

Scurvy, Megaloblastic Anaemia and Osteoporosis

D. E. HYAMS*, MB, MRCP & E. J. ROSS, PH.D, MD, MRCP
University College Hospital and Medical School, London, England

Clinical scurvy in the adult is uncommon in this country so that the opportunities for observing its complications are infrequent. One of these, megaloblastic anaemia, is well recognized, but osteoporosis of a degree sufficient to produce crush fractures of vertebrae is rare. This paper records observations on a patient with scurvy complicated by megaloblastic anaemia and osteoporosis who was treated with vitamin C as the sole medication.

Case History

Mrs. D. K., a housewife aged 54, was admitted to University College Hospital (St. Pancras Hospital) on 30th June, 1959. She had been well until a year before admission. Low back pain then developed and later she experienced cramps in the calves and difficulty in walking. Her ankles then became swollen. Extensive ecchymoses appeared on the lower limbs two weeks before admission. The patient thought that she had lost 3-4 inches in height in the past year, during which she had attended another hospital for low back pain. She had been provided with a plaster cast, and later a spinal brace, but these appliances had made her back stiffer and she had refused further treatment. She had also consulted an osteopath.

The day before admission to hospital she had developed very severe lumbar pain, 'like a knife in my back'; her husband volunteered the information that the pain had been so severe that she had threatened to put her head in a gas oven.

The patient was menopausal, menstruation having ceased at the age of 50. In her past history she had diphtheria at the age of 18, but nothing else of note apart from the exanthemata of childhood.

The patient's husband's place of work was 40 miles away from home. He left at a very early hour in the morning and returned home late at night. The patient felt lonely and neglected and did not trouble to prepare cooked meals for herself. A dietary history showed that the patient's diet had been very deficient of vitamin C for about 3 years, although her intake of calcium and vitamin D had been reasonable (Table I). She had lived almost entirely on sandwiches. Vegetables

TABLE I

Calculated daily dietary intake of patient	
Calories	1540
Carbohydrate (g.)	212
Fat (g.)	59
Protein (g.)	40
Calcium (mg.)	566
Iron (mg.)	8
Vitamin C (mg.)	3
Vitamin D (I.U.)	151

had rarely been eaten since she always had meat out of a tin. Fresh fruit was never eaten. She said that she 'had bought a bottle of cod-liver oil last winter' and had taken 6 'calcium' tablets daily 'for a time'. She regularly took cascara and liquid paraffin although her bowels were regular without them.

On Examination:

The patient was dirty, unkempt and garrulous. She complained bitterly of pain in her back. She looked much older than her stated age. She was orientated in time and space but repeatedly attributed her present misfortune to 'radioactive dust in the atmosphere'. She used frequent malapropisms.

She was clinically anaemic but not jaundiced. Her skin was a dirty grey colour. Her legs were oedematous and there were extensive ecchymoses over both legs, feet and elbows. There were no haemorrhages on the mucous membranes of her gums, which showed no tendency to bleed.

Her heart was not enlarged; cardiac rhythm was normal and no murmurs were present. The blood pressure was 130/80 mm.Hg. The peripheral pulses were all present. The fundi were normal. No abnormalities were detected in the respiratory or alimentary systems. She said she felt weak, but had no demonstrable motor weakness or sensory loss. Extreme tenderness was present over all lumbar vertebrae. Measurement showed a loss of 3½ inches in trunk height, the crown-pubis measurement being 30 inches, pubis-heel 33½ inches. She had lost all her pubic and axillary hair.

Investigations:

Haemoglobin 7.68 grams per cent (52% Haldane); white cells 1,500 per cu.mm.; erythrocyte sedimentation rate 35 mm. in 1 hr.; red cells 3,000,000 per cu.mm.; mean cell volume 80cu.µ; mean cell diameter

* Now senior medical registrar, Addenbrooke's Hospital, Cambridge

7.2 μ ; mean corpuscular haemoglobin concentration 33 per cent; packed cell volume 24 per cent; reticulocytes 3.4 per cent. The serum B₁₂ concentration was normal (360 μ g./ml.). A serum folic acid clearance test was normal (70 μ g./ml. 3 minutes after intravenous dose of 15 μ g./kg., 17 μ g. at 24 minutes and 12 μ g. at 30 minutes after dose (Chanarin, Mollin and Anderson 1958). Folic acid absorption was normal. The bone marrow was megaloblastic:

Neutrophils	30%
Eosinophils	0.8%
Basophils	0
Lymphocytes	3.0%
Monocytes	0
Myelocytes	2.2%
Blast cells	1.4%
Plasma cells	1%
Proerythroblasts	0.6%
Normoblasts: early	0.8%
intermediate	1.6%
late	7.2%
Megaloblasts: early	9.2%
intermediate	13.6%
late	4%
Megakaryocytes	not reduced
No evidence of haemosiderosis.	

Plasma electrolytes: Na 143; K 3.7; Cl 106 mEq./l.; HCO₃ 20 m.Mol./l. Blood urea 21mg. per 100ml. Plasma calcium 8.2mg. per 100ml.; phosphorus 2.7mg. per 100ml.; alkaline phosphatase 8.3 K.A. units per 100ml.

Serum magnesium 2.2mg. per 100ml. Serum proteins: total 5.9g. per 100ml.; electrophoresis of serum proteins showed a low albumin and raised alpha₁ and alpha₂ globulins. Serum flocculation tests were normal.

Fat balance (on intake of 60g. per day) 91.2 per cent absorbed.

Vitamin A absorption test normal.

