

## THE ANAEMIA OF SCURVY.

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It has been known for many years that clinical scurvy is frequently accompanied by anaemia. Much has been written on the causation of this anaemia, but the part played by ascorbic acid deficiency in its production is still in dispute.

The purpose of the present paper is to present the haematological findings in forty-three patients with scurvy who were studied in hospital during the past seven years, and to discuss these findings in the light of what has already been written on the subject.

### CLINICAL AND LABORATORY DATA.

Observations were made on forty-three cases of frank scurvy admitted to the Royal Infirmary and to the Southern General Hospital, Glasgow, between 1944 and 1949. Both the clinical picture and the etiological factors were typical. Most of the patients were males, who had been living alone for at least a year in poor conditions or in a lodging house, and most were over fifty years of age. All gave a history of almost complete absence of vegetables from their diets over a period of at least a year, and only rarely was fresh milk or freshly cooked meat taken. The staple diet in such patients consisted of bread and tea to which tinned condensed milk might be added. In thirteen patients there was a history of previous admission to hospital with scurvy.

In the majority of the patients it was difficult to establish the duration of symptoms attributable to scurvy, but the symptoms which led to admission to hospital, almost invariably pain in the limbs with swelling and discolouration, had usually been present for one to two months. The clinical findings in these patients were characteristic of frank scurvy. A haemorrhagic state was a constant feature. It consisted of ecchymoses, which were usually most marked on the thighs, and a petechial rash which was seen on the lower limbs, to a less degree on the lower part of the trunk, and only occasionally on the forearms. The majority of the patients were edentulous but in those who still had teeth the typical gum changes of scurvy were present.

*Laboratory findings.* The vitamin C saturation test described by Harris (1943) was performed in twenty-eight patients. All showed delayed 'saturation' beyond five days. In a further eight patients plasma vitamin C levels were estimated. Three were over 0.2 mg. per cent, the highest

being 0.7 mg. per cent. Examination of gastric function by test meal was carried out in fourteen patients. Eight were achlorhydric, and of these only two secreted acid in response to histamine.

*Haematological findings.* Of the forty-three patients, nine presented with haemoglobin concentrations over 11 g. per cent (80%), thirty-one were moderately, and three were severely, anaemic (Table 1). The blood, as indicated by the colour index, was sometimes hypochromic, sometimes normochromic and sometimes 'hyperchromic.' This was confirmed by examination of stained blood smears, and also, in a limited number of cases, by estimation of the absolute values (Table 1).

TABLE I.  
Haematological data in forty-three cases of scurvy.

| Hb. %<br>(100 = 14.8 g.) |          | Colour Index |          | M.C.H.C. % |          | M.C.V.<br>cu. $\mu$ . |          |
|--------------------------|----------|--------------|----------|------------|----------|-----------------------|----------|
| 80—                      | 9 cases  | 0.6—         | 7 cases  | Under 20.5 | 12 cases | Under 80              | 2 cases  |
| 60—                      | 21 "     | 0.9—         | 18 "     | Over 30    | 6 "      | 80—                   | 9 "      |
| 40—                      | 10 "     | 1.1—         | 13 "     |            |          | 100—                  | 7 "      |
| 20—                      | 3 "      |              |          |            |          |                       |          |
| Total                    | 43 cases | Total        | 38 cases | Total      | 18 cases | Total                 | 18 cases |

*Bone marrow examination.* Bone marrow examination by sternal puncture was carried out in ten patients, among whom were four with macrocytic anaemia which was confirmed by repeated examination of stained blood films and estimation of the M.C.V. In all cases erythropoiesis was normoblastic. Evidence of megaloblastic erythropoiesis was sought, especially in cases with a macrocytic blood picture, but none was found. Sections of marrow were not made, but, on the evidence obtained from smears there seemed to be no uniform picture of marrow activity. In some instances there were numerous fat spaces and in others the smears were hypercellular.

*Comment.* There was no constant haematological picture in this series of patients with scurvy. Normal blood values were present in about a fifth, and the presence or absence of anaemia bore no obvious relationship to the clinical evidence of scurvy. When anaemia was present it was sometimes macrocytic, sometimes normocytic, and sometimes microcytic. In the majority, hypochromia was present in mild degree, sometimes associated with a colour index of unity owing to the coexistence of slight macrocytosis. This lack of uniformity in the occurrence, and in the type of the anaemia in scurvy suggests that deficiency of ascorbic acid is not the sole factor involved. This is in keeping with the nutritional history of the great majority of scorbutic patients.

The following cases, described in detail, give some indication of the multiplicity of factors involved in the causation of the anaemia of clinical scurvy.

CASES RESPONDING TO ASCORBIC ACID.

*Case 1.* J. M., aged 66, had been living alone and mostly in lodging houses for about 25 years and for most of this time his diet had consisted almost entirely of bread and tea. He had been treated in hospital for scurvy on two previous occasions, fifteen and four years before his present attack. On this occasion he complained of dyspnoea, anorexia and pain in the legs of about two months' duration. During this period, and also during the preceding month, his teeth had become loose and many had fallen out, leaving only three in the lower jaw.

*Clinical examination.* He was a spare poorly nourished individual, with swollen hyperaemic gums around the teeth in the lower jaw. His skin was dry and rough, and follicular hyperkeratosis was marked on legs, thighs and forearms. There was a petechial rash in the same distribution. From the mid-thigh to the ankle the left leg was swollen, brawny, and discoloured by numerous large ecchymoses. The right leg showed similar changes in less degree.

