintain that there is a form of anæmia which is present at or shortly after birth, neither hæmolytic in type nor due to any obvious disease, which is a nutritional anæmia curable by supplying the missing dietetic factors. Such cases have been described by one of us⁸, and their counterpart in the rat has been discussed in the preceding paper (Part II). Before the identification of anæmia in a new-born child as a congenital nutritional anæmia can be accepted, in addition to the history of anæmia since birth or the presence of pallor in the new-born child, it is essential to exclude the occurrence of an abnormal hæmolysis. This may be done, first, by the absence of icterus and of a sudden dramatic increase in anæmia shortly after birth; secondly, by the presence of a blood count showing a typical hypochromic anæmia and without evidence of a marrow response; and thirdly, by the occurrence of a reticulocytosis after treatment with the missing factor or factors. If pathological hæmolysis has occurred the blood picture is quite different, the anæmia is of the hyperchromic type, and unless the marrow is completely paralysed there is a marked reticulocytic response before or without treatment by any of the hæmatopoietic factors such as iron which produce a cure in nutritional anæmia, proving that the infant has no shortage of these factors and can at once start to turn out new cells to replace those which have been destroyed.

The nutritional anæmia of later infancy and early childhood.—This differs in no way from the congenital form, or from the nutritional anæmias of early infancy, except that it is not noticed until the seventh month of life or later. These children have usually been fed on cows' milk or artificial food, but in the instances in which anæmia has occurred in the breast-fed child it has been due to the continuance of breast feeding beyond the normal weaning period, or to the fact that the child has suffered from some infection.

The nutritional anæmias of earlier infancy.—This constitutes an intermediate group between the two foregoing forms. In it the pallor is first noted at about the fourth month and it is probable that there is a combined pre-natal and post-natal deficiency. The incidence of this variety of anæmia is higher in twins than in single pregnancies; thus, out of 30 of our most severe nutritional anæmias, all in this group, 8 were twins.

Ætiology of nutritional anæmia.—The diets taken by the mothers of infants suffering from congenital nutritional anæmia are not infrequently very inadequate and the mothers themselves may exhibit hypochromic anæmia. Their obstetric history may reveal the occurrence of still-births or of weakly babies, and we are of opinion that congenital nutritional anæmia can be prevented by an adequate dietary for the mother, if she is otherwise healthy. This view is directly contrary to that held by Baar and Stransky⁹ who believe that the anæmia of the mother does not produce anæmia in the new-born child. The maternal diet is also an important ætiological factor in the nutritional anæmia of early infancy. Following on Helen Mackay's findings, and using the administration of iron as a therapeutic test that the anæmia is nutritional in origin, Neale and Hawksley have been able to collect a series of cases in which a nutritional anæmia has occurred in mother and child (in some instances twins) in all possible combinations and permutations which can be diagrammatically represented as follows:—

	1	2	3	4	5	6
Mother	N	N	N	A	A	A
Infant	N	A	A	N	A	A
Twin	N	N	A	N	N	A
N=Normal.			A=Anæmic.			

The clinical details and discussion of these cases are contained in a subsequent paper (Part VI), and it suffices to point out here that some mothers have the power to retain their iron to the detriment of the fœtus, a state of affairs entirely different from that which obtains with calcium, although in other ways the metabolism of these two elements in the body is very similar.

Clinical characters of nutritional anæmia.—The children are usually fairly well nourished and of normal size for their age, and their appearance is striking only because of their pallor. This varies from a slight to an extreme degree of whiteness according to the intensity of the anæmia. There is an absence of any icteric tinge of skin or conjunctivæ and the mucous membranes are pale. Before the existence of an anæmia can be recognized by inspection the hæmoglobin must have fallen to somewhere in the neighbourhood of 60 per cent., and even at that figure if the child be near a fire or begins to cry the colour will improve so much that the anæmia is not obvious. The spleen is often palpable, but the lymph glands are of normal size. Evidence of infection in the form of bronchitis or otorrhœa is, as emphasized by Mackay, frequently present. No other findings are constant, but we have noticed that the proportion of nutritionally anæmic infants who show mental backwardness is greater than that found in normal children. This fact is perhaps related indirectly as cause and effect, because the difficulty in getting such children to take a mixed diet leads to prolonged milk feeding. Some of the children suffering from nutritional anæmia of later infancy are also the subjects of rickets, but there is no evidence that the anæmia and rickets have any relationship, except that a diet which is deficient in one factor is also

liable to be deficient in other factors. In these instances cure of the anæmia and of rickets can be effected by appropriate treatment, either synchronously or consecutively.

The hæmatological picture varies, but it is always of the hypochromic type, the colour index in a case of moderate severity being about 0.6. The less severe anæmias show a fall in hæmoglobin with little if any diminution in the red cell count, whereas when the anæmia is more severe the hæmoglobin values are still lower, and the fall in the red cells is proportionately rather smaller. Reticulocytes are either absent from the blood or at most reach a figure of 0.4 per cent. of the red cells. Isolated readings of reticulocytosis as high as 1.5 per cent. have been met, but these are always very transient. Price-Jones curves (Fig. 1) show that the anæmia is of the microcytic variety. In the more severe cases a few normoblasts are found in the peripheral blood. The white cells do not show any constant qualitative or quantitative changes and reactions to infections are often present. The number of platelets is normal or slightly reduced, and the fragility of the red cells is normal.

The blood counts in a few typical cases of nutritional anæmia of infants, demonstrating the varying degrees of the severity of the anæmia, are shown in the following lists:—

Red cells	4,520,000	4,300,000	4,244,000	3,302,000	2,120,000
Hæmoglobin per cent.	55	55	48	28	16
Colour index	·6	·64	·57	·42	·4
Leucocytes	17,500	13,000	10,300	5,800	8,400
Reticulocytes per cent.					
of red cells	0·5	0	0·2	0	0·8
Platelets	190,000	220,000	444,000	plentiful	160,000
Neutrophil polymorph.	37	38	54		20·5
,, metamyelocytes	1		0·5		2
,, myelocytes ...					1·5
Eosinophils per cent.	5	1	0		0·5
Basophils per cent. ...	nil	nil	1		1·0
Lymphocytes per cent.	53	52	39		61·5
Plasma cells per cent.		0·5			
Türk cells per cent.					0·5
Monocytes per cent. ...	4	8·5	5·5		12·5
Normoblasts per cent.					
of leucocytes	0	0	0	0	5·5
Macro-normoblasts per cent. of leucocytes ...	0	0	0	0	1
Megaloblasts per cent. of leucocytes	0	0	0	0	0

Iron therapy.—The method used in determining which factor is deficient in the diet has been to give the child a medicinal preparation of iron. Usually this has produced a cure, but sometimes only a partial recovery occurred, and then another dietetic factor has been added and further effects noted. The diet itself has not been changed and no other treatment given unless this

has been essential because of untoward symptoms. We believe that the experiments have been thus controlled as far as is possible in a clinical investigation.

