STUDIES IN THE ANAEMIA OF INFANCY AND EARLY CHILDHOOD

Part X.—The anaemia of infantile scurvy

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Although every writer on infantile scurvy comments on the characteristic changes in the complexion of the patient, stressing the development of a sallow muddy tint and, in advanced cases, of pallor, the occurrence of actual anaemia is not so universally accepted; further, the existence of a special form of anaemia due to absence or deficiency of ascorbic acid (vitamin C), and only curable when that vitamin is administered in efficient amounts, is a modern conception which still awaits general recognition. Nevertheless a perusal of Barlow's¹ two classical papers shows that he was under no misapprehension as to the presence of anaemia and his comments on this symptom are illuminating; in his first paper he writes: 'The anaemia in severe cases was profound, besides the pallor there was noted sometimes a peculiar sallow muddy tint on the complexion,' and in his second paper the point is further elaborated:

'With respect to the constitutional symptoms . . . the most important is the profound anaemia which is developed. Whatever there may have been at the onset when once the limb affection has become pronounced the pallor becomes intensified. The anaemia is proportional to the amount of limb involvement. As the case proceeds there is a certain earthy-coloured or sallow tint which is noteworthy in severe cases, and when once this is established bruise-like ecchymoses may appear and more rarely small purpurae.'

An interesting contrast to these statements is found in a recent article written by Barlow's most distinguished pupil. 'The blood shows no characteristic change in its cell count. A simple secondary anaemia with diminution especially of haemoglobin has been found in some cases; but this is not always so, the writer has found the number of red cells rather above the normal in some pronounced cases of scurvy' (Still²).

Quotations from many writers could be given for and against the view that anaemia is frequent in scurvy; indeed some authors regard the

pallor of scurvy as due to circulatory changes in the skin and not the result of anaemia. Barlow thought that the muddy tint of the complexion was due to the absorption of altered haemoglobin, but since a similar tint is sometimes seen in erythronoclastic anaemias, agranulocytic angina, and even in acute osteomyelitis it is also possible that it is an indication of some injury to the bone marrow; moreover it has been found that in scurvy neither this tint nor the pallor is indicative of the severity or even of the presence of anaemia. For instance, a child (case 5) suffering from severe scurvy (as shown by the presence of scorbutic gingivitis, swelling of legs with pseudoparesis, orbital haemorrhage, recession of sternum and cartilaginous ribs, 15-20 red cells in the uncentrifugalized urine per high power field), although markedly pale presented a normal blood picture, the red cells being $5\frac{1}{2}$ millions per cubic millimetre and the haemoglobin 98 per cent. In 1932 Rohmer and Bindschedler³ published a paper recording the results of an examination of the blood in fifteen cases of infantile scurvy seen during the preceding five years. They found anaemia in only seven instances and came to the conclusion that anaemia could not be regarded as a constant and essential symptom of scurvy, but considered that its appearance was probably connected with certain super-added conditions which did not form part of the picture of uncomplicated scurvy. Baar⁴ found anaemia in only one-third of his cases; Shipley⁵, on the other hand, found a degree of anaemia in every case of his series. These results suggest that anaemia is far less common in scorbutic infants than in scorbutic adults, because in the latter 70-80 per cent. of the recorded cases whose blood has been examined, have been found to have anaemia of severe or moderate degree⁶.

The blood in scurvy.

Frank scurvy is nowadays a rare disease and in the last three years we have only been able to study six cases by modern haematological methods, yet these have been sufficient to demonstrate conclusively both that severe scurvy may occur without any evidence of anaemia and that scurvy may be associated with an anaemia which is solely the result of a deficient supply of vitamin C. The anaemia is in fact a characteristic symptom of scurvy, but just as every case, even of severe scurvy, does not present the whole gamut of the scorbutic syndrome, so sometimes anaemia occurs and sometimes the blood is normal. The results obtained in our series are set out in table 1, a reference to which shows that anaemia was present in four cases but only reached a severe degree in one case (case 1). This child had a red cell count of 2,810,000 per c.mm. and haemoglobin 35 per cent., giving a colour index of 0.76, and actually during the stay in hospital the colour index at one time was as low as 0.6. Shipley⁵ has reported even lower haemoglobin figures, for instance a 29 per cent. haemoglobin with a red cell count of 2,480,000 per c.mm. The anaemia is either orthochromic or hypochromic. The red cells show ring staining when the colour index is low and may show a moderate degree of anisocytosis. Three of the four cases showing anaemia were investigated

TABLE 1.