*Special investigations.* A test meal revealed a histamine-fast achlorhydria. Blood examination showed a moderately severe, slightly macrocytic, normochromic anaemia with a normal total and differential white cell count (R.B.C. 2.2 million/cu.mm., Hb. 7 g.%, (47%), M.C.V. 100 cu. $\mu$ , M.C.H.C. 31%, W.B.C. 4,900/cu.mm.). Platelets numbered 450,000 per cu.mm. Bone marrow smears obtained by sternal puncture showed normoblastic erythropoiesis. Appearances suggested reduced activity. Vitamin C saturation test resulting in 'saturation' on the 6th day.

*Treatment and subsequent course.* The patient was given full bed rest and a diet consisting of bread, fish, and tea. Administration of ascorbic acid (625 mg. daily) was commenced on the 7th hospital day and continued for 3 weeks. During this period there was marked haematological improvement (Fig. 1).

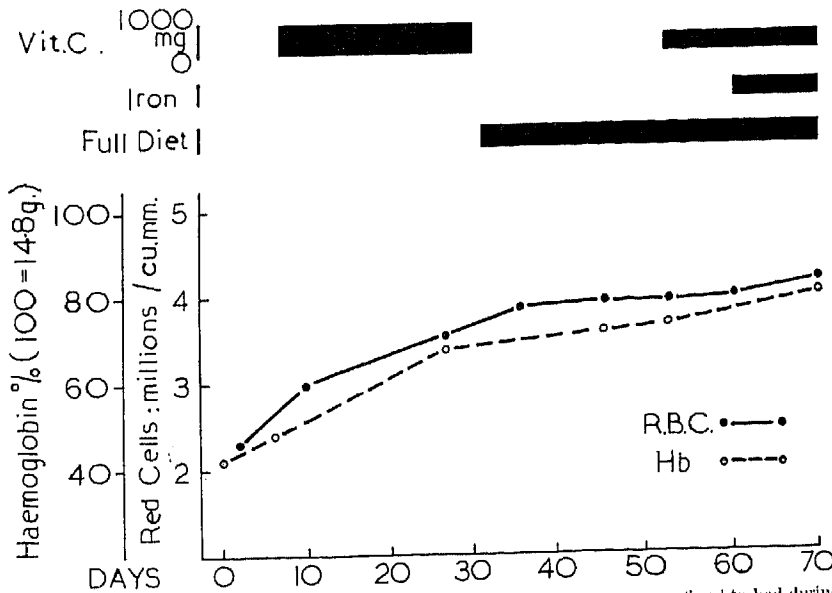


Fig. 1. The haematological response of Case 1 to treatment. This patient was confined to bed during the first two weeks.

*Conclusion.* Vitamin C may have been responsible for the haematological recovery. Bed rest may have been a contributory factor as improvement occurred too rapidly to be attributed to ascorbic acid alone (Fig. 1).

*Case 2.* H. M., aged 70, had been living in a lodging house for many years. His diet had consisted almost entirely of tea and bread and he did not remember when he had last tasted fruit or vegetables. His complaint was one of pain in the legs and anorexia of about a month's duration.

*Clinical examination.* He was verminous, dirty and ill-nourished with a marked petechial rash and ecchymoses on the legs from about the mid-thigh downwards. The thigh and calf muscles were indurated and tender. The skin on the lower limbs was rough and dry. He was edentulous and there were no oral changes.

*Special investigations.* A test meal revealed a histamine-fast achlorhydria. Blood examination showed a macrocytic, slightly hypochromic anaemia with a normal white cell count (R.B.C. 2.8 million/cu.mm., Hb. 9.5 g.% (64%), M.C.V. 120 cu. $\mu$ , M.C.H.C. 28%, W.B.C. 5,900/cu.mm.). The bone marrow, obtained by sternal puncture, was normoblastic. Appearances suggested increased erythropoietic activity. A vitamin C saturation test resulted in 'saturation' on the 8th day.

*Treatment and subsequent course.* The patient was given full bed rest and a diet low in animal protein, potatoes, and other vegetables. It consisted of bread, fish, and tea. A rapid and complete recovery to normal blood levels in 40 days accompanied the daily administration of 700 mg. ascorbic acid (Fig. 2).

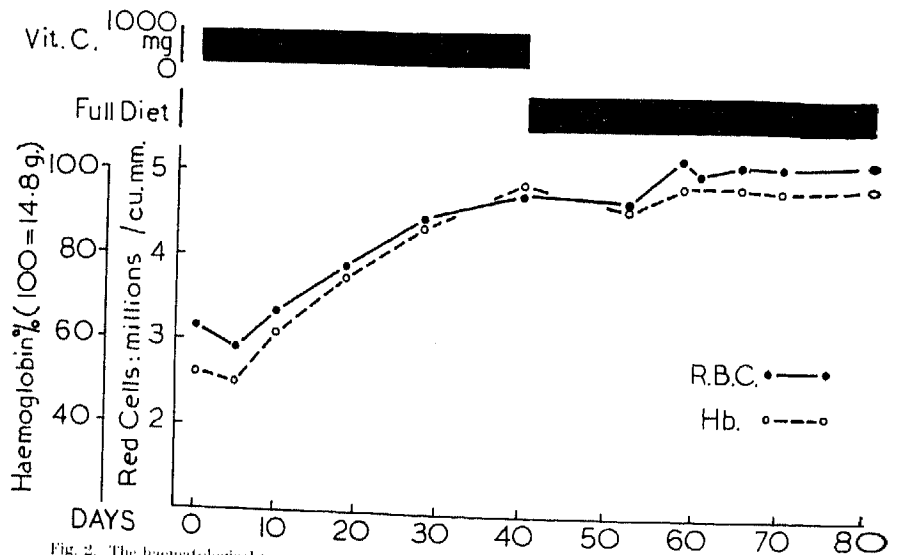


Fig. 2. The haematological response of Case 2 to treatment. This patient was confined to bed during the first two weeks.