The preparation most often used has been reduced iron, which has been given in doses of one half to one grain three times a day. The results of adding iron to the diet of an infant suffering from nutritional anæmia due to lack of iron are as follows:—a reticulocytosis; a fairly rapid rise of erythrocytes to normal or slightly above normal, counts of over six million per c.mm. being regarded as excessive; a more gradual return of hæmoglobin to normal; and finally a reduction in the number of red cells to normal directly after the final stages of the hæmoglobin rise, a phenomenon first recorded by Hagen. Accompanying these changes there is marked improvement in the physical condition; colour returns to the skin and mucous membranes, the child becomes more active although the weight does not necessarily increase, and catarrhal infections, which have previously been resistant to treatment, begin to improve. If splenomegaly was present before the commencement of treatment it may persist until some considerable time after cure has been obtained, although it is quite probable that in many cases infection may be an important factor in causing the splenic enlargement.

Some of these points are demonstrated on Graphs I, II and III. Graph I shows the effect of iron on the red cells and the degree of reticulocytosis

GRAPH I.—Effect of iron on reticulocytes and red cells in anæmia due to iron deficiency.

produced in three severe cases of anæmia; and Graph II illustrates the effect of iron on the hæmoglobin of infants of differing ages, showing that in each case the hæmoglobin has risen to the normal height for the age. The variations in the rates of recovery in these cases are remarkable and rather difficult to understand. There are at least four possible explanations; first,

the presence of an intercurrent infection; secondly, differing degrees of regenerative power owing to the abeyance of marrow function; thirdly, varying degrees of iron shortage; fourthly, the preparation of iron used. Reimann and Fritsch¹⁰ have recently shown that reduced iron is only effective by virtue of the formation of ferrous chloride by the action of the hydrochloric acid of the gastric juice. Hypo-acidity of the gastric juice is not infrequently found in sick and weakly infants and it is possible that thereby the amount of iron absorbed may vary in different individuals and even in the same infant at different times. The failure of the child to respond to reduced iron when an infection is present may also in part be explained by this mechanism since in infections the gastric juice shows hypo- or even an-acidity.

Copper.—The experience of Hart and his colleagues that, whereas impure inorganic salts of iron cured nutritional anæmia, the pure salts failed to do so unless supplemented by small amounts of copper, have already been

GRAPH II.—Effect of iron on hæmoglobin in infants of various ages.

applied by clinicians in the treatment of anæmia. The most carefully controlled experiments are those by Josephs,¹¹ who compared a series of cases of anæmic infants treated with iron with a series in which both copper and iron were present. He found that in the latter series in which copper was used as a supplement a more rapid rise in hæmoglobin occurred. In a few of our cases, where the hæmoglobin failed to rise to normal with iron, the effect of adding other substances was tried. In one case with iron therapy the hæmoglobin rose, but did not reach normal, and actually a continuance of the treatment led to the rising curve of hæmoglobin becoming flattened out and eventually being replaced by a fall. In another case treatment with iron and yeast over a period of several months failed to produce any effect. All these cases responded rapidly and the hæmoglobin rose to normal

(Graph IV) when copper was added. The form in which copper was administered was that advised by Josephs, namely 1 c.cm. of a 0.5 per cent. solution of copper sulphate per kgrm. body weight given daily in milk. Although the addition of copper resulted in the hæmoglobin becoming

GRAPH III.—Effect of iron administration on hæmoglobin.

normal, there was no effect on reticulocytosis nor on the red cell count. This was originally observed by Josephs and indicates that, although copper is necessary for hæmoglobin synthesis, it has no effect on the manufacture of

GRAPH IV.—Effect of copper as a supplement to iron, or iron and yeast.

red cells. The number of cases in which we have used copper as a supplement to iron has been small, but the experiments were carefully controlled as described above and the results can, we submit, be accepted as examples of the action of copper.

Relative importance of iron and copper in nutritional anæmia.—The mechanism whereby copper produces its effect has been a subject of considerable speculation and experiment. Several workers have come to the conclusion that copper mobilises the iron in the liver, and Elvehjem and Sherman¹² have shown that in nutritional anæmia of the rat in the absence of copper, inorganic iron is readily assimilated and stored in the liver and spleen. The iron so stored cannot be used for hæmoglobin formation until copper is supplied, when the greater part of the iron in the liver is removed and built into hæmoglobin. Copper is not necessary for iron assimilation, but it is necessary for the synthesis of hæmoglobin. Applying these experimental investigations to the three cases we have described it would appear that owing to deficiency in the copper supply these infants had depleted their available copper storage and were unable to turn their absorbed iron into hæmoglobin until further copper was supplied.

In attempting to assess the relative values of iron and copper in treatment such factors must be borne in mind as the variation of the amount of iron in milk from different countries, in different samples from the same cow or from different cows; its increase from storage in iron vessels, and the possible increase produced by the method of drying milk, which have been discussed in the preceding paper (Part II). Again it is important to remember that according to J. H. Sheldon⁷ at least 80 per cent. of medicinal preparations of iron contain copper as an impurity, and that the amounts of copper present in the various preparations are not constant, varying not only with the particular preparation used, but also in individual specimens of the same preparation. The difficulties in determining the real importance of copper in the treatment of nutritional anæmia in infants are obvious, nevertheless it is advisable that this should be attempted. From the evidence we have put forward and from Joseph's work it is obvious that in some cases it is necessary to give copper completely to cure the anæmia. The question we have to answer, if possible, is whether all children suffering from nutritional anæmia require the administration of copper to ensure recovery; or to put the question in another way:—can the administration of a pure salt of iron cure nutritional anæmia in the infant?