Augmented histamine test showed a histamine-fast achlorhydria.

Ascorbic acid saturation test (after 700mg. given by

mouth), 3.5mg. in 2¼ hr. (significance: over 50mg. indicates saturation).

Phenolic acid chromatography of urine (method of Armstrong, McMillan and Shaw 1957) showed the presence of large quantities of p-hydroxyphenylacetic and p-hydroxyphenyl lactic acids, indicative of ascorbic acid deficiency (Boscott and Cooke 1954).

X-ray of the lumbar spine showed osteoporosis with ballooning of the inter-vertebral discs of L 1, 2, 3 and 4 and almost complete collapse of the vertebral body at L 1. The dorsal spine also showed osteoporosis with wedging of the mid-dorsal vertebrae. The skull, pelvis and hands radiologically were not osteoporotic.

Hospital Course

A diagnosis was made of megaloblastic anaemia and osteoporosis due to scurvy. It was decided to treat the patient with ascorbic acid only, since her intake of calcium and vitamin D appeared to have been adequate during the period when the vitamin C content of her diet had been negligible. Treatment was commenced with ascorbic acid 500mg. daily and she was placed on a normal ward diet.

The urinary excretion of ascorbic acid rose to 23mg. in 2¼ hours by the sixth day, but then fell again to 1.5mg. in 2¼ hours. There was some doubt as to whether the patient was taking her tablets of ascorbic acid; these were therefore crushed, dissolved in water and swallowed from then on in the presence of a nurse.

The response of the haemoglobin concentration and reticulocyte count is shown in Table II. The daily urinary excretion of calcium is shown in Table III. After treatment with ascorbic acid for 3½ weeks megaloblasts were still present in the bone marrow. After 8 weeks' treatment the marrow still contained chromatin deficient normoblasts. Small numbers of these cells were still present in the marrow after treatment for 11 weeks.

The patient's back pain responded to bed-rest on a

TABLE II
Haematological response to treatment with ascorbic acid

Date	Treatment	Haemoglobin concentration g./100ml.	Reticulocytes %	Bone Marrow
1. 7.59	Nil	7.7	3.4	Megaloblasts, 24%
10. 7.59	Ascorbic acid, 500mg./day	8.1		
13. 7.59	Ascorbic acid, 500mg./day	8.6	5.0	
20. 7.59	Ascorbic acid, 500mg./day	9.9	2.2	
24. 7.59	Ascorbic acid, 500mg./day	10.1	2.6	'Still contains megaloblasts'
10. 8.59	Ascorbic acid, 500mg./day	12.2		
19. 8.59	Ascorbic acid, 500mg./day	12.0	1.2	
24. 8.59	Ascorbic acid, 500mg./day	12.1	2.4	
27. 8.59	Ascorbic acid, 500mg./day	12.7	1.0	
31. 8.59	Ascorbic acid, 500mg./day	12.7	1.0	
7. 9.59	Ascorbic acid, 500mg./day	12.7	1.0	'Chromatin-deficient normoblasts'
15. 9.59	Ascorbic acid, 500mg./day	12.3		
28. 9.59	Ascorbic acid, 500mg./day	12.6		
26.10.59	Ascorbic acid, 500mg./day	12.4		'Chromatin-deficient normoblasts still present'
18. 1.60	Ascorbic acid, 500mg./day	13.4		
14. 3.60	Ascorbic acid, 100mg./day	13.8		
12.12.60	Ascorbic acid, 100mg./day	13.9		
13. 3.61	Ascorbic acid, 100mg./day	15.4		

TABLE III

Urinary excretion of calcium in patient D.K.	
Date	Urinary calcium excretion mg./24hrs.
8.7.59	250
13.8.59	360
22.8.59	210
1.9.59	280
8.9.59	250
15.9.59	160

fracture board and analgesics. Mobilization was commenced after 8 weeks. Some ankle oedema reappeared when the patient was first on her feet; this responded to the administration of hydrochlorothiazide. She also complained of burning feet at this stage. The ecchymoses cleared within two weeks of the commencement of vitamin C therapy.

A surgical corset was fitted and she was discharged from hospital after 11 weeks. She wore the corset for only a month as she said that this made her back stiff. After discharge she adhered to advice as to diet, was able to do more and more of her housework and to do the shopping. She complained of stiffness in the back but no pain. A year after discharge she complained of cramps in the legs at night, which responded to treatment with quinine. Two years after discharge her haemoglobin concentration is 15g. per cent, she still has some stiffness in the back, but no pain. She thinks that she loses height during the day and puts it on again during the night; her husband says that her height is 1½-2 inches less at night than when she gets up in the morning. Her height has not decreased further during the past two years. She refuses to wear a spinal brace.

Serial X-rays of the thoracic and lumbar vertebrae showed that no further porotic changes occurred over the two years of follow-up, but the bones have not recalcified.

DISCUSSION

Anaemia in Scurvy

The co-existence of scurvy and megaloblastic anaemia in this patient raises once again the question of what part, if any, vitamin C plays in haemopoiesis. This problem has been repeatedly studied for over 40 years, and yet no generally acceptable conclusions have been reached. The subject is reviewed by Vilter, Woolford and Spies (1946), Cartwright (1947), Vilter (1947), Brown (1951, 1955), Lind (1960) and Cox, Meynell, Cooke and Gaddie (1962).