Case	Date	Red corpuscles per c.mm.	Haemoglobin per cent.	Colour index	Volume index	Saturation index	Mean red cell diameter μ	Standard deviation μ	Coefficient of variation per cent.	Reticulocytes per cent.	Nucleated reds per c.mm.
1. J. R., aet 9 mth.	24.3.32	2,310,000	35	0.76			7.009	9.688	9.82	2.0	100
	29.3.32	3,276,000	41	0.62			7.065	0.604	8.54	7.5	2,250
2. A. L., aet 9 mth.	14.9.34	4,190,000	69	0.82	0.87	0.95	7.284	0.611	8.39	0.9	
3. J. H., aet 10 mth.	14.9.34	3,990,000	70	0.87	0.98	0.90	7.186	0.518	7.21	0.2	
4. B. M., aet 8 mth.	21.7.33	5,130,000	82	0.80	0.82	0.96				0.2	
5. G. G., aet 11 mth.	14.11.34	5,500,000	98	0.89	0.98	0.92	7.128	0.480	6.73	1.1	
6. J. F., aet 6 mth.	22.5.33	4,530,000	98	1.01	1.08	1.01				0.2	

by means of Price-Jones' curve, and in each case the cells were of normal average diameter (see fig. 1). In two of these anisocytosis of moderate degree was present as shown by a high coefficient of variability, i.e., 8.54 and 8.93 per cent., the normal limits according to Price-Jones being 5.64 to 7.26 per cent. (see fig. 1).

FIG. 1.

The microhaematocrit method as devised by our colleague, the late R. J. Gittins, is, in our opinion, the best clinical method for estimating the average size of the red cells, and this gave a volume index (the mean volume of a single cell relative to normal) under 0.9 in two cases, indicating a slight degree of microcytosis such as is found in the mild 'secondary' anaemias of infective origin or those resulting from small haemorrhages. The saturation index (the mean corpuscular haemoglobin concentration relative to normal) revealed normal packing of the red cells with haemoglobin. The bleeding and clotting times and clot retrac-

tion were all normal, and there was no diminution in the number of blood platelets. The differential white cell count showed no constant change. In two cases (3 and 6) a lymphocytosis (77 per cent. and 68 per cent. respectively) was present. A polymorphonuclear leucocytosis may occur owing to the presence of an infection, a not improbable complication since, to borrow a simile from Shipley the incidence of an infection not infrequently fans the embers of a latent scurvy into the intense flame of an acute attack.

As in nutritional anaemia the occurrence of an infection may also be a factor in increasing the anaemia of the scorbutic infant, and further, in the long-standing cases (which provide the most outstanding examples of anaemia), the effect of repeated haemorrhage is added to the original scorbutic blood picture, and the anaemia may then become hypochromic. In the quotation from Barlow's paper already given it is stated that the pallor became intensified when limb involvement was pronounced and was proportional to the amount of limb involvement. It seems reasonable to suppose that this may have been the result of large sub-periosteal haemorrhages. For instance, the child already referred to (case 1), had suffered from pseudo-paralysis for a period of two months before coming to hospital but only became pale shortly before admission thereto. She had large sub-periosteal haemorrhages and a severe hypochromic anaemia which became even more hypochromic shortly after admission, an occurrence which seems to be added proof of the effect on the blood of recent large haemorrhages.