It will be remembered that whereas the views of Hart and his colleagues that pure iron will not cure nutritional anæmia in the rat are generally accepted, Beard and Myers contend that a cure can be obtained with iron only. Iron is stated by Heubner¹³ and by Starkenstein¹⁴ to be effective in anæmia only if it is absorbed in the divalent condition, i.e., as a ferrous salt; and the work of Reimann and Fritsch¹⁰ showing that reduced iron is only effective when converted into ferrous chloride in the stomach has already been quoted. In view of these statements we were anxious to try the effect of giving pure ferrous salts to children in nutritional anæmia, but we have been unable to purchase ferrous chloride which is guaranteed free from copper.

Ferrous sulphate has therefore been used, the particular preparation being ferrous sulphate (A.R.) made by British Drug House, Ltd,

A difficulty in using ferrous salts for medicinal purposes is that their solutions readily take up oxygen and thus become converted to the ferric form.

In Germany this difficulty has been overcome by giving them in tablet form, but such a form of medicament is unsuitable for infants. We have, however, found that oxidation can be prevented by using syrup as a vehicle and this has been prepared by dissolving pure glucose (as used for intravenous injection) in water to form a thin syrup. The scale preparations of which iron and ammonium citrate has been used by Helen Mackay are undoubtedly efficacious in nutritional anæmia, and it is probable that in the stomach they are slowly broken down and ferrous salts formed. The iron content of various iron preparations have been set forth in a table by Clark¹⁵, which shows that 1 grn. of reduced iron (B.P.) contains 54 mgrm., 1 grn. of ferrous sulphate (B.P.), 12 mgrm., and 1 grn. of iron and ammonium citrate (B.P.), 13.5 mgrm. of iron respectively. Assuming that 3 grn. of reduced iron daily is an average dose for an infant suffering from nutritional anæmia, approximate equivalent amounts of iron would be supplied by $13\frac{1}{2}$ grn. of ferrous sulphate, and 12 grn. of iron and ammonium citrate. We have therefore given 12 grn. of pure ferrous sulphate daily divided into three doses, an amount which in iron value is slightly greater than the iron value of the maximum dose (9 grn.) of iron and ammonium citrate used so successfully by Mackay. If the ferrous salt is more efficacious than the scale preparation better results should be obtained by using this drug, and this has in fact proved to be the case. By a happy chance we had the opportunity of showing to Dr. Helen Mackay some infants under treatment with ferrous sulphate, and she informed us that the response we had obtained was quicker than anything she had seen with iron and ammonium citrate. The following case may be quoted to illustrate these points:—

Case 1.—H. M., male, aged 4 months, the survivor of twins, had been fed on cows' milk and water and was admitted to hospital (19.10.32) for anæmia and loose stools. On physical examination with the exception of anæmia nothing abnormal was discovered. An examination of the blood showed that the hæmoglobin was 50 per cent., the red blood cells 4,231,000 per c.mm. and the colour index 0.59, and there was a reticulocytosis of 1.4 per cent.

In the paper on nutritional anæmia in the rat, mention has been made of the extraordinarily rapid increase in hæmoglobin which took place when anæmic rats were given ferrofax (powder). Ferrofax is prepared by British Colloids, Ltd., and contains iron, copper, manganese, and yeast. We therefore tried the effect of giving ferrofax (liquid) to this child; this was started on October 24th and four days later a reticulocyte response of 3.2 per cent occurred. The ultimate result was very disappointing, for although there was an increase in red cells by one million per c.mm., the hæmoglobin only rose 4 per cent. as a result of 17 days treatment. On the 13th November, therefore, pure ferrous sulphate was started in daily amounts of 12 grn., and the result was extraordinarily good, for in an exactly similar period of time the hæmoglobin rose by 21 per cent.

The results of this experiment were communicated to Mr. John F. Ward, Chief Chemist to British Colloids, Ltd., who, in giving us the mode of preparation of the two forms of ferrofax, pointed out that ferrofax powder is largely ferrous iron, whereas ferrofax liquid is ferric iron. This not only explains why the result in the child differed so much from that obtained in

rats, but taken in conjunction with the improvement which occurred after the administration of ferrous sulphate, also shows that iron in the ferrous form is greatly superior to iron in the ferric form. These two varieties of ferrofax are manufactured as follows:—

Ferrofax (powder). Freshly precipitated ferrous carbonate is mixed with a mixture of glucose and sugar, and dried. By the use of glucose the iron is largely preserved in the ferrous state. The dried powder is mixed with an equal weight of yeast powder and a definite proportion of copper hydroxide and manganese hydroxide added; when mixed with water the powder forms a fine colloidal suspension.

Ferrofax (liquid). This is made by precipitating ferric hydroxide and carefully washing until free from salts. It is then mixed with sugar and evaporated to dryness. The powder is then dissolved in water and a true ferric hydroxide colloid is formed. The necessary amount of manganese is added to the final product.

In view of the result of administering ferrofax liquid to this child, British Colloids, Ltd., have now prepared a new ferrofax liquid. In the new preparation ferrous hydroxide is formed in the presence of glucose solution which on account of its reducing action keeps the iron in the ferrous state.

Although the amount of copper in ferrous sulphate (A.R.) is scarcely sufficient to estimate (the makers say less than $\frac{1}{2}$ mgrm. per cent.), we have found that the 'pure' glucose prepared for intravenous use unfortunately does contain a definite amount of copper, namely 0.3 mgrm. per cent. The amount of glucose consumed daily by this child was 11.25 gm. and less than 1 gm. of ferrous sulphate, which means an intake of about 0.031 mgrm. (0.03—0.001) of copper per day. According to Beard and Myers the amount of copper required as an effective supplement to a daily dose of 0.5 mgrm. of iron in rats suffering from nutritional anæmia and fed on milk only is 0.025 mgrm. Accepting that statement, a daily supply of 0.031 mgrm. of copper would be manifestly insufficient to activate the amount of iron given to this child which was 144 mgrm. We, however, recognize that a mathematical argument of this type will not compare in value with clinical results obtained by completely eliminating the copper intake, other than that contained in the milk diet, and we are now endeavouring to accomplish this. There is in this particular instance an adequate reply to the suggestion that copper took no part in the cure because the child had been given copper in ferrofax (liquid) which doubtless had been stored in its body, and was therefore available for hæmoglobin synthesis when a sufficient amount of iron was forthcoming. Such a reply is, however, not applicable to the next case:—