The first detailed account of an 'anaemia

of scurvy' was given by Mettier, Minot and Townsend (1930), but these authors also pointed out that anaemia may be absent even when scurvy is severe. Several workers have since shown that vitamin C deficiency without clinical scurvy is not associated with an increased incidence of anaemia (Croft and Snorf 1939; Lui, Chu, Yu, Hsu and Cheng 1941; Lozner 1941; Schulze and Morgan 1946; Vilter *et al* 1946). Nevertheless, cases of scurvy with anaemia which respond to the administration of vitamin C alone, with no other haemopoietic factor, continue to be described (Parsons and Hawksley 1933; Parsons and Smallwood 1935; Dunlop and Scarborough 1935; McFarlane 1936; Nisenson and Cohen 1937; Jennings and Glazebrook 1938; Parsons 1938; Young 1938; Kenney and Rapoport 1939; Braganca and Saha 1943; Vilter *et al* 1946; C. Vilter 1947; R. Vilter 1947; Brown 1951; Brontë-Stewart 1953; Brown 1955; Neilson 1960; Will and Murdoch 1960; Cox *et al* 1962 and the present authors).

In man, experimentally-produced vitamin C deficiency has not been accompanied by anaemia (Crandon, Lund and Dill 1940; Bartley, Krebs and O'Brien 1953). This, together with the lack of correlation between clinical vitamin C deficiency and anaemia, has led some authors to deny that vitamin C is necessary for normal haemopoiesis (Lozner 1941; Zuelzer, Hutaff and Apt 1949), but Brontë-Stewart (1953) has suggested that anaemia is the last feature to appear in the clinical picture of human scurvy, and that if the deficient state had been more protracted, anaemia might well have developed. Vilter *et al* (1946) discuss the variability of the blood picture in scurvy, and relate this to the interplay of the several deficiencies which may co-exist.

This view is also taken by Constable (1960), who was unable to produce anaemia in guinea-pigs fed on diets deficient in vitamin C but containing adequate amounts of other vitamins and nutrients.

When anaemia does occur in scurvy, its severity may bear no relationship to that of the scurvy (Ungley 1938; Aron 1939; Ralli and Sherry 1941), though Proehl and May (1952) and Brontë-Stewart (1953) did find

such a relationship. The anaemia is usually normochromic and normocytic, but if severe it may be somewhat macrocytic; occasionally it is microcytic and hypochromic, especially if there is much haemorrhage, but there is no correlation between the extent of ecchymoses or external blood loss and the severity of the anaemia (McMillan and Inglis 1944; Vilter *et al* 1946; Brown 1951; Grusin and Kincaid-Smith 1954).

The bone marrow has most often been described as normoblastic (Mettier *et al* 1930; McMillan and Inglis 1944; Vilter *et al* 1946; Brown 1951), but it may be megaloblastic as in the present case (Jennings and Glazebrook 1938; McMillan and Inglis 1944; Vilter *et al* 1946; R. Vilter 1947; Brontë-Stewart 1953; Brown 1955; Neilson 1960; Will and Murdoch 1960), hyperplastic (Mettier *et al* 1930; Brontë-Stewart 1953) or hypoplastic (Harris 1928; Wolbach 1937; Israëls 1943). Witts (1932) considered that vitamin C deficiency led to a maturation defect in the bone marrow.

The role of vitamin C in iron metabolism has been studied by Moore and Dubach (1952) and Moore (1955), and it has been shown to potentiate iron absorption. Experimental chronic vitamin C deficiency in monkeys led to iron-deficiency anaemia (Greenberg and Rinehart 1955) which responded to combined treatment with vitamin C and iron. It was not clear whether the iron deficiency was due to impaired absorption or utilization of iron, or to blood loss alone, but Mouriquand (1958) has reported defective mobilization of iron from body depots in states of vitamin C deficiency and Mazur (1961) reported a marked inhibition of the incorporation of plasma iron into tissue ferritin depots.

From time to time, the suggestion has been made that haemolysis plays a part in the anaemia of scurvy. This was first put forward by Meyer and McCormick (1928) on rather flimsy evidence. Vilter *et al* (1946) consider it a possibility, in view of the common findings of reticulocytosis and increased urobilinogen excretion, but other workers explain these features in a different way: reticulocytosis may occur in scorbutic patients having bed-rest alone, when it is presumed that the re-

duced metabolic demands allow what little vitamin C remains in the tissues (see Pirani 1952) to be used for erythropoiesis; and increased urobilinogen excretion may be due to purely extravascular haemolysis of red cells lost into the tissues (Proehl and May 1952; Brontë-Stewart 1953). However, Merskey (1953) showed that the survival time of red cells transfused into scorbutic patients is reduced, although he could not be sure that the red cells of similar patients who were not transfused were affected by a similar haemolytic process. In one adult male with scurvy, studied by Lind (1960), the red cell survival time was estimated using ^{51}Cr and the biological half-life was found to be reduced to 10 days. In this patient the serum haptoglobins were reduced, which, in the presence of normal liver function, was taken to confirm the idea of a haemolytic process.

The incidence of megaloblastic erythropoiesis in the anaemia of scurvy is much disputed. Zuelzer and Ogden (1946) and Amato (1946) described a megaloblastic anaemia of uncertain aetiology in infants. Folic acid had a curative effect. Aldrich and Nelson (1947) reported six similar cases, of whom three were scorbutic; each infant had been fed on a similar diet of humanized milk containing no vitamin C, and no supplement of vitamin C had been given. May, Nelson, Lowe and Salmon (1950a) later reported that addition of vitamin C to this milk food had eliminated megaloblastic anaemia of infancy from their clinic. These authors considered that megaloblastic anaemia was often associated with scurvy; they cite as evidence the reports just mentioned, and those of McMillan and Inglis (1944) and Vilter *et al* (1946).