The fact that there is a true anaemia of scurvy, the result of a specific deficiency, and that this deficiency is of vitamin C, is shown by the effect of treatment since all the cases responded rapidly both haematologically and clinically to treatment with orange juice. In all our observations on the deficiency anaemias of childhood we have adopted a method whereby the child is kept on the diet on which the anaemia has developed and then the factor which it is considered may be deficient, e.g., iron, is added. If after a short period a reticulocytosis, together with an improvement in the anaemia, does not take place, some other factor, e.g., copper, is tried, and so on. If a partial improvement only occurs the effect of a combination of factors, e.g., iron, copper and yeast, is tried. The most striking result of treatment with vitamin C is shown in case 1 (see fig. 2). This child, aged nine months was fed on milk. When orange juice was added a brisk reticulocytosis occurred, reaching its maximum on the eighth day, and on the fifteenth day the red cells were normal in number, having been more than doubled, and the haemoglobin had increased from 35 to 70 per cent. The anaemia eventually progressed to a complete cure. The increase in the nucleated red cells following the onset of treatment was interesting and may be regarded as the result of normoblastic proliferation in the bone marrow. Incidentally it is perhaps worthy of note that both

iron and liver preparations free from iron and vitamin C have been proved to be useless in the treatment of scorbutic anaemia in adults⁶.

FIG. 2.

The blood in latent scurvy.

The occurrence of a condition which has been called latent or sub-scurvy has been challenged by some authorities and it must be admitted that proof of its existence has hitherto been lacking; nevertheless, on first principles it does seem feasible that if frank scurvy is the result of a grossly defective vitamin C intake, less severe defects should produce a condition of affairs predisposing to the onset of acute manifestations. In other words the deficiency in vitamin C does not produce an 'all or nothing response'; indeed the influence of infection in determining the onset of acute scurvy can only be adequately explained by such a conception. Incidentally, as pointed out by L. J. Harris and Ray⁷, it may be that in future we shall be able to recognize latent scurvy by the estimation of ascorbic acid in the urine, and particularly by the effect of the oral administration of ascorbic acid on its urinary output. The question whether anaemia may occur as the result of latent scurvy has been raised by some writers, and in 1922 Weill and Mouriquand⁸ described a form of anaemia in infants which resisted treatment by iron but was cured by the administration of lemon juice. Ten years later Rohmer and Bindschelder³ published the results of an investigation of a group of twenty-two anaemic infants; in six of these children the anaemia was unaffected by the administration of iron, but when vitamin C was given in addition to iron a prompt cure resulted.

These authors suggest that vitamin C may have some effect on the metabolism of iron, but it is much more probable that these cases were instances of deficiency anaemia due to the absence of more than one factor, since it is not unusual for a diet which is defective in one essential to be defective in others also. Hence it is quite conceivable that a child who has nutritional anaemia may develop scurvy and the anaemia of scurvy and that therefore for its complete cure both iron and vitamin C would be required, although it must be admitted that those occasional cases of nutritional anaemia which in our experience have proved resistant to iron have never shown any haematological improvement as the result of intensive vitamin C therapy.

Maturation of the red cell.

In his various communications on anaemia Witts⁹ has set out a scheme showing how the maturation of the red cell depends on the supply to the bone marrow of certain building materials; thus the haematinic factor produced by the interaction of intrinsic factor in the gastric juice with the extrinsic factor in the diet is necessary to ensure the maturation from the megaloblast to the normoblast, and for the maturation from the normoblast to the erythrocyte he postulates the necessity for iron, copper, vitamin C and thyroxin. Further, in the event of the absence of any of these factors, anaemia having certain characteristics develops, and according to the level at which haemopoiesis is arrested the marrow is megaloblastic or normoblastic. Thus in the absence of the haematinic factor the bone marrow becomes hyperplastic and megaloblastic and a megalocytic hyperchromic anaemia results. In the absence of iron or copper or vitamin C or thyroxin the bone marrow becomes hyperplastic and normoblastic, a microcytic anaemia resulting. Whilst this is a simple and attractive scheme it does not tell the whole story and in our opinion may not be entirely correct; for instance, haemin is an iron porphyrin, and porphyrin is made up of a number of five-ring carbon compounds (the pyrrol ring) which cannot be synthesized in the body. Therefore substances containing the pyrrol ring are necessary for the maturation of the red cell, and incidentally this may furnish a partial explanation of the beneficial effect of yeast in some forms of anaemia and also of the proprietary compound Phyllosan, since both these contain porphyrins (cytochrome and chlorophyll respectively). Again it is probable that one of the factors necessary for the budding of the reticulo-endothelial cells to form the haemangioblast which in turn become the megaloblast is an anoxaemia; possibly also there may be an unknown specific food factor responsible for this step, in the absence of which an aplastic anaemia occurs. The existence of such an unknown factor is envisaged by Witts in his last communication. Finally, it has already been stated in this paper that the anaemia of scurvy is usually normocytic and orthochromic; certainly it cannot be called microcytic in the sense that iron deficiency anaemias are microcytic.