Case 2.—P. F., male, aged 8½ months, a premature twin, fed from birth on a roller process dried milk, was admitted to hospital for nutritional anæmia on December 14th, 1932. Except for the anæmia and an attack of diarrhœa in association with an influenzal infection, which occurred during the fourth week of his stay in hospital, there was nothing of importance in his physical condition. At the outset his red blood count was approximately normal but the hæmoglobin was 57 per cent. He was in fact a mild case of nutritional anæmia and a Price-Jones curve (Fig. 1) of his blood on the day after admission showed a very definite degree of microcytosis and a moderate degree of anisocytosis. On December 17th he was put on pure ferrous sulphate, 12 grn. per day made up with glucose as before, and 14 days later his hæmoglobin had increased to 70 per cent., and in spite of the influenzal infection his hæmoglobin had reached 82 per cent. on January 13th, 1933. Another Price-Jones

curve done on January 21st, although still showing a degree of microcytosis and even an increase in anisocytosis, had moved well to the right into the normal area. A final Price-Jones curve (March 8th, 1933) showed very little anisocytosis and is otherwise a normal curve. This series of curves demonstrates very well how the size and shape of the red cells alter under treatment.

FIG. 1.—Case 2. Price-Jones curves showing effect of treatment.

- ×—× 15.12.32. before treatment with iron: mean diameter 6.348 μ .
- 21.1.33. after five weeks' treatment: mean diameter 6.559 μ .
- 8.3.33. curve within normal limits: mean diameter 7.001 μ .

It is difficult to understand the rationale of cure in this case if copper in the amounts indicated is as essential for the cure of nutritional anæmia in the infant as it is in the rat. The suggestion that the child had sufficient stored copper for use when adequate iron supplies were forthcoming is a possible explanation, although the acceptance of such a solution is not easy because the only source from which copper could be obtained was from the mother in utero. It is, of course, also a possibility that this child had never had sufficient ante-natal iron storage nor a sufficient post-natal supply of iron to make use of all its stored copper; a possibility which seems unlikely because it is usually assumed that the ante-natal iron and copper storage proceed along parallel lines. In this particular instance it is probably quite true that ante-natal iron storage was poor because the child was both premature (7 months) and a twin.

At the time of writing this is the only case in which we have been able to show the effects of a pure ferrous salt where there was no other possible

source of copper than the amount supplied in the glucose and ante-natal storage. We have had, however, other examples which further demonstrate the value of ferrous sulphate and as will be described later remarkable improvement in the general condition of the child and rapid cure of the hypochromic anæmia of coeliac disease have occurred. We have no hesitation in saying that in our hands ferrous sulphate has proved by far the most effective source of iron in the iron-deficiency anæmias. The results obtained with pure ferrous sulphate do not, of course, vitiate the experiments detailed in the section on copper which show that in some cases at any rate the cure of nutritional anæmia of infants will not take place unless an adequate supply of copper is given to the child.

Yeast therapy.— In view of the results of our experiments on rats (Part II) in which nutritional anæmia was cured by adding dried yeast to a milk diet, we investigated the effect of giving yeast to infants suffering from nutritional anæmia. The yeast was given in four different ways: (1) as the sole treatment; (2) given alone at first and later supplemented by iron; (3) as a supplement to iron; (4) in combination with iron from the commencement of treatment.

GRAPH V.—Effect of iron after employment of yeast (3 cases).

The preparation of dried yeast used was yestamin and this was given three times a day in doses rising from $\frac{1}{2}$ to 4 drms., and as in other forms of treatment the diet, on which the anæmia had either developed or failed to improve, was continued unchanged. The results obtained varied considerably and in only one instance was there complete recovery. In three cases a small reticulocyte 'kick' was obtained on the third or fourth day, and although there was a slight rise in hæmoglobin of about 10 per cent. complete cure was obtained only when the yeast was supplemented by iron; in each instance the addition of iron was followed at first by a fall in erythrocytes from half to one million per c.mm. (Graph V). These infants, however, had

an approximately normal red blood cell count when the yestamin was started and this phenomenon may be that as described by Hagen to which reference has been made above. In three other cases yestamin did not produce any effect, not even a reticulocyte 'kick,' but in each case a normal reticulocytosis and a return to a normal hæmoglobin was produced by the addition of iron (Graph VI). Finally, in two instances in which iron had failed to

GRAPH VI.—Effect of iron after yeast has failed.

produce complete recovery that result was obtained by the addition of yestamin (Graph VII). In these two cases copper was not administered, so that it is possible to argue that the cure was due to the presence of copper in

GRAPH VII.—Effect of yeast supplementing iron.

yestamin. We have not arrived at any definite conclusion as to whether iron and yeast given in combination produce a more rapid cure of nutritional anæmia than iron alone; the children of the former group certainly seem to

show greater general improvement but this may well be due to beneficial factors in the yeast which have no direct effect on the hæmatopoiesis. It is obvious, however, that the yeast is much less efficacious in the treatment of nutritional anæmia in the child than in the rat, a state of affairs for which we can advance no adequate explanation. The factor or factors in yeast which have a beneficial effect in hæmatopoiesis have been discussed in the preceding paper.

Natural cure of nutritional anæmia.—When the normal child reaches the end of the lactation period and begins to take a mixed dietary, and in consequence an increased amount of minerals (iron and copper), the hæmoglobin begins to rise and rises steadily until at about the age of eighteen months the adult level is attained. It is quite obvious that many mild cases of nutritional anæmia in this way achieve a spontaneous recovery since, when a purely milk diet is changed to a mixed dietary in nutritional anæmia, a reticulocytosis and gradual improvement in hæmoglobin value occurs. This improvement can be accelerated in any stage by adding iron, particularly as after a time unless iron is given the hæmoglobin curve is liable to become flattened out and only to approach very slowly to the normal. These points are illustrated in a Graph VIII which shows the effect on a child aged 17

GRAPH VIII.—Effect of mixed diet on nutritional anæmia: its reinforcement with iron.

months of changing from a diet which had previously been only milk to a mixed dietary. In this particular case the increase in iron in the diet was from 3.6 to 25.64 mgrm. per diem. The effect of giving extra iron, as reduced iron, is also seen in the graph. It is interesting to note that the most recent work indicates that the iron requirements for growth are 0.2 mgrm. per kgrm. body weight daily, and that the percentage of iron absorbed is increased by increasing the iron intake.