*Conclusion.* Vitamin C may have been responsible for the recovery. The effect of rest alone was not observed.

*Case 3.* M. M., aged 64, a married man living with his wife in very poor circumstances gave a history of unusual dietary habits in addition to economic limitations. For many years he had taken scarcely any meat, and had not taken any potatoes or other vegetables. He complained of swelling and pain in the left calf, of about 3 months' duration. There were no other symptoms.

*Clinical examination.* The legs from the hips down were the seat of follicular petechiae and considerable deep-seated ecchymoses. The latter were most severe in the left calf which was swollen and indurated. Hyperkeratosis was prominent in the lower limbs. He was edentulous.

*Special examinations.* Blood examination revealed a normocytic hypochromic anaemia and a normal white cell count (R.B.C. 3.53 million/cu.mm., Hb. 8 g.% (54%), M.C.V. 90 cu. $\mu$ , M.C.H.C. 25.5%, W.B.C. 7,300/cu.mm.). Vitamin C saturation test revealed 'saturation' on the 10th day. The plasma ascorbic acid level was 0.12 mg.%.

*Treatment and subsequent course.* The patient was allowed complete bed rest for a week, and during this time, in spite of his being on a diet deficient in vitamin C, marked improvement in the haemorrhagic state occurred. Treatment was then commenced with vitamin P (Hesperidin), 600 mg. daily. Complete bed rest was stopped and the patient was allowed to assist in ward work. His diet was continued as before. Within 48 hours relapse occurred with extensive ecchymoses into the muscles in thigh and calf region and recurrence of petechiae in both lower limbs. Deterioration continued throughout the period of administration of 'Hesperidin.' Neither the clinical evidence of scurvy nor the blood levels improved until, on the 17th day, administration of vitamin C was begun (Fig. 3). The clinical and haematological response was almost immediate, and within 4 weeks of commencing ascorbic acid treatment, clinical evidence of scurvy had disappeared and the red cell count had reached 4.8 million per cu.mm.

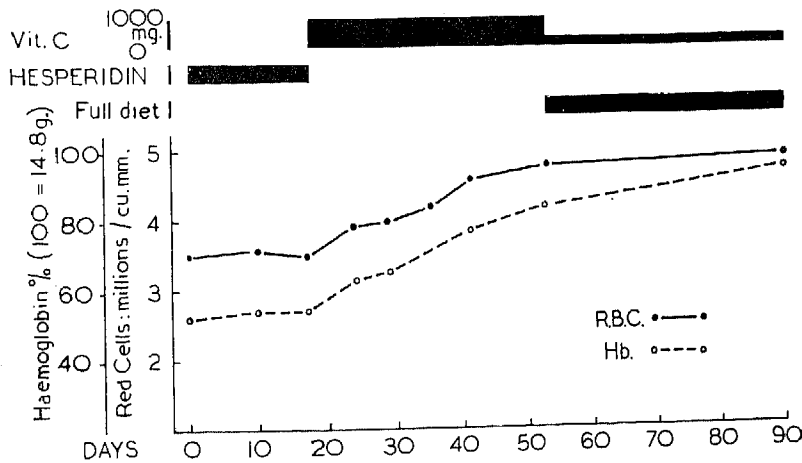


Fig. 3. The haematological response of Case 3 to treatment. This patient was not confined to bed (for details see text).

*Conclusion.* Vitamin P given as 'Hesperidin' in daily doses of 600 mg. was ineffective in controlling the haemorrhagic tendency of scurvy or the anaemia, and bed rest alone was a potent factor in alleviating the condition at an early stage in treatment. The haematological recovery in this case is attributed to ascorbic acid alone.

#### CASES WHICH DID NOT SHOW A SATISFACTORY RESPONSE TO ASCORBIC ACID.

*Case 4.* J. F., a man aged 61, had been living in a lodging house for many years, and during this time his diet had consisted almost entirely of tea and bread. He had been treated in hospital for scurvy on two previous occasions, one year and ten years before his present illness. On this occasion he complained of swelling of both legs, of about four weeks' duration. During this time numerous large bruises had appeared on the legs and he had suffered much local discomfort.

*Clinical examination.* He was poorly nourished, with oedema of the feet and ankles. Both legs, and the right thigh were the seat of numerous ecchymoses. The muscles in both leg and thigh were swollen and firm, although not unduly tender. Follicular petechiae were numerous on the legs, thighs and forearms. The skin in these regions, especially in the thighs showed follicular hyperkeratosis and was rough and dry. Over the tibiae the skin was smooth indurated and inelastic. The gums were edentulous and showed nothing abnormal. General clinical examination was otherwise negative.