We have never been able to understand Witt's view that when red cell maturation is held up at the level of normoblastic development the

resulting erythrocytes must necessarily be microcytic. None of the normoblasts that we have been able to measure in blood films and smears of bone marrow stained with the usual blood stains has been obviously smaller than the red cells present in those preparations; in fact many of them (frequently classified as macronormoblasts) have a diameter larger than normal. With the exception of certain of the congenital dystrophies of the erythron such as acholuric jaundice in which the red cells are more globular or fatter than normal, definite microcytosis is only found in two groups of blood disease. The first includes those anaemias of which pernicious anaemia is the outstanding example, in which poikilocytosis is prominent, and the microcytosis is probably the result of excessive cell fragmentation. The second group is that of the iron deficiency anaemias, which includes the nutritional anaemia of infancy, the idiopathic hypochromic anaemia of middle life, the hypochromic anaemia of coeliac disease and the anaemia of chronic haemorrhage. In all the anaemias of this group there is a disproportionate reduction of haemoglobin so that the colour index is low, and the microcytosis may be explained as an adjustment on the part of the body and its red cell factories to ensure the best utilization and distribution of the available haemoglobin, since, by packeting this in relatively large numbers of smaller cells a more extensive surface area for oxygen exchange is provided.

Bone marrow in scurvy.

A study of the bone marrow in scurvy is important in determining the action of vitamin C in the maturation of the red blood cell.

References in the literature on this point are scanty, but MacCallum¹⁰, Naegeli¹¹, Shipley⁵, Holt and McIntosh¹² all describe a disappearance of the blood-forming tissues from the marrow and their replacement by fibrous tissue. Mettier, Minot and Townsend described the bone marrow as moderately hyperplastic and it is on their work that Witts bases his views on red cell maturation in scurvy. These observers studied two specimens of bone marrow taken from the sternum of one of their adult patients who showed scorbutic anaemia, the first before the commencement of treatment, and the second at the height of the reticulocytosis which occurred after giving orange juice. Concerning the first specimen (before treatment) they say, 'The tissue shows moderate cellular hyperplasia and contains a few isolated fat cells. There are scattered, small, varying sized groups of nucleated red blood cells . . . There is no evidence of fibrosis.' On the other hand in the second specimen (showing the result of treatment) they found 'Quantitatively more nucleated red blood cells. Mitotic figures among the precursors of these cells were not apparent in the specimen obtained from the patient prior to any treatment whereas in the specimen obtained at the time of the peak of the reticulocyte rise, a few mitotic figures appear in each field of the microscope.' As a result of their study of these two specimens they suggest that vitamin C 'can promote in some fashion the development of nucleated erythrocytes,' and conclude that 'in scurvy and in anaemias responding to iron perhaps the effective substance hastens maturation of normoblasts.'