2. Anæmia of prematurity.

In an infant born before term, the number of red cells and the proportion of nucleated cells at birth are higher than in the full term child, and increase in direct proportion to the degree of prematurity. Thus in an eight months foetus the red cells number about eight millions per c.mm. The changes which take place after birth are essentially similar to those which occur in the full-term new-born child, differing only in that they are more pronounced. The fall in the red cells and hæmoglobin is greater, more rapid and more prolonged, and is likely to be more marked the smaller the infant and the greater the degree of prematurity. From the first week or so, or even up to the fourth or fifth week, the premature behaves like a full-term infant, but after that time shows a much more marked drop in hæmoglobin and a continuous fall in red cells which reach a minimum from the eighth to the twelfth week. At this stage the hæmoglobin is about 45 to 55 per cent. and the red cells $2\frac{1}{2}$ to 3 millions. Subsequently the hæmoglobin begins to rise again in a similar manner to the earlier rebound that occurs in the full-term infant, until at the sixth to eighth month the percentage has reached that of the normal child. The red blood cells also begin to increase in number at the same time and reach the level of the normal rather earlier than the hæmoglobin.

Three main hypotheses have been put forward to explain this so-called physiological anæmia of the new-born premature child.

(1) That it is the result of deficient ante-natal storage of iron, and perhaps of copper, in the liver and spleen, since, as already stated, Hugounenq has shown that in the human foetus two-thirds of the iron present in the full-term child is laid down during the last three months of intra-uterine life. (2) Josephs¹⁶ maintains that, as in the normal child, the fall in red cells and hæmoglobin is due to the adjustment of blood formation and destruction at a lower level than at birth, but that this failure of the hæmopoietic tissue is more profound and prolonged in the premature child. (3) van Creveld and Heybroek¹⁷ stress the importance of blood destruction rather than a failure of formation and regard many of these anæmias as being of the hæmolytic type and due to an increased severity and prolongation of the hæmolysis which normally occurs at birth. The hæmolysis which normally occurs at birth is due to alterations in oxygen tension. The anoxæmia of the foetus, which results from its living in a low oxygen tension environment, requires a larger number of red cells and high hæmoglobin; whereas, after birth, the child lives in a high oxygen tension environment and destruction of redundant red cells occurs. The premature infant's need for oxygen is much less than that of the full-term child, and therefore in the premature the destruction of red cells will be greater and last for a longer period. As proof of their view of this increased hæmolysis they point out that whilst the bilirubin in the blood (icteric index) in the full-term child returns to normal at the end of the second week, in the premature child it takes much longer, and until it has reached normal the red cells continue to decrease. In this connection it is interesting to remember that icterus neonatorum is more frequent, more severe and more prolonged in premature than in full-term babies.

Many observations have been made which show that the administration of iron does not prevent the anæmia of prematurity, and it has therefore been suggested that the ante-natal shortage of iron is of no importance in these anæmias. In our opinion this is quite a wrong conception for, on the one

hand, Josephs has pointed out that the initial fall in hæmoglobin in the normal child cannot be prevented by the administration of iron; on the other hand, once the fall of hæmoglobin in the premature infant has reached its lowest point, iron administered in adequate amounts will cure the resulting anæmia. In other words, the storage of iron in the depots of the foetus, be it great or small, has nothing to do with the initial fall of hæmoglobin, either in the premature or in the full-term infant. The mechanism of the fall in the two groups of children is the same, whether it is, as Josephs says, largely a matter of lessened blood formation, or, as van Creveld and Heybroek maintain, of increased blood destruction resulting from an increased oxygen stimulation, or, as is perhaps most likely, a combination of the two. The question of the adequacy of ante-natal iron storage, and incidentally also of the post-natal supply, only arises when the hæmoglobin has reached its lowest value. In the full-term child this supply may be sufficient to ensure that the child never suffers from nutritional anæmia, but in the premature child with its lack of iron stores, the occurrence of nutritional anæmia is probable, and also it is probable that this will occur early (nutritional anæmia of early infancy). The anæmia of prematurity must be distinguished from nutritional anæmia of the new born, because the latter occurs at an earlier period, shows no evidence of abnormal hæmolysis and is amenable to iron therapy much sooner. It is, of course, possible that anæmia of the new born may occur in a premature infant, and that if the baby did not come under observation until it was two or three months old the anæmia might then be a combination of anæmia of the new born and anæmia of prematurity.

Clinically the appearance of babies suffering from anæmia of prematurity does not differ from those suffering from nutritional anæmia, with the exceptions that (a) splenomegaly and lymphatic hyperplasia are perhaps more common when the anæmia has fully developed, and (b) in the earlier stages the anæmia is of the hyperchromic type. After the anæmia has become fully developed the blood picture changes to that of a nutritional anæmia, but treatment is usually required for a longer period to produce a complete cure. In a previous paper⁵, under the heading of 'constitutional nutritional anæmia,' one of us has referred to a group of cases in which anæmia occurred in early infancy and was resistant to treatment. In the light of further experience we should now regard most of these cases as examples of the anæmia of prematurity or of nutritional anæmia of the new-born, and we have found that with improved treatment the number of cases which resist treatment, except during the progress of an infection, becomes smaller and smaller.

The possibility of preventing the development of anæmia of prematurity has been investigated. Abt and Nagel¹⁸ found that if iron and ammonium citrate were administered with the dried liver fraction suitable for a secondary anæmia, made according to the formula of Whipple and Robscheit-Robins, from the beginning of the second week of life, a less severe grade of anæmia developed; whereas the liver fraction alone or the administration of dessicated pig's stomach had no prophylactic value. Van Creveld and

Heybroek found that a combination of liver and vitamin D, or of reduced iron and vitamin D, also prevented the development of severe grades of anæmia. Finally, Blackfan, Baty and Diamond¹⁹ state that the development of this anæmia has been prevented by repeated blood transfusions. Such results encourage the belief that some adequate means of prevention will eventually be found. The beneficial effect of the administration of serum in checking the hæmolysis of *icterus gravis neonatorum* suggests that such a form of treatment might prevent the development of anæmia of prematurity, and possibly this is the explanation, at least in part, of the good results obtained by repeated blood transfusions. It may be recalled that Hampson²⁰ has put forward the view that serum supplies an anti-hæmolytic factor which is lacking in *icterus gravis*, and it is possible that the premature child also is deficient in this factor or in something which stimulates its formation.