*Special examinations.* Examination by test-meal revealed a histamine-fast achlorhydria. Blood examination revealed a normocytic normochromic anaemia with a normal white cell count (R.B.C. 3.47 million/cu.mm., Hb. 9.3 g.% (63%), M.C.V. 92 cu. $\mu$ , M.C.H.C. 29.5%, W.B.C. 4,700/cu.mm.). Bone marrow examination showed that erythropoiesis was normoblastic. Smears were cellular and the appearances suggested increased rather than diminished activity. A vitamin C saturation test resulted in 'saturation' on the 8th day.

*Treatment and subsequent course.* The patient was given full bed rest and a diet low in vitamin C and animal protein. It consisted of bread, fish, and tea. Administration of ascorbic acid (700 mg. daily) was commenced on the fourth hospital day, and continued for a week. Thereafter the daily dose was reduced to 200 mg., and in addition iron was given as ferric ammonium citrate, 90 gr. daily. During the first three weeks of treatment his red cell count rose to almost 4 million per cu.mm. Signs of scurvy rapidly disappeared, and his general health was much improved. For five weeks thereafter the blood count remained unaltered. Consumption of a full hospital diet supplemented with autolyzed yeast (Marmite 1 oz. daily) was then accompanied by a rise in the red cell and haemoglobin levels to normal (Fig. 4).

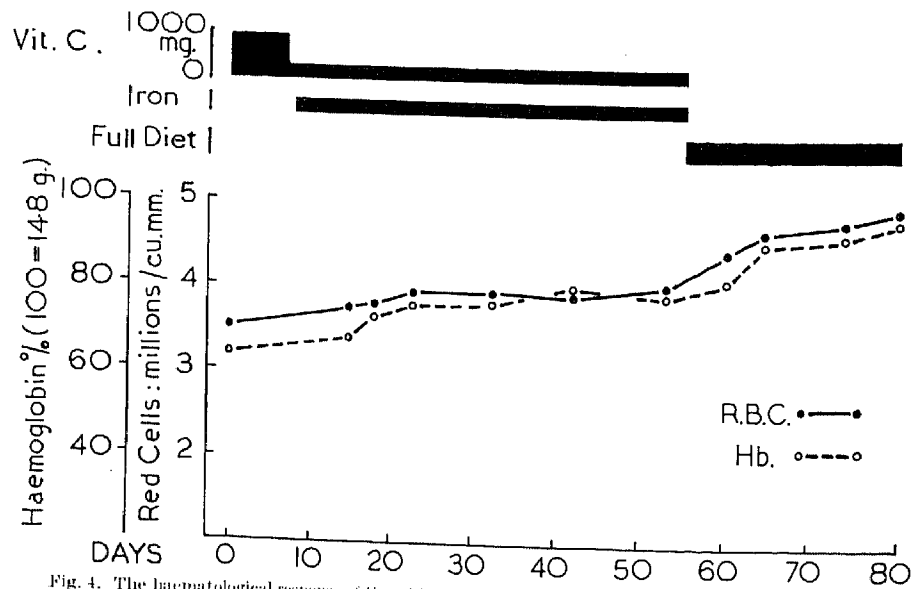


Fig. 4. The haematological response of Case 4 to treatment. The term full diet in this and subsequent cases signifies a full hospital diet supplemented with autolyzed yeast.

*Conclusion.* In this case administration of ascorbic acid was followed by disappearance of the clinical evidence of scurvy, but only partial improvement occurred in the anaemia. Return to full diet supplemented with autolyzed yeast provided some other factor which was necessary for full recovery.

*Case 5.* W. F., a man aged 73, was a widower who had lived in a lodging house for many years. His history was one of a monotonous inadequate diet. He rarely had a cooked meal and never ate fresh fruit or vegetables. His complaint was one of pain and stiffness in the legs of about two months' duration.

*Clinical examination.* He was a poorly nourished man who showed a severe haemorrhagic state which was confined to his lower limbs. It was most marked on the left side, where the calf and thigh muscles were swollen, firm and unduly tender. Much bruising was visible beneath the skin. Follicular hyperkeratosis and petechiae were marked on the legs and thighs. The gums were edentulous and showed nothing abnormal. General clinical examination showed no other significant feature.

*Special examinations.* A test meal revealed free hydrochloric acid in the gastric juice. Blood examination showed that he had a normocytic hypochromic anaemia, and a normal white cell count (R.B.C. 2.8 million/cu.mm., Hb. 6.6 g.% (45%), M.C.V. 95 cu. $\mu$ , M.C.H.C. 25%, W.B.C. 5,700/cu.mm.). Smears of sternal bone marrow were hypercellular: erythropoiesis was normoblastic. A vitamin C saturation test resulted in 'saturation' by the 11th day.

*Treatment and subsequent course.* The patient was given full bed rest and the diet, consisting of bread, fish, and tea, low in vitamin C and animal protein. Administration of ascorbic acid (700 mg. daily) was begun on the fifth hospital day (Fig. 5). On the twentieth day the daily dose was reduced to 200 mg. During