Cartwright (1947) showed that in species which can synthesize ascorbic acid, diets deficient in vitamin C do not produce megaloblastic anaemia. Dyke, Della Vida and Delikat (1942) described some cases of typical pernicious anaemia which did not respond fully to liver extract until vitamin C was added. This occurred on war-time diets and had a seasonal incidence, being noted in the spring. Alt, Chinn and Farmer (1939) reported a significant reduction in plasma ascorbic acid in pernicious anaemia. Minot (1943), however,

was sceptical of these last two reports.

Holly (1951) found vitamin C of therapeutic value in certain cases of megaloblastic anaemia of pregnancy.

Proehl and May (1952) described the appearance of megaloblastic anaemia in monkeys as experimentally-produced scurvy progressed. Brown (1955) described a man of 57 with hepatic cirrhosis who developed scurvy and was found to have a severe megaloblastic anaemia. Treatment with synthetic ascorbic acid alone produced complete remission of the anaemia, with a reticulocytosis of 19 per cent and progressive reversion of the marrow to normoblastic erythropoiesis by the 19th day. In a critical discussion of the relationship between vitamin C and anaemia, he declares himself dissatisfied with the view that megaloblastic erythropoiesis is common in the anaemia of scurvy. He comments that he has searched the literature in vain for any well-authenticated instance of an adult megaloblastic anaemia which responded to synthetic ascorbic acid alone, and he considered that the presence of such an anaemia in his patient was only partly due to the vitamin C deficiency; a predisposing factor may have been abnormal folic acid metabolism due to the concomitant liver disease.

Since then, however, there have been acceptable reports of scurvy with megaloblastic anaemia responding to synthetic vitamin C alone (Neilson 1960; Will and Murdoch 1960). The present case affords another example. In none of the cases in these reports was there any evidence of deficiency or abnormal metabolism of vitamin B₁₂ or folic acid. Further, Booth and Mollin (1957) found that normal amounts of orally administered radioactive vitamin B₁₂ were absorbed in megaloblastic anaemia associated with scurvy.

MacIver and Back (1960), in a review of 50 cases of megaloblastic anaemia of infancy in Jamaica, point out that scurvy is rare there, so that it seemed to these authors unlikely that vitamin C deficiency was an aetiological factor in their cases; they describe, however, one child who had a good reticulocyte response to folic acid but who relapsed on this treatment and developed clinical

signs of scurvy. Administration of ascorbic acid (folic acid being continued) led to a second reticulocytosis of 20 per cent and a rapid rise in haemoglobin level. They concluded that vitamin C did not play a specific role in erythropoiesis, but considered that it was important in the proper utilization of folic acid.

Possible Inter-Relationships of Vitamin C, Folic Acid and Vitamin B₁₂

Relation of Vitamin C to Folic Acid

In a series of experiments on monkeys it was shown that megaloblastic anaemia could be readily produced by feeding a diet low in folic acid and devoid of vitamin C (May *et al* 1949, 1950a, 1950b, 1951, 1952, 1953; Sundberg, Schaar and May 1952). Treatment with folic acid produced rapid cure of the anaemia, and folic acid gave an even better response; vitamin C produced a more gradual remission. The anaemic monkeys had low folic acid levels in their livers, but effective treatment produced a rise in both folic and folic acids in the liver. The authors concluded that vitamin C deficiency interfered with folic acid metabolism, leading to a deficiency of folic acid, resulting in megaloblastic haemopoiesis.

Several reports have indicated that vitamin C enhances the conversion of folic to folic acid (Nichol and Welch 1950; Broquist, Stokstad and Jukes 1951; Welch, Nichol, Anker and Boehne 1951; Gabuzda, Phillips, Schilling and Davidson 1952; Silverman and Gardiner 1956; Doctor 1958, 1960). In this reaction the vitamin C probably acts simply as a reducing agent (Broquist, Kohler, Hutchison and Burchenal 1953; Doctor and Trunnell 1954; Doctor 1960), though in chicks it has been shown to activate an enzyme which liberates folic acid from its conjugates in the liver (Hill and Scott 1952). Folic acid ('citrovorum factor') is N⁵ formyltetrahydrofolic acid, and this is isomerised to N¹⁰ formyltetrahydrofolic acid which is then involved in the transfer of 1-Carbon fragments in the biosynthesis of purines, pyrimidines and amino-acids (Girdwood 1959; Haurani *et al* 1960). However, Cox *et al* (1962) present evidence

against the importance not only of vitamin C in the folic-folinic conversion but also of folinic acid itself in the 'folic complex'. They put forward a hypothesis to explain the cure of megaloblastic anaemia in scurvy by vitamin C alone, in terms of the demand and supply of the 'folic complex'.

Vitamin C has also been shown to be required for normal tyrosine metabolism. Levine and his co-workers (Levine *et al* 1939, 1941a, 1941b; Levine 1947) found that premature infants fed on cows' milk (that is, a diet of relatively high protein content, giving 5g. or more protein per kg. bodyweight per day) excreted appreciable amounts of hydroxyphenyl compounds in their urine. This abnormality did not occur if the babies were fed on human milk, and it was accentuated by feeding tyrosine or phenylalanine in pure form. Although the infants showed no clinical evidence of scurvy, the administration of vitamin C led to a prompt decline in the excretion of the abnormal compounds.