3. Anæmia of scurvy.

There is some difference of opinion concerning the frequency of anæmia in scurvy. It is well known that pallor is a characteristic, common, and early symptom of the disease, but whereas A. F. Hess²¹ regards this as due in a large measure to anæmia, Rohmer and Bindschedler²² say that it is not always the expression of real anæmia but only of circulatory changes in the skin. The latter writers point out that anæmia is not an essential symptom, and that a certain number of cases of scurvy without anæmia are recorded in the literature, and quote Baar as having found it in only one-third of his cases. In a series of fifteen cases of scurvy they observed seven instances of anæmia, and are of the opinion that its appearance is connected with certain super-added conditions which do not form a part of true scurvy. The only suggestions they make as to the reason why anæmia occurs in some cases and not in others is that it may depend on the existence of more than one factor in vitamin C and of 'constitutional differences' in different children.

The anæmia of scurvy which may reach a profound degree is of the hypochromic type and the hæmatological picture does not differ from those other forms of deficiency anæmia to which reference has already been made. It is not possible to say to what extent this anæmia is due to the loss of blood from scorbutic hæmorrhages, although the picture presented is quite different from that which arises from sudden loss of blood. In the latter an attempt is at once made to compensate for the anæmia by regenerative efforts on the part of the bone marrow with the consequent occurrence of reticulocytosis, whereas in scorbutic anæmia this does not happen until after adequate quantities of vitamin C have been taken. It therefore appears that

hæmatopoiesis does not occur in the absence of vitamin C. Graph IX illustrates very clearly the effects on hæmoglobin, red cells and reticulocytes of administering orange juice to a child who became very anæmic during a severe attack of scurvy. No other medication was given and the child was kept on a milk diet, but complete cure resulted. Shipley²³ insists on an important practical point in the treatment of the anæmia of scurvy, namely, that copper should not be given with vitamin C because its action is to destroy that vitamin.

GRAPH IX.—Effect of orange juice on scorbutic anæmia.

The existence of an anæmia due to the absence of vitamin C, but occurring before frank symptoms of scurvy become manifest (pre-scorbutic anæmia), has been insisted upon by Weill and Mouriquand²⁴ who have described the existence of anæmia which resisted treatment by iron but which was cured by lemon juice. Recently Rohmer and Bindschelder²² investigated a group of 22 anæmic infants with a view to determining the existence of this 'pre-scorbutic anæmia.' In six of these cases the administration of iron did not produce any effect, but when vitamin C was given in addition to the iron a prompt cure resulted. They suggest that it is possible that vitamin C has some effect on the metabolism of iron, and that in regard to iron it plays a rôle similar to that played by other vitamins in relation to certain elements of the diet. A simpler and quite adequate explanation of the observed facts is, however, that more than one factor may be lacking in some cases of deficiency anæmia; for instance, a child suffering from nutritional anæmia may also develop scurvy and the anæmia of scurvy, in which case for its complete cure vitamin C as well as iron will be required.

4. Anæmia of cœliac disease.

The anæmia of cœliac disease is in reality one of that important group of deficiency symptoms which are so characteristic of that disorder and is of peculiar interest amongst deficiency anæmias in that not only is it manifested as hypochromic anæmia similar to those already discussed, but also in some cases as a hyperchromic megalocytic anæmia.

In his original description of the 'cœliac affection' Gee²⁵ wrote:— 'Cachexia, a fault of sanguinification betoken by pallor and a tendency to dropsy, is a constant symptom: the patients become white and puffy'; and although the symptom is not by any means constant some degree of anæmia of the hypochromic type is not infrequently present. The hæmatological picture differs in no way from that found in the nutritional anæmia of infants and like theirs it is usually an iron, or iron and copper, deficiency anæmia. There is nothing characteristic about it except that sometimes scurvy may be an element in its production.

Recently, however, Strauss and Castle, and also Bennett, Hunter and Vaughan²⁶ have drawn attention to the existence of a hyperchromic megalocytic anæmia in cœliac disease. This form of anæmia is of great rarity and according to the latter authors is indistinguishable from that found in sprue, in tropical megalocytic anæmia, and in association with gastro-colic fistula, but differs from Addisonian pernicious anæmia. The points of difference are that in the first group the indirect van den Bergh reaction is low, there is a striking absence of poikilocytosis, free hydrochloric acid is frequently present in the gastric juice, or may return on treatment, and the anæmia responds to marmite; whereas in pernicious anæmia the indirect van den Bergh reaction is high, poikilocytosis is marked, free hydrochloric acid is rarely present in the gastric juice and does not return on treatment, and marmite has no therapeutic value. The statement that marmite is ineffective in pernicious anæmia requires some modification in view of recent work which shows that it is of value particularly as a maintenance measure.

In order that the maturation of the megaloblast to the normoblast may occur it is essential to supply the bone marrow with the hæmatinic factor which is produced by the interaction of an intrinsic factor present in normal gastric juice with an extrinsic factor. The maturation will not take place, therefore, unless the intrinsic factor is present in the gastric juice; the extrinsic factor is supplied in the food and the resulting hæmatinic factor is absorbed. Strauss and Castle now hold that the extrinsic factor is closely related to vitamin B₁₂, if not that vitamin itself. Now marmite is rich in this vitamin and its efficacy in preventing or curing the megalocytic anæmia of cœliac disease is due to the fact that this form of anæmia will occur when lack of the extrinsic factor has prevented the specific reaction taking place.