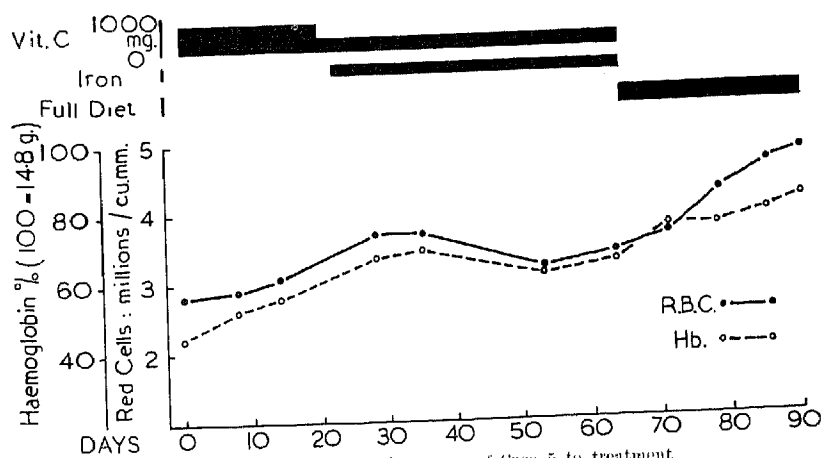


Fig. 5. The haematological response of Case 5 to treatment.

the first four weeks the red cell count and haemoglobin level rose to 3.7 million per cu.mm. and 10 g. per cent (68%) respectively, and all clinical evidence of scurvy disappeared. During the next four weeks the improvement in the anaemia failed to continue, in spite of the addition of iron to this treatment (150 gr. ferric ammonium citrate daily), and from the eighth to the ninth week levels fell to about 3.2 million per cu.mm. and 9 g.% (60%). Within three weeks of commencing a full hospital diet supplemented with autolyzed yeast (Marmite 1 oz./day) the red cell count had risen to 4.74 million per cu.mm. and the haemoglobin to 80 per cent.

*Conclusion.* Ascorbic acid was effective against the clinical manifestations of scurvy but failed to cure the anaemia. A full hospital diet supplemented by autolyzed yeast contained some other factor essential for this purpose.

*Case 6.* W. L., a man aged 65, had been living in a lodging house for four years and had eaten no vegetables or fruit during that time. He rarely cooked food and had lived almost entirely on bread and tea to which he added condensed milk. He was admitted to hospital with a history of a painful swelling in the left thigh of about six weeks' duration. For two to three weeks he had noticed a rash over both lower limbs.

*Clinical examination.* The skin on the thighs showed follicular hyperkeratosis and a petechial rash. Extensive superficial ecchymoses were present and the thighs were swollen and discoloured. The legs below the knees, and the forearms were also the seat of petechial bleeding and over the tibiae the skin was firm, inelastic and pigmented. The upper jaw was edentulous, but the lower contained several carious teeth. Periodontal sepsis was marked and the gums were swollen and congested.

*Special examinations.* Blood examination showed a normocytic normochromic anaemia with normal white cell and platelet counts (R.B.C. 3.78 million/cu.mm., Hb. 11 g.% (74%), M.C.V. 84 cu. $\mu$ , M.C.H.C. 33%, W.B.C. 7,200/cu.mm., platelets 270,000/cu.mm.). Smears of bone marrow were hypercellular. Erythropoiesis was active, and normoblastic in type. The plasma vitamin C concentration was 0.5 mg. per 100 ml. and a saturation test resulted in 'saturation' on the 8th day.

*Treatment and subsequent course.* With a view to assessing the therapeutic effect of vitamin P the patient was allowed up during the day and was given a diet previously described, which was low in vitamin C and animal protein. He received 450 mg. vitamin P (Hesperidin) daily from the fourth hospital day. This treatment was continued for ten days, and during that time there was deterioration in the general manifestations of the scorbutic state and also in the anaemia (Fig. 6). Vitamin P administration was stopped and ascorbic acid was given from the fourteenth day in daily doses of 500 mg. for eleven days. By the end of this period all clinical evidence of active scurvy had disappeared and there was some improvement in the patient's general health. On the other hand, the anaemia was more severe (R.B.C. 3.46 million cu.mm.). From this time onwards, the daily dose of ascorbic acid was reduced to 150 mg. and a full diet was given supplemented by autolyzed yeast. Within four weeks the red cell count and haemoglobin had risen to 4.5 million per cu.mm. and 13.6 g. (92%) respectively.

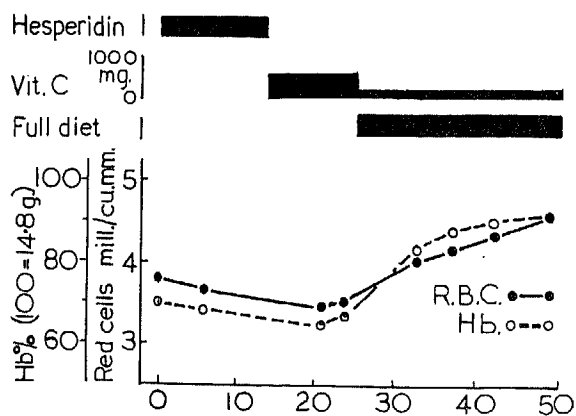


Fig. 6. The haematological response of Case 6 to treatment.

*Conclusion.* Vitamin P had no effect on the clinical or haematological manifestations in this case of scurvy. Ascorbic acid was effective against the clinical features but not against the anaemia which responded to a hospital diet supplemented by autolyzed yeast.

#### DISCUSSION.

There are no characteristic haematological findings in scurvy. The present figures are in keeping with what has been generally accepted for many years, that as many as a third of all cases of scurvy show little or no anaemia (Mettier *et al.*, 1930). Furthermore, the anaemia, when present, does not conform to any particular type. Mild hypochromia is common but not invariable, and the anaemia may be macrocytic, normocytic, or microcytic. Bone marrow studies have also failed to reveal any cell picture characteristic of the disease. Haemopoiesis is essentially normoblastic. The rarity with which megaloblastic erythropoiesis has been described indicates that such a change is related to disturbances other than those usually present in scurvy (McMillan & Inglis, 1944). The degree of erythropoietic activity in the marrow in scurvy is a variable feature, as may be judged from the present findings and from the reports by Israels (1943) and Vilter *et al.* (1946).