It appears to us, however, that this picture of increased numbers of normoblasts actively dividing is an indication of greater production rather than maturation of these marrow elements. The best description of the

scorbutic bone marrow that we have found is in a paper by H. A. Harris¹³, in which he gives a detailed account of the bones and bone marrow obtained at post-mortem from a case of scurvy. He describes the manifestations of scurvy as consisting of areas of haemorrhage, areas of excessive development of fibrous tissue, and areas of gelatinous marrow devoid of blood-forming cells, and concludes that 'anaemia in scurvy is not only due to the succession of haemorrhages but is due to the formation of gelatinous marrow with failure of differentiation of the marrow into erythroblastic and leucoblastic areas.' His specimens showed some healing of the scorbutic process at the bone ends in contiguity with the epiphyseal line, and in this situation a few normal marrow cells were seen which he regards as a clear indication that 'the process of healing is not dependent on extension of the normal tissue but on a special differentiation in situ as a result of blood-borne substances.' These findings, which represent the investigations of the whole bone and are in accord with the findings of MacCallum, Naegeli, Shipley, Holt and McIntosh, probably represent a truer account of the state of the marrow in scurvy than that quoted above of the examination of small samples of sternal marrow obtained by biopsy which cannot claim justly to represent changes present throughout the whole erythropoietic system. Nevertheless it is well known that hyperplasia is frequently followed by degeneration and aplasia, especially in bone marrow, and the findings reported by Mettier and his colleague may quite possibly represent a stage prior to a gelatinous degeneration.

The maturation of the red cell in scurvy.

Vitamin C probably functions in the body by forming an oxidation-reduction system, taking up oxygen in the tissues, and subsequently by its power of reversible oxidation functioning as an oxygen carrier and thereby playing an important part in the processes of tissue respiration and metabolism. Confirmation of this theory exists in two sets of experiments. First the work of Harrison¹⁴ and of Euler and Klusmann¹⁵, who have shown that slices of the fresh tissues of scorbutic animals have a low oxygen uptake which is restored by the addition of ascorbic acid; secondly that of Söderström and Törnblom¹⁶ who have shown that in scurvy in animals the oxygen consumption is lowered. It seems probable, therefore, that like thyroxin, vitamin C is responsible for cell metabolism and that its action upon the cells of the bone marrow is throughout the whole range of maturation from endothelial cell to adult erythrocyte and not restricted to the stage of maturation of the normoblast, as suggested by Witts.

In our opinion the anaemia of scurvy results from a general slowing down of the whole process of erythropoiesis which may be so marked as to result in marrow degeneration and aplasia, the resulting anaemia being therefore usually orthochromic and normocytic; in chronic cases associated with large haemorrhages into the tissues and from mucous membranes a post-haemorrhagic blood picture becomes superimposed and the anaemia may then become hypochromic and it is conceivable that in extreme cases it might even become truly microcytic. On this hypothesis it might be

expected that a megalocytic anaemia should occur at times the result of a disproportionate slowing up of red cell development at the stage of maturation of megaloblast to normoblast. We have not observed this but Mettier, Minot and Townsend say of the red cells in adult scurvy that 'occasionally there may be a sufficient number of nonachromic cells slightly larger than normal to suggest the possibility of pernicious anaemia.' Unfortunately these workers did not estimate the size of the red cells, but this description is of blood films from untreated cases in which 'about one per cent. of the cells are usually polychromatophilic.' It is clear, therefore, that these larger cells were not reticulocytes and the description almost warrants the assumption that a megalocytic blood picture does occur in scurvy*.

The rôles played by vitamin C and thyroxin in the maturation of the red cell are in our opinion very similar since the anaemia of cretinism in our experience is also usually orthochromic and normocytic, occasionally macrocytic and never microcytic.

Conclusions.

1. Anaemia is a characteristic but not invariable symptom of infantile scurvy.
2. The anaemia of infantile scurvy is due to a deficiency in vitamin C and is cured by its administration in adequate quantities.
3. The anaemia of infantile scurvy is usually orthochromic and normocytic, microcytosis if present is slight in degree and cannot be compared with that present in the iron deficiency anaemias.
4. Reasons are given for the belief that vitamin C is required in all stages of maturation of the red cell from the reticuloendothelial cell to the erythrocyte.

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* Since this paper was written we have observed an example of macrocytic anaemia in infantile scurvy. (L. G. P. and W. C. S.)