From a view of the literature Bennett, Hunter and Vaughan accept 21 cases, including two of their own, as examples of hyperchromic megalocytic anæmia associated with a condition which was probably cœliac disease. Of these only five cases occurred in children of twelve years or under, the actual

ages being $1\frac{1}{2}$, 3, $4\frac{1}{2}$, 9 and 12 years. The ages of the other cases varied from 16 to 62 years. Of the five cases described in children three (aged 3, $4\frac{1}{2}$, and 12 years) seem to be above criticism, but in the other two cases the colour index was considerably below unity. It will be seen, therefore, that in children this form of anæmia is of the greatest rarity. It seems to us that a possible explanation of this rarity is that two conditions are necessary for its development, namely:—first, the coeliac disease must be of long-standing; secondly, its treatment must have been inadequate. If the case records of megalocytic anæmia in coeliac disease are examined they will be found to support this explanation, because the majority have occurred in adults whose clinical history shows that they have suffered from coeliac disease for years, in some instances from childhood, and that they have not received adequate treatment. For instance, we have seen one typical example of this form of anæmia in a woman, aged 23, who at the age of 10 years had obvious symptoms of coeliac disease, but had never adequately carried out the dietetic treatment advised. It may perhaps be added that the term 'adequate treatment' includes the administration of marmite or some form of dried yeast which we have regarded for some years as an essential part of the treatment of coeliac disease. If time really be a factor in the development of this megalocytic anæmia it should be possible to trace the transition from the hypo- to the hyper-chromic type of anæmia; indeed Witts has said that if a fatty diarrhoea persists for more than a few months an anæmia always develops which tends to pass through three phases, (a) hypochromic anæmia with a normoblastic marrow, (b) megalocytic anæmia with a megaloblastic marrow, and (c) aplastic anæmia; and he has quoted a statement of Fanconi to the effect that a child with coeliac disease may pass through these three phases.

There is yet another variety of anæmia which has been described in coeliac disease, namely an erythroblastæmia resembling Cooley's anæmia. Bennett, Hunter and Vaughan have found this form in two adults suffering from coeliac disease who also showed in mild degree the bone changes and facial characteristics described by Cooley. These are the only cases on record and they differ from the form described by Cooley in that they responded to treatment with iron, whereas all forms of treatment have been ineffective in the cases of Cooley's anæmia in childhood so far recorded.

For the purpose of this paper we have reviewed 19 cases of coeliac disease which have come under our observation during the last few months; 14 of them were in the initial stages of their treatment, and the remaining 5 had been under treatment for a more lengthy period. The ages of the children varied from 18 months to 10 years, 9 of them were free from anæmia, 6 showed anæmia of the hypochromic type, 3 a mild degree of hyperchromic anæmia, and in one the blood showed a condition approximating to a hyperchromic megalocytic anæmia. Splenomegaly sometimes occurs in coeliac disease, a fact originally pointed out by Gee; it has not been present in this series and we have only met it twice in over a hundred cases of the disease.

ANÆMIA IN CHILDHOOD

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Hypochromic anæmia.—It has already been stated that this anæmia is in all respects identical with the ordinary nutritional anæmia of infants. The statement is borne out by a reference to the following case:—

Case 3.—F. A., male, aged 2 years, who died of influenza. Below are shown the results of the examinations of the blood over a period of nine months. The anæmia is microcytic, and in Fig. 2 is shown the Price-Jones curve made from a blood film of this child taken a week or two before death. This boy did not receive any iron during the whole course of his illness.

DATE.	31.3.32.	3.10.32.	5.12.32.	19.12.32.
Red blood cells	4,404,000	3,907,000	4,520,000	4,160,000
Hæmoglobin per cent.;	60	43	42	44
Colour index	0.68	0.55	0.47	0.53
Leucocytes	11,350		17,400	16,750
Reticulocytes per cent. of red cells	1.0	0.8	0.7	3.1
Platelets	plentiful			
Neutrophil polymorph.	19.5		22	
„ metamyelocytes	.5			
Large lymphocytes	74.5		50	
Small lymphocytes	4.5		24	
Monocytes	1.0		4	
Normoblasts	1		1	
Anisocytosis	+		++	+++
Polychromasia	+			++
Eve's halometer reading				7.25 μ

FIG. 2.—Case 3. Price-Jones curve showing the microcytic character of the hypochromic anæmia of celiac disease.

AUTOPSY (26 hours after death, December). The shaft of the femur was thinned. Bony trabeculae were few and thin. The marrow was red throughout; there was a well-defined patch of 'red currant jelly' at its lower end and some ill-defined patches were scattered elsewhere.

Histologically low-power magnification of the section (which was stained by hæmatoxylin and eosin) showed a structureless matrix, staining pink, in which were scattered small aggregations of red cells like minute hæmorrhages into the matrix, and also small foci of hæmatopoiesis. Higher magnification (Fig. 3) showed that these foci consisted of granular myelocytes and metamyelocytes with a fair proportion of young nucleated red cells. These latter were usually about 5μ with nuclei 4μ in diameter which practically filled the cells and stained deeply. A minority showed stippling, but the majority were rather of normoblastic type. More mature nucleated red cells with small nuclei were rare. Rather prominent endothelial cells with pale oval nuclei were scattered through the groundwork. In the more cellular areas, the erythroblasts were very numerous, and the myeloid cells were normal except that polymorphonuclear cells were scanty. Smears of the cellular areas of marrow showed cells, which generally stained badly; normoblasts, myelocytes and metamyelocytes were present, but definite megaloblasts were not found. Smears from the jelly-like areas showed normoblasts, normoblastic nuclei and rather large

FIG. 3.—Case 3: coeliac disease; marrow $\times 700$; showing erythropoietic focus; cells almost entirely normoblasts; mitosis is seen (arrow).

pale cells which were possibly endothelial elements. The outstanding features of these histological appearances were (1) the replacement of a large part of the marrow by structureless jelly-like material; (2) the presence of erythropoiesis, in which the cells were generally rather immature, although definite megaloblasts were not seen; (3) slight immaturity of the myeloid series.

Reference has been made to the fact that the hypochromic anæmia of coeliac disease is the result of an iron, or an iron and copper, deficiency. This deficiency is largely due to the disturbance of absorption which is so characteristic of coeliac disease, but it may also be due to lack of mineral supply and this is particularly the case during those periods when protein skimmed milk is the only food taken by the child. Some of the difficulty in absorption may be due to gastric hypo-acidity because achlorhydria is not uncommon in coeliac disease although we have never failed to obtain free

hydrochloric acid by subcutaneous injection of histamine. In all cases of cœliac disease it is quite as essential to supply iron in an available form, and in sufficient quantity as it is to supply the various vitamins. We have found that hypochromic anæmia responds very quickly to ferrous sulphate given in adequate doses, and that associated with the improvement in the anæmia there is also a marked improvement in the general condition of the child.

An example of the results obtained with this drug is given here: ferrous sulphate in doses of 12 grains daily were given, commencing on November 13th, 1932, to a child suffering from the hypochromic anæmia of cœliac disease.