There appear to be two points at issue in relation to scurvy and anaemia. The first of these concerns the occurrence and type of anaemia which occurs in scurvy, and its causation. With regard to this question there is good reason to believe that the anaemia may result from a variety of causes. This is the only reasonable explanation of the different types of anaemia encountered in clinical scurvy, and the variability of response to different types of treatment. The second point at issue is the haemopoietic significance of ascorbic acid in the human subject. Experimental work in animals has shown that anaemia is a regular feature of scurvy in the guinea-pig and that ascorbic acid will prevent or cure the anaemia (Cartwright, 1947). In the human subject proof of a specific haemopoietic activity for ascorbic acid has been difficult to obtain. This is probably in great part due to the variability in the occurrence and in the type of the anaemia, and to the variable and apparently contradictory results obtained from therapeutic trials in patients with scurvy. Failure to find haematological changes in experimental scurvy in man has added further to the doubt that ascorbic acid plays any part in erythropoiesis.

Lack of uniformity in the type of anaemia encountered in scurvy is suggestive of a diversity of causes rather than a single etiological factor, and perhaps it is not surprising that evidence from clinical therapeutic trials has not always provided good evidence of the effect of vitamin C on the anaemia. In the early reports, orange juice was used as a source of vitamin C and the results were satisfactory (Mettier *et al.*, 1930; Witts, 1932). Later reports that recovery might occur without increased intake of ascorbic acid, and the knowledge that orange juice contains substances other than vitamin C led to the feeling that there was no justification for ascribing to ascorbic acid any role in haemopoiesis (Wintrobe, 1946).

Many factors have combined to confuse the issue. The early use of relatively crude sources of ascorbic acid has been referred to, but much more important has been the lack of controlled and careful investigation of cases of scurvy, and a failure to appreciate that many factors apart from ascorbic acid may be deficient in the scorbutic patient. In considering the many reports of therapeutic trials of various substances in scurvy with anaemia it should be borne in mind that it is desirable that vitamin C should be given as synthetic ascorbic acid; that there should be as little complicating disease as possible which might influence blood values; that the diagnosis should be obvious clinically, and that the diagnosis of vitamin C deficiency should not rest on estimation of plasma vitamin C levels alone. A preliminary control period is desirable and the possible beneficial effect of bed-rest should be excluded before the therapeutic test is applied. During the test the diet should be low in vitamin C and in vitamins of the B complex.

In favour of ascribing a role in erythropoiesis to ascorbic acid are several authors who based their observations on the use of natural sources of vitamin C (Mettier *et al.*, 1930 ; Witts, 1932). In 1935 Dunlop and Scarborough reported two cases of scurvy one of which was associated with moderately severe anaemia. This patient showed no alteration in red cell count during a control period in spite of the presence of increased proportion of reticulocytes (14.6%). Associated with the administration of 60 mg. ascorbic acid daily for seventeen days the red cell count rose from 2.57 million to 4.22 million per cu.mm. The patient was on a deficient diet low in iron content during this period. Jennings and Glazebrook (1938) described two cases of adult scurvy with anaemia. The first showed a macrocytic anaemia (M.C.V. 114 cu. $\mu$ ). Liver extract and iron treatment were without effect on the anaemia but recovery occurred following administration of 500 mg. ascorbic acid daily by mouth. The second patient had a normocytic normochromic anaemia which also responded to ascorbic acid. The bone marrow in the first case was said to be megaloblastic, but the differential count indicated that the 'megaloblasts' amounted to only 0.5 per cent of the cells present. The marrow in the second case contained 1 per cent megaloblasts but this was not regarded as significant. Although there is doubt regarding the nature of the marrow picture, the evidence favours the view that ascorbic acid plays some role in erythropoiesis. In reporting on forty cases of adult scurvy, McMillan and Inglis (1944) described the results of treatment in twenty-five. Four patients on hospital diet which provided about 15 mg. of vitamin C and 14 mg. of iron per day, showed a rapid haematological recovery. Eleven patients, on the same diet supplemented by 500 mg. of ascorbic acid daily until 'saturation' and then by 100 mg. daily, showed equally beneficial effect. Ten patients were kept on a vitamin C free diet for 9-14 days. Three showed a rise of Hb. of 10 per cent or more. Six of these ten patients were later given iron therapy and only one showed further improvement: and subsequent administration of vitamin C to these six patients resulted in further improvement in four. The results of these investigations are not easy to assess. All the patients were confined to bed during treatment. The haematological findings are given in tabular form at 9-14 days interval. The authors concluded that 'Lack of vitamin C alone was not the cause of the anaemias although it might have helped in their development.' A more definite report regarding the haemopoietic significance of ascorbic acid was made by Vilter *et al.* (1946) who described the haematological findings in eleven cases of scurvy. Two patients with mild or moderately severe scurvy improved clinically and haematologically after bed rest alone. In nine severely scorbutic patients, despite persistent reticulocytosis, erythrocyte counts and haemoglobin levels were unchanged or fell while the patients were in bed on a vitamin C restricted diet. Haematological and clinical improvement

occurred in each after the administration of ascorbic acid. In all cases the diets were low also in vitamins of the B complex.