Plasma levels of vitamin C were low or nil before treatment, and tended to remain low even when the hydroxyphenyluria had cleared. It was presumed that the degree of vitamin C saturation of the tissues, relative to the level of intake of tyrosine and phenylalanine, was the important factor in determining the abnormal excretion.

A similar defect in tyrosine metabolism was produced by a tyrosine load in normal full-term infants (Levine *et al* 1941b), in scorbutic infants (Morris, Harpur and Goldbloom 1950; Woodruff 1950), in scorbutic adults (Rogers and Gardner 1949a, 1949b), and in scorbutic guinea-pigs (Sealock and Silberstein 1940; Painter and Zilva 1947, and Woodruff and Darby 1948). It was pointed out by Painter and Zilva (1947) and Rogers and Gardner (1949a) that this abnormality might have no relation to clinical scurvy or normal nutrition because of the unphysiological tyrosine load required to demonstrate the defect. But Swendseid, Burton and Bethell (1943) described hydroxyphenyluria in scurvy without a tyrosine load, and Aterman, Boscott and Cooke (1953) reported p-hydroxyphenylacetic acid (pHPA) and p-hydroxyphenyl lactic acid

(pHPL) as the main hydroxyphenyl compounds in the urine of scorbutic guinea-pigs, also without a tyrosine load. In all instances quoted, vitamin C rapidly abolished the defect, and Aterman *et al* (1953) suggest that the finding of pHPA and pHPL in the urine may be the most sensitive index of vitamin-C status available. The urine of the present patient contained large quantities of both pHPA and pHPL, which disappeared after treatment with vitamin C.

There is some evidence that folic acid can prevent or abolish the tyrosine-induced hydroxyphenyluria in vitamin C deficient patients and experimental animals (Woodruff and Darby 1948; Woodruff, Cherrington, Stockell and Darby 1949; Morris *et al* 1950) though the effect is not predictable (Govan and Gordon 1949; Woodruff 1950) and very large doses may be required (La Du and Zannoni 1961). This suggests another relationship between folic acid and vitamin C, but the effect of these substances on tyrosine metabolism is quite distinct from anti-scorbutic activity possessed by vitamin C. It may be noted here that vitamin C promotes the synthesis of folic acid *in vivo* by the chick (Dietrich, Nichol, Monson and Elvehjem 1949) whilst a folic-acid antagonist decreased the synthesis of vitamin C in the rat (Schwartz and Williams 1952).

It will be apparent that vitamin C-folic acid relationships are still far from clear.

Relation of vitamin C to vitamin B₁₂.

Swendseid *et al* (1947) noted an increased amount of total phenols and hydroxyphenyl acids in the urine of patients with pernicious anaemia in relapse, and a decrease in the hydroxyphenyl acids with treatment of the anaemia.

Boscott and Cooke (1954) found excess pHPA in the urine of patients with megaloblastic anaemia associated with idiopathic steatorrhoea. They also reported that it had proved difficult to saturate these patients with ascorbic acid, although the apparent deficiency in the latter was not explained by

dietary or absorptive defects.

A significant reduction in plasma ascorbic acid levels has been reported in patients with pernicious anaemia, despite a normal dietary intake of vitamin C (Alt *et al* 1939; Wallerstein, Harris and Gabuzda 1952). The observations of Dyke *et al* (1942) and Holly (1951) have been mentioned above. Will, Mueller, Glazer, Friedman and Vilter (1953) and Mueller and Will (1955) found that the rate of removal of intravenously injected ascorbic acid was increased in 5 out of 7 patients with pernicious anaemia, but the plasma levels of dehydroascorbic acid were increased in all five. These abnormalities had disappeared one week after starting vitamin B₁₂ injections.

Cox, Matthews, Meynell, Cooke and Gaddie (1958) showed that the plasma ascorbic acid levels, both resting and at stated intervals after an intravenous injection of sodium ascorbate, were lower in patients with reduced serum B₁₂ levels than in normal controls.

These workers did not confirm the finding of Will *et al* (1953) that an undue rise in plasma dehydroascorbic acid occurred, nor did the resting plasma ascorbic acid levels rise or the ascorbic clearance tests improve in patients with pernicious anaemia after 7-14 days of vitamin B₁₂ treatment. The conclusions drawn were that ascorbic acid was passing rapidly from plasma to tissues, due to tissue depletion, or increased demand or destruction of ascorbic acid. No support could be given by these workers to Lester Smith's (1956) suggestion that vitamin B₁₂ may be important in keeping ascorbic acid in a reduced state, in view of the lack of improvement in the ascorbate clearance test after vitamin B₁₂ therapy for 7-14 days. Nevertheless, prolonged vitamin B₁₂ treatment did improve significantly the resting plasma ascorbic acid levels and the intravenous ascorbate tests, indicating some sparing action on vitamin C by vitamin B₁₂. Evidence was presented to show that improved diet was not necessarily responsible for this. It was not possible to assess the full significance of vitamin C metabolism in relation to vitamin B₁₂ deficiency, but it was concluded that the abnormal vitamin C metabolism played no fundamental part in producing megaloblastic anaemia in

vitamin B₁₂ deficiency.

The same workers (Cox *et al* 1960) found a significant reduction in the concentration of vitamin C in the bone marrow of all of a group of patients with megaloblastic anaemia. They also noted a correlation between the serum levels of vitamin B₁₂ and vitamin C and their respective levels in the bone marrow, but not all patients with low vitamin C levels had vitamin B₁₂ deficiency.

Further work will be required before a clearer statement of the relationship of vitamin C to vitamin B₁₂ and folic acid can be made.