DATE.	14.11.32.	21.11.32.	23.11.32.	1.12.32.	5.2.33.
Red blood cells ...	5,340,000		6,000,000	5,440,000	5,300,000
Hæmoglobin per cent.	54		63	75	100
Colour index ...	0.41		0.53	0.69	0.94
Reticulocytes per cent.					
of red cells ...	1.01	5.1	3.75	3.6	
Punctate basophilia ...				+	
Polychromasia ...	+		++	++	
Anisocytosis ...	+		++	++	

Hyperchromic anæmia.—Three children showed a mild degree of hyperchromic anæmia and two of these were particularly interesting, because the administration of marmite failed to produce a normal blood picture.

Case 4.—P. W., female, aged 18 months, was treated in the routine way for cœliac disease, which included the consumption of $\frac{1}{2}$ oz. of marmite specially prepared to remove some of the salts. After she had taken the marmite for one month an examination of her blood gave the following results:—red blood cells 3,591,000 per c.mm.; hæmoglobin 76 per cent.; colour index 1.05; reticulocytes 1.0 per cent. of red cells.

It had occurred to us that the cause of cœliac disease itself might possibly lie in the absence of some intrinsic factor in the gastric juice or more probably in the intestinal juices because the metabolic defect is one of absorption. We therefore tried the effect of giving to children suffering from this disease the dessicated mucosa of hog's stomach or of hog's duodenum and jejunum in addition to the routine administration of marmite. So far we have not obtained any improvement in the hypochromic anæmia nor any striking improvement in absorption, but an interesting thing happened when dessicated gastric mucosa was given in Case 4, in that three weeks later an examination of her blood showed that it was normal. The red cells were 5,000,000 per c.mm., the hæmoglobin 90 per cent., and the colour index 0.9.

Case 5.—D. B., female aged $2\frac{1}{2}$ years, was admitted into hospital under the care of our colleague, Dr. J. M. Smellie, to whom we are indebted for permitting us to record the case. She was given 3 drm. of marmite daily, and 12 days later an examination of her blood gave the following results:—red blood cells 4,370,000, white blood cells 6,850 per c.mm.; hæmoglobin 88 per cent.; colour index 1.0; reticulocytes 0 per cent. of red cells; well-marked anisocytosis and megalocytosis. A recent

examination of the blood, four months after starting the continuous administration of marmite in the amounts stated showed that the degree of anæmia had increased and that it was still of the megalocytic type, the actual figures being:—red blood cells 3,500,000, leucocytes 7,350 per c.mm.; hæmoglobin 68 per cent.; colour index 0.97; reticulocytosis less than 0.5 per cent. of red cells; well-marked anisocytosis and a degree of polychromasia. The Price-Jones curve (Fig. 4) made at this time demonstrates quite clearly the anisocytosis and the megalocytosis, the mean diameter of the red cells being 7.905μ whereas the largest mean diameter within normal limits is 7.718μ (Price-Jones).

FIG. 4.—Case 5. Price-Jones curve of a case of megalocytic anæmia of coeliac disease.

These two cases suggest very strongly that some children with coeliac disease are lacking in Castle's intrinsic factor. An objection might be raised that the extract of marmite in our first case did not contain vitamin B. This objection cannot be sustained for the following reasons:—First, the vitamin-B complex is soluble in alcohol, but vitamin B₁ is insoluble in 92 per cent. and B₂ insoluble in 70 per cent. alcohol and upwards²⁷. The extract used is prepared by shaking marmite with 65 per cent. alcohol for some hours, filtering and evaporating the filtrate; the resultant residue is then made up with water in such a way that one fluid ounce represents one ounce of marmite. Secondly, extracts prepared in this way have proved effective in curing two children suffering from pellagra. In any case this criticism cannot apply to the second child who received untreated marmite. This

child has not yet been given dessicated gastric mucosa but we anticipate that this will prove effective.

The importance of these observations is increased by the fact that Castle and Rhoads⁴ state that there is a lack of intrinsic factor in some cases of sprue. Of course it is possible that the child (Case 4) was not lacking in intrinsic factor but that during the period she was taking gastric mucosa the absorption improved, so that the product of the interaction of intrinsic and extrinsic factors which had previously been indifferently absorbed was absorbed in sufficient amounts to produce a normal blood picture. Such an explanation might also hold in the cases of sprue described by Strauss and Castle, a possibility which doubtless was considered by them.

Case 6.—D. H., aged 2 years, showed a mild anæmia with a colour index of nearly unity (0.97) in the only examination carried before death. At autopsy the bone marrow was found to have a typical red-currant jelly appearance. The replacement of the normal marrow by the jelly-like material was more extensive than in the fatal case of hypochromic anæmia (Case 3) described above, and occupied the whole shaft of the femur. The histological features of the marrow were similar in the two cases except that in this instance the hæmatopoietic areas were more minute and more difficult to recognize. Many of these appeared to be composed of endothelial cells and were scattered widely in the matrix.

5. Other forms of hyperchromic megalocytic deficiency anæmia.

There are two other forms of hyperchromic megalocytic deficiency anæmia which may occur in childhood, namely:—pernicious anæmia and *Bothriocephalus* anæmia. Both are of extreme rarity.

The question whether pernicious anæmia ever occurs in early life has been a subject of debate, since the majority of the cases reported are unconvincing, some being clearly examples of acute hæmolytic anæmia. We have no clinical observations of our own to offer as evidence for or against the existence of pernicious anæmia in children, but we would insist that before an anæmia can be classed as Addisonian pernicious anæmia it must show certain features in addition to megalocytosis: these are:—(1) a high indirect van den Bergh reaction; (2) marked poikilocytosis; (3) almost always absence of free hydrochloric acid in the gastric juice; (4) a reticulocytosis with liver extract. In 1928 H. K. Faber²⁸ described a case of anæmia in an infant 9½ months old which fits these criteria more closely than any other instances in the literature.

Bothriocephalus anæmia is almost unknown in the first decade of life, only three cases having been recorded.²⁹ The clinical manifestations do not differ from those in adults, and the anæmia is probably due to the destruction by the worm of the hæmopoietic product of the interaction of the extrinsic and intrinsic factors, or to its diminished absorption as the result of the action of the worm on the intestinal mucosa.

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