It would appear from these various reports that there is good evidence from certain therapeutic trials that synthetic ascorbic acid is capable of producing effects equally as satisfactory against anaemia of scurvy as those claimed for orange juice. In the present series of six cases described in detail, two showed a satisfactory haematological and clinical response to ascorbic acid while being given bed rest and a diet deficient in vitamin C and B complex. In the third case it was possible to provide the same result with the patient ambulatory to a degree which, in the previous control period, had been sufficient to cause severe clinical relapse. The clinical and haematological response to ascorbic acid alone was rapid and complete (Fig. 3).

Against the view that vitamin C plays a part in haemopoiesis are several clinical reports. Croft and Snorf (1939) have been cited as presenting evidence that the anaemia of scurvy is due to lack of factors other than vitamin C (Lozner, 1941; McMillan & Inglis, 1944). Lozner (1941) is quoted as having demonstrated that anaemia of scurvy may respond spontaneously, or to iron therapy without the addition of ascorbic acid (Wintrobe, 1946). Certain limitations of these reports have been clearly outlined by Cartwright (1947). Croft and Snorf (1939) drew their conclusions from therapeutic trials with vitamin C in a series of patients suffering from a wide variety of diseases. None had the signs and symptoms of scurvy. The only common factor was a low plasma ascorbic acid level. There is no reason to believe that the anaemia in these patients was related to scurvy. Lozner (1941) described five cases of 'presumptive vitamin C deficiency and anemia.' Unfortunately these were not typical cases of scurvy and the response of several of the cases to iron alone is not surprising. The second case was complicated by a positive blood Hinton test, the third by a bleeding peptic ulcer and pyloric obstruction, the fourth by alcoholic pellagra (diagnosis of sub-clinical scurvy was based on low plasma vitamin C levels in this case), and the fifth patient was a woman with achlorhydria, chronic urinary infection, and a history of nine pregnancies.

Recent investigations on experimental vitamin C deficiency in the human subject have failed to demonstrate a relationship between ascorbic acid and erythropoiesis. In 1939 Crandon (Crandon *et al.*, 1940; Lund & Crandon, 1941) subjected himself to a diet almost completely deficient in vitamin C. Early in the third month of the experiment, there was a slight fall in blood haemoglobin levels, but this was rectified by the administration of iron. After six months on this defective diet, although signs of scurvy were apparent, there was no anaemia. In a further study of this type (Medical Research Council, 1948) nineteen men and one woman, aged 21-34, lived a normal life without strenuous physical work

on a basal diet as low as possible in vitamin C but complete in other respects. It was calculated that each individual obtained not more than 1 mg. ascorbic acid daily from this diet. The first changes observed were in the skin, 17-26 weeks after commencing the experiment. Increasing follicular keratosis was accompanied by perifollicular congestion and haemorrhage. As these changes became more severe, the gums began to show small interdental haemorrhages culminating in typical scorbutic gingivitis of varying degrees of severity at 33-34 weeks. From the 30th week delayed healing of wounds was apparent and a tendency to ecchymoses after exercise was observed. Throughout this study no development of anaemia was observed.

From these investigations it is apparent that many of the features of scurvy which are attributable to ascorbic acid deficiency may develop without there being any anaemia. It does not necessarily follow that the anaemia which occurs frequently in scurvy is never due to defective intake of vitamin C. The deficiency state in the experimental studies cannot be compared with that encountered in clinical scurvy. After 6-7 months on a diet low in vitamin C haemorrhagic phenomena comprised only follicular petechiae and a tendency to ecchymoses after exercise. In clinical scurvy the history of dietary inadequacy may cover many years and the patient is admitted to hospital usually with massive bleeding both subcutaneous and intramuscular which has been in evidence for several weeks at least.

The possibility that blood loss may contribute to or be a major factor in producing anaemia in scurvy has been suggested. This may well be so in the occasional case, but in the majority of the patients in the present series there was no history of obvious external blood loss. Vilter *et al.* (1946) are also of the opinion that haemorrhage contributes little if at all to the genesis of the anaemia. Chronic occult blood loss, *e.g.*, from the alimentary tract, might be regarded as a possibility, but proof of the occurrence of this, and of its significance, has yet to be presented. It should be remembered in this connection that all cases of anaemia in scurvy are not hypochromic.

The suggestion that a haemolytic process might play a part in the production of the anaemia was made by Vilter *et al.* (1946). Almost all their patients showed reticulocytosis (some with a hypoplastic marrow), slight or moderate jaundice, elevated urobilinogen output in the stools and urine, but no bile in the urine. All these signs disappeared 4-12 days after ascorbic acid was administered. In these patients there was no evidence that significant liver insufficiency was present. The occurrence of jaundice has not been given any prominence previously in reports on scorbutic patients, and in the present series obvious jaundice was not seen. Chemical evidence of increased bile pigment metabolism was not sought but it might well have been found in view of the invariable

occurrence of massive ecchymoses and evidence of haemoglobin breakdown in the tissues. Vilter and his colleagues admit the possibility of this explanation and it may well be that such blood destruction, although not entailing loss of essential materials from the body, does contribute to the anaemia by increasing the need for marrow activity, in patients whose supplies of essential substances are already below normal.