Scurvy and osteoporosis

The softening of callus around old healed fractures during attacks of scurvy is an observation that has frequently been reported over many hundreds of years. During Lord Anson's voyage round the world (1740-4) it is recorded that the callus of a fracture sustained 50 years previously had broken down when the crew were hit by scurvy. Similar occurrences have often been repeated in ships and during wars since that time (Bourne 1956).

The development of osteoporosis in scurvy appears to result from non-production of new bone in the face of continued destruction of existing bone. Why this should be is not very clear. Follis (1951) concluded that ascorbic acid depletion is characterized by the inability of specialized mesenchymal cells — fibroblasts, osteoblasts, and odontoblasts — to promote the production of their respective fibrous proteins, namely collagen, osteoid and dentin. As a consequence of failure of formation of bone matrix, calcification is deficient and the process of formation of bone impaired.

Whether vitamin C is directly concerned in the calcification of bone is more open to question. Wolbach and Bessey (1942), reviewing the subject at that time, concluded that the vitamin plays no part in calcification. Bourne (1943) produced a little evidence that it did, but the effect noted may have been due to an effect of vitamin C on calcification secondary to an effect on matrix formation. Some authors report a normal calcium con-

tent of bone from scorbutic animals (Kapp and Schetty 1937). Osteoporosis in scorbutic guinea-pigs is said to be confined to the shaft of the bone, new bone at the epiphysis not being porotic (Murray and Kodicek 1949). Many workers (Bourne 1943; Zorzoli and Nadel 1950; van Versch 1954) have noted that there is less phosphatase activity in the bones of scorbutic animals. Cytochrome oxidase activity in osteoblasts is also reduced (Follis 1951). Decreased incorporation of ^{35}S into chondroitin sulphate has also been observed.

Although osteoporosis has been described in children (Park, Guild, Jackson and Bond 1935), mention of this complication among adult white scorbutics is difficult to find, except in the chronic scurvy of wars. Some authors mention backache as a symptom in acute scurvy (Vilter, Woolford and Spies 1946). Osteoporosis, however, is commonly associated with acute scurvy in the South African Bantu (Grusin and Kincaid-Smith 1954), perhaps because their calcium intake is also low. Of 48 Bantu with acute scurvy who were X-rayed by Grusin and Samuel (1957) over a period of a year, 18.7 per cent showed radiological evidence of osteoporosis.

The present patient was menopausal, and her osteoporosis might be ascribable to that cause. The response to saturation with vitamin C, as shown by the relief of pain and halting of the progression of vertebral collapse, led us to ascribe it to scurvy. Whilst on treatment the patient has not lost further height and, apart from stiffness in her back, is now pain-free.

Acknowledgements

We wish to thank DR. D. L. MOLLIN and DR. I. CHANARIN, of Hammersmith Hospital, for the serum B_{12} determination and the folic acid studies performed on our patient; and DR. E. BOWERS for his unfailing help with all the other laboratory investigations.

