SCORBUTIC PSEUDOSCLERODERMA

AN ASPECT OF BANTU SIDEROSIS

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The purpose of this article is to draw attention to the occurrence of sclerotic changes in the skin and subcutaneous tissues, clinically resembling scleroderma, which have been found in cases of chronic scurvy. These changes develop secondarily to, and persist long after, the initial haemorrhage into muscle, subcutaneous tissue and dermis, which occurs in acute scurvy.

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The first description of this condition found in the literature is that by Grusin and Kincaid-Smith.[1] They described 30 adult scorbutic Bantu patients presenting with haemorrhages into the muscles of the lower limbs. The

diagnosis was confirmed by biopsy evidence of recent haemorrhage into muscle, subcutaneous tissue or skin, which responded rapidly to the administration of vitamin C. In 5 of these patients chronic changes persisted, in which the skin and subcutaneous tissues became indurated and tightly bound down to the underlying structures. In 2 patients with acute haemorrhage into one leg, the opposite limb showed these scleroderma-like changes resulting from previous acute attacks. An autopsy on the only patient who died showed, besides the haemorrhage into the calf muscles and subcutaneous tissue, severe siderosis of the liver, spleen and duodenum.

Siderotic disease of the Bantu is characterized by the abnormal deposition of iron, called cytosiderin by Gillman,[2] in the cells of the liver and the reticulo-endothelial system. Next to the liver, the organs most commonly affected are the spleen, duodenum and upper jejunum, lymph nodes and bone marrow. Other parenchymal tissues are only occasionally involved.[3,4] Siderosis of the liver has been found to occur in more than 80% of postmortem examinations carried out on adult Bantu subjects.[4,5] Chronic malnutrition[2] and abnormally high dietary intake of iron[6] have been suspected as causes of siderosis.

In addition to the patient described by Grusin,[1] the simultaneous occurrence of lower-leg scurvy and diffuse Bantu siderosis has been observed in 3 postmortem examinations by Simson.[7]

Recently, 3 further cases of pseudosclerodermatous change in scurvy, associated with siderosis, have come to our attention. In 2 of these, extensive vitamin-C saturation tests were performed, and a peculiar disturbance of vitamin-C metabolism was found to exist.

Pallister[8] has described a similar sclerotic condition of the lower legs occurring in association with long-standing oedema and malnutrition in patients in Malaya. However, the oedema, which was the presenting complaint, seems to have been more marked than that usually occurring in scurvy, and further clinical details and histological studies are lacking in his report.

VITAMIN-C SATURATION TESTS

These tests are based on the assumption that, if the subject is suffering from a deficiency, the tissues will take up large amounts of the vitamin, and little or none will be excreted in the urine. Persons whose intake has been adequate will, however, excrete appreciable amounts.[9]

Van Eekelen[10] found that 3·2 G. of vitamin C were needed to saturate body tissues depleted by a vitamin-C deficient diet. Crandon, Lund and Dill[11] estimated that 4 - 6 G. of vitamin C were necessary to saturate a depleted subject.

The following 3 methods of estimating vitamin-C excretion were used in our investigations:

(a) Two-hour Urine Specimen after Oral Dose

In this method, which is described by Varley,[9] only 1 specimen of urine is collected covering the period 4 - 6 hours after taking the vitamin C, when excretion is at its maximum. A loading dose of 11 mg. of vitamin C per kg. body weight is recommended, but we usually gave somewhat higher doses to our patients.

In a normal nutritional state the excretion should be 40 - 50 mg. of vitamin C on the first or second day. Patients with severe deficiency may require up to 3 weeks of such treatment before this amount is excreted.[9]

(b) Intravenous Vitamin-C Administration

(i) After intravenous injection of 500 mg. of ascorbic acid in 5 ml. of distilled water, at least 200 mg. should be excreted in the urine within the first 4 hours.[9]

(ii) After 1,000 mg. have been injected intravenously, an excretion of 400 mg. of vitamin C or more in the first 5 - 6 hours indicates a normal degree of saturation.[12]

(c) Twenty-four-hour Urine Specimens

The method of ascorbic acid preservation used was that employed by the Medical Research Council,[13] in which 40 G. of metaphosphoric acid are placed in the collecting bottle at the start of the experiment. Vitamin-C titration was performed with dichlorophenolindophenol only in our cases.