The possibility that vitamin C, a powerful reducing agent, may play a part in iron metabolism, particularly in maintaining alimentary iron in the reduced state and thereby facilitating its absorption, must be considered. There is evidence that ascorbic acid may influence the absorption of iron (Moore *et al.*, 1939; Powell, 1944). Whether the amounts present in a normal diet have a significant effect in this direction is less certain, but the possibility must be admitted. This effect, in conjunction with slight but persistent oozing of blood may well contribute to the fairly common defect in haemoglobination, and the not infrequent occurrence of microcytic hypochromic anaemia in scurvy. That ascorbic acid deprivation always causes anaemia by interfering with iron metabolism in this way is highly improbable. In the three patients in the present series in whom a clinical and haematological response was obtained with ascorbic acid alone, and in similar cases described by Vilter *et al.* (1946) there was no constant evidence of haemoglobin deficiency. Furthermore, successful treatment of the anaemia of scurvy with ascorbic acid and a diet low in iron has been reported by Dunlop and Scarborough (1935). Jennings and Glazebrook (1938) and McMillan and Inglis (1944) found that a response might follow administration of vitamin C when previously iron had failed to influence the anaemia.

Clinical scurvy is a product of dietary deficiency of long duration and evidence that anaemia in scurvy may respond to a variety of treatments does not necessarily bear any relation to the question of the erythropoietic activity of ascorbic acid. On the basis of therapeutic trials there is evidence that pure ascorbic acid possesses specific erythropoietic activity. The first three patients in the present series, and especially Case 3, are very much in favour of this conclusion. The failure to produce anaemia in experimental human vitamin C deficiency has not been explained, but it must be borne in mind that the duration of the deficiency was relatively short and the objective evidence of the deficiency relatively mild, before the experiments were discontinued. The clinical evidence which has hitherto been cited as evidence against a relationship between ascorbic acid and erythropoiesis does no more than suggest that, in scurvy, factors other than the absence of ascorbic acid may in some patients be responsible for the anaemia. Cases 4-6 in the present series are examples of the partial or negligible effect of vitamin C against the anaemia of scurvy and the need for other factors active in erythropoiesis

which are present in a full hospital diet, supplemented by autolyzed yeast.

There can be little doubt that, as has been emphasized by Vilter *et al.* (1946), the concept of the multiple deficiency state with many factors besides vitamin C deficiency adversely affecting the bone marrow can explain the many conflicting reports on scorbutic anaemia which have appeared since 1930.

#### SUMMARY.

In a study of forty-three patients with severe clinical scurvy, nine showed little or no anaemia. Anaemia when present was sometimes macrocytic, sometimes normocytic, and sometimes microcytic. A mild degree of hypochromia was common.

Examination of the bone marrow by sternal puncture in ten patients, among whom were four with severe macrocytic anaemia, revealed that in all cases erythropoiesis was normoblastic in type. There was no uniform picture of marrow activity, some specimens showing evidence of increased, and some of diminished, regenerative activity.

Three cases are described in detail in which a sustained clinical and haematological response followed the administration of ascorbic acid. The patients were given diets low in naturally occurring vitamin C and in the 'B' complex. Two of these patients were given complete bed rest during treatment. In the third case, clinical improvement followed a short period of bed rest, but relapse occurred when the patient was allowed full activity. Administration of ascorbic acid to this ambulatory patient was followed by prompt and ultimately complete clinical and haematological recovery. Three cases are described in which there was no sustained haematological response to ascorbic acid, with or without iron, although marked clinical improvement occurred. Haematological recovery occurred only after the patients were given a full hospital diet supplemented with autolyzed yeast.

These findings are regarded as supporting the view that scurvy is almost invariably a multiple deficiency disease and that no single factor can be uniformly effective against the anaemia of this condition. On the other hand, from the evidence available in the literature and from the results reported here, there would seem to be good evidence that vitamin C plays a part in erythropoiesis.

The influence of other factors on the development of anaemia in scurvy is discussed.

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## REFERENCES.

- Cartwright, G. E. (1947). *Blood*. 2: 111, 256
- Crandon, J. H., Lund, C. C. & Dill, D. B. (1940). *New England J. Med.* 223: 353
- Croft, J. D. & Snorf, I. D. (1939). *Amer. J. med. Sci.* 198: 403
- Dunlop, D. M. & Scarborough, H. (1935). *Edinb. med. J.* 42: 476
- Harris, L. J. (1943). *Lancet*. 1: 515
- Israels, M. C. G. (1943). *Lancet*. 1: 170
- Jennings, G. H. & Glazebrook, A. J. (1938). *Brit. med. J.* 2: 784
- Lozner, E. L. (1941). *New England J. Med.* 224: 265
- Lund, C. C. & Crandon, J. H. (1941). *J. Amer. med. Ass.* 116: 663
- McMillan, R. B., Inglis, J. C. (1944). *Brit. med. J.* 2: 233
- Medical Research Council (1948). *Lancet*. 1: 853
- Mettier, S. R., Minot, G. R. & Townsend, W. C. (1930). *J. Amer. med. Ass.* 95: 1089
- Moore, C. V., Arrowsmith, W. R., Welch, J. & Minnich, V. (1939). *J. clin. Invest.* 23: 755
- Powell, J. F. (1944). *Quart. J. Med.* 13: 19
- Wintrobe, M. M. (1946). *Clinical Hematology*. London: Kimpton
- Witts, L. J. (1932). *Lancet*. 1: 495, 549, 601, 632
- Vilter, R. W., Woolford, R. M. & Spies, T. D. (1946). *J. Lab. clin. Med.* 31: 609