REFERENCES

- Aldrich, R. A., Nelson, E. N. (1947) *Journal - Lancet*, **67**, 399.
 Amato, M. (1946) *Pediatrics*, **54**, 71.
 Alt, H. L., Chinn, H., Farmer, C. J. (1939) *Amer. J. Med. Sci.*, **197**, 229.
 Armstrong, M. D., McMillan, A., Shaw, K. N. F. (1957) *Biochim. Biophys. Acta*, **25**, 422.
 Aron, H. C. S. (1939) *J. Nutr.*, **18**, 375.
 Aterman, K., Boscott, R. J., Cooke, W. T. (1953) *Biochem. J.*, **55**, XVII.
 Bartley, W., Krebs, H. A., O'Brien, J. R. P. (1953) *Spec. Rep. Ser. M.R.C. Lond.* No. 280.
 Booth, C. C. and Mollin, D. L. (1957) — quoted by Mollin (1959) *Brit. med. Bull.*, **15**, 8.
 Boscott, R. J., Cooke, W. T. (1954) *Quart. J. Med. n.s.* **23**, 307.
 Bourne, G. (1943) *Quart. J. exper. Physiol.*, **32**, 1.
 Bourne, G. H. (1956) Editor. *The Biochemistry and Physiology of Bone*. New York Academic Press.
 Braganca, B. de M., Saha, K. C. (1943) *Ann. Biochem. & Exper. Med.*, **3**, 47.
 Brontë-Stewart, B. (1953) *Quart. J. Med. n.s.* **22**, 309.
 Broquist, H. P., Stokstad, E. L. R., Jukes, T. H. (1951) *J. Lab. Clin. Med.*, **38**, 95.
 Broquist, H. P., Kohler, A. R., Hutchison, D. J., Burchenal, J. H. (1953) *J. Biol. Chem.*, **202**, 59.
 Brown, A. (1951) *Glasgow med. J.*, **32**, 95.
 Brown, A. (1955) *Brit. J. Haemat.*, **1**, 345.
 Cartwright, G. E. (1947) *Blood*, **2**, 111, & 140.
 Chanarin, I., Mollin, D. L., Anderson, B. B. (1958) *Brit. J. Haemat.*, **4**, 435.
 Constable, B. J. (1960) *Brit. J. Nutrition*, **14**, 259.
 Cox, E. V., Gaddie, R., Matthews, D., Cooke, W. T., Meynell, M. J. (1958) *Clin. Sci.*, **17**, 681.
 Cox, E. V., Matthews, D. M., Meynell, M. J., Cooke, W. T., Gaddie, R. (1960) *Blood*, **15**, 376.
 Cox, E. V., Meynell, M. J., Cooke, W. T., Gaddie, R. (1962) *Amer. J. Med.*, **32**, 240.
 Crandon, J. H., Lund, C. C., Dill, D. B. (1940) *New Engl. J. Med.*, **223**, 353.
 Croft, J. D., Snorf, L. D. (1939) *Amer. J. med. Sci.*, **198**, 403.
 Dietrich, L. S., Nichol, C. A., Monson, W. J., Elvehjem, C. A. (1949) *J. Biol. Chem.*, **181**, 915.
 Doctor, V. M. (1958) *J. Biol. Chem.*, **233**, 982.
 Doctor, V. M. (1960) *Endocrinology*, **67**, 90.
 Doctor, V. M., Trunnell, J. B. (1954) *Proc. Soc. Exp. Biol. Med.*, **87**, 498.
 Dunlop, D. M., Scarborough, H. (1935) *Edin. med. J.*, **42**, 476.
 Dyke, S. C., Della Vida, B. L., Delikat, E. (1942) *Lancet*, **2**, 278.
 Follis, R. H. Jr. (1951) *Bull. Johns Hopk. Hosp.*, **89**, 9.
 Gabuzda, G. J., Phillips, G. B., Schilling, R. F., Davidson, C. S. (1952) *J. Clin. Invest.*, **31**, 756.
 Girdwood, R. H. (1959) *Brit. med. Bull.*, **15**, 14.
 Govan, C. D. Jr., Gordon, H. H. (1949) *Science*, **109**, 332.
 Greenberg, L. D., Rinehart, J. F. (1955) *Proc. Soc. Exp. Biol. Med.*, **88**, 325.
 Grusin, H., Kincaid-Smith, P. S. (1954) *Amer. J. Clin. Nutr.*, **2**, 323.
 Grusin, H., Samuel, E. (1957) *Amer. J. Clin. Nutr.*, **5**, 644.
 Harris, H. A. (1928) *Quart. J. Med.*, **21**, 499.
 Haurani, F. I., Wang, G., Tocantins, L. M. (1960) *Blood*, **16**, 1546.
 Hess, A. F. (1920) *Scurvy, past and present*: J. B. Lippincott.
 Hill, C. H., Scott, M. L. (1952) *J. Biol. Chem.*, **196**, 195.
 Holly, R. G. (1951) *Proc. Soc. Exp. Biol. Med.*, **78**, 238.
 Israëls, M. C. G. (1943) *Lancet*, **1**, 170.
 Jennings, C. H., Glazebrook, A. J. (1938) *Brit. med. J.*, **2**, 784.
 Kapp, H., and Schetty, A. (1937) *Biochem. Ztschr.*, **290**, 58.
 Kenney, A. S., Rapoport, M. (1939) *J. Paediat.*, **13**, 161.
 La Du, B. N., Zannoni, V. G. (1961) *Ann. N.Y. Acad. Sci.*, **92**, 175.
 Lester Smith, E. (1956) *Brit. med. Bull.*, **12**, 52.
 Levine, S. Z. (1947) *Harvey Lectures*, **42**, 303.
 Levine, S. Z., Marples, E., Gordon, H. H. (1939) *Science*, **90**, 620.
 Levine, S. Z., Marples, E., Gordon, H. H. (1941a) *J. Clin. Invest.*, **20**, 199. (continued overleaf)

- Levine, S. Z., Marples, E., Gordon, H. H. (1941b) *J. Clin. Invest.*, **20**, 209.
- Lind, I. (1960) *Nord. Med.*, **63**, 575.
- Liu, S. H., Chu, H. I., Yu, T. F., Hsu, H. C., Cheng, T. Y. (1941) *Proc. Soc. Exp. Biol. Med.*, **46**, 603.
- Lozner, E. L. (1941) *New Engl. J. Med.*, **224**, 265.
- McFarlane, W. D. (1936) *Biochem. J.*, **30**, 1472.
- MacIver, J. E., Back, E. H. (1960) *Arch. Dis. Child.*, **35**, 134.
- McMillan, R. B., Inglis, J. C. (1944) *Brit. med. J.*, **2**, 233.
- May, C. D., Nelson, E. N., Salmon, R. J. (1949) *J. Lab. Clin. Med.*, **34**, 1724.
- May, C. D., Nelson, E. N., Lowe, C. U., Salmon, R. J. (1950a) *Amer. J. Dis. Child.*, **80**, 191.
- May, C. D., Sundberg, R. D., Schaar, F. (1950b) *J. Lab. Clin. Med.*, **36**, 963.
- May, C. D., Sundberg, R. D., Schaar, F., Lowe, C. U., Salmon, R. J. (1951) *Amer. J. Dis. Child.*, **82**, 282.
- May, C. D., Hamilton, A., Stewart, C. T. (1952) *Blood*, **7**, 978.
- May, C. D., Hamilton, A., Stewart, C. T. (1953) *J. Nutr.*, **49**, 121.
- Mazur, A. (1961) *Ann. N.Y. Acad. Sci.*, **92**, 223.
- Merskey, C. (1953) *Brit. med. J.*, **2**, 1353.
- Mettier, S. R., Minot, G. R., Townsend, W. C. (1930) *J. Amer. Med. Ass.*, **95**, 1089.
- Meyer, A. W., McCormick, L. M. (1928) *Stanford Univ. Public., Univ. Series, M.Sc.*, **2**, 199.
- Minot, G. R. (1943) *The 1943 Yearbook of General Medicine*, p. 368. Yearbook Publishers, Chicago.
- Moore, C. V. (1955) *Amer. J. Clin. Nutr.*, **3**, 3.
- Moore, C. V., Dubach, R. (1952) *Science*, **116**, 527.
- Morris, J. E., Harpur, E. R., Goldbloom, A. (1950) *J. Clin. Invest.*, **29**, 325.
- Mouriquand, C. (1958) *Sem. Hôp., Paris*, **34**, 1116.
- Mueller, J. F., Will, J. J. (1955) *Amer. J. Clin. Nutr.*, **3**, 30.
- Murray, P. D. F., Kodicek, E. (1949) *J. Anat.*, **83**, 205.
- Neilson, J. McE. (1960) *Scot. med. J.*, **5**, 42.
- Nichol, C. A., Welch, A. D. (1950) *Proc. Soc. Exp. Biol. Med.*, **74**, 52.
- Nisenson, A., Cohen, A. G. (1937) *Amer. J. Med. Sci.*, **194**, 63.
- Painter, H. A., Zilva, S. S. (1947) *Biochem. J.*, **41**, 511.
- Park, E. A., Guild, H. G., Jackson, D., Bond, M. (1935) *Arch. Dis. Child.*, **10**, 265.
- Parsons, L. G. (1938) *Lancet*, **1**, 65.
- Parsons, L. G., Hawksley, J. C. (1933) *Arch. Dis. Child.*, **8**, 117.
- Parsons, L. G., Smallwood, W. C. (1935) *Arch. Dis. Child.*, **10**, 327.
- Pirani, C. L. (1952) *Metabolism*, **1**, 197.
- Proehl, E. C., May, C. D. (1952) *Blood*, **7**, 671.
- Ralli, E. P., Sherry, S. (1941) *Medicine*, **20**, 251.
- Rogers, W. F., Gardner, F. H. (1949a) *J. Clin. Invest.*, **28**, 806.
- Rogers, W. F., Gardner, F. H. (1949b) *J. Lab. Clin. Med.*, **31**, 1491.
- Schulze, H. V., Morgan, A. F. (1946) *Amer. J. Dis. Child.*, **71**, 593.
- Schwartz, M. A., Williams, J. N., Jr. (1952) *J. Biol. Chem.*, **197**, 481.
- Sealock, R. R., Silberstein, H. (1940) *J. Biol. Chem.*, **135**, 251.
- Silverman, M., Gardiner, R. C. (1956) *J. Bacteriol.*, **71**, 433.
- Sundberg, R. D., Schaar, F., May, C. D. (1952) *Blood*, **7**, 1143.
- Swendseid, M. E., Burton, I. F., Bethell, F. H. (1943) *Proc. Soc. Exp. Biol. Med.*, **52**, 202.
- Swendseid, M. E., Wandruff, B., Bethell, F. H. (1947) *J. Lab. Clin. Med.*, **32**, 1242.
- Ungley, C. C. (1938) *Lancet*, **1**, 925.
- van Versch, H. J. (1954) *Scurvy as a skeletal disease*. Utrecht. Dekker and van de Veeg.
- Vilter, C. (1947) quoted by Vilter, R. W. (1947).
- Vilter, R. W. (1947) *Symposia on Nutrition*, Vol. I, p. 179. Robert Gould Research Foundation, Inc.; Cincinnati.
- Vilter, R. W., Woolford, R. M., Spies, T. D. (1946) *J. Lab. Clin. Med.*, **31**, 609.
- Wallerstein, R. O., Harris, J. W., Gabuzda, G. J., Jr. (1952) quoted in *Lancet* (1952) **2**, 284.
- Welch, A. D., Nichol, C. A., Anker, R. M., Boehne, J. W. (1951) *J. Pharmacol.*, **103**, 403.
- Will, G., Murdoch, W. R. (1960) *Postgrad. med. J.*, **36**, 502.
- Will, J. J., Mueller, J. F., Glazer, H. S., Friedman, B. I., Vilter, R. W. (1953) *J. Lab. Clin. Med.*, **42**, 967.
- Witts, L. J. (1932) *Lancet*, **1**, 549.
- Wolbach, S. B. (1937) *J. Amer. Med. Ass.*, **108**, 7.
- Wolbach, S. B., Bessey, O. A. (1942) *Physiol. Rev.*, **22**, 233.
- Woodruff, C. W. (1950) *J. Lab. Clin. Med.*, **36**, 640.
- Woodruff, C. W., Darby, W. J. (1948) *J. Biol. Chem.*, **172**, 851.
- Woodruff, C. W., Cherrington, M. E., Stockell, A. K., Darby, W. J. (1949) *J. Biol. Chem.*, **178**, 861.
- Young, J. B. (1938) *Lancet*, **1**, 1385.
- Zorzoli, A., Nadel, E. M. (1950) *J. Nat. Cancer Inst.*, **6**, 1366.
- Zuelzer, W. W., Ogden, F. N. (1946) *Amer. J. Dis. Child.*, **71**, 211.
- Zuelzer, W. W., Hutaff, L., Apt, L. (1949) *Amer. J. Dis. Child.*, **77**, 128.

The fundamental treatment
for hay fever, asthma
and other allergies is
SPECIFIC DESENSITISATION

The Bencard Allergy Unit will be glad to send you full details of desensitisation techniques. All desensitising vaccines may be prescribed for N.H.S. patients. Over 1,000 allergens are available from



The **BENCARD** Allergy Unit of
Beecham Research Laboratories Limited,
Brentford, England · ISLeworth 4111