According to Varley,[9] the daily output of ascorbic acid is roughly half the intake, the usual amount being 20 - 30 mg. Bernstein and Weiner[14] found the average daily excretion of vitamin C in Europeans to be 33·2 mg. and in Bantu mine recruits 14·3 mg.

CASE 1

This patient was a 55-year-old Xhosa male. Painful, pitting swelling of both lower legs had started 8 months before admission. After 2 months the left leg had recovered, but the right lower leg had become withered, stiff and painful. Bleeding and ulcerating gums for 5 years had necessitated extraction of all his teeth just after the onset of the leg trouble.

On examination, the right lower leg was found to be thinner than the left, and warm and tender. The skin from below the knees to the toes was sclerotic, darkly pigmented, and tightly bound down to the underlying structures. This scleroderma-like change ended just below the popliteal fossa with a well-demarcated edge. A deeper sclerosis could be felt to extend slightly beyond the edge, where the surface was 'hidebound'. The calf muscles were atrophied and hard and the ankle movements markedly limited (Fig. 1).

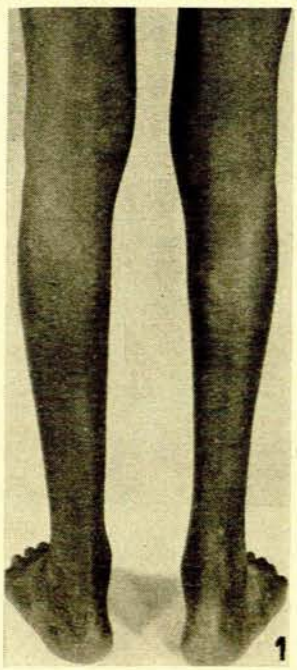

Fig. 1. Atrophy and sclerosis of lower right leg.

The liver was enlarged, hard and smooth. There were no other abnormalities noted on admission to hospital, but the patient later developed a mild transient jaundice.

Histology

Histological examination of the skin of the affected leg showed the following changes (Figs. 2 and 3):

The epidermis was normal in appearance except for a mild hyperkeratosis and an increase in pigment in all the layers, including the hyperkeratotic stratum corneum. The papillary

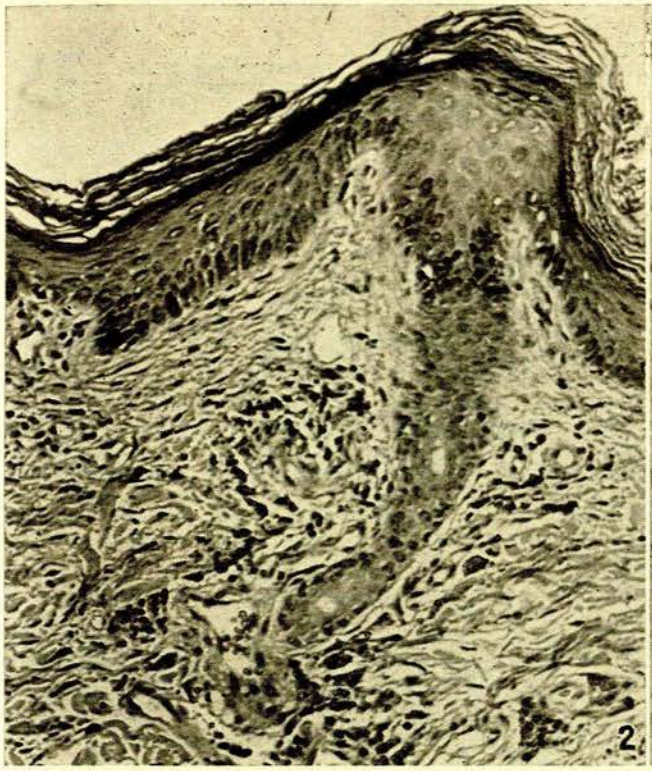

Fig. 2. Sclerotic changes in dermis (hematoxylin and eosin × 1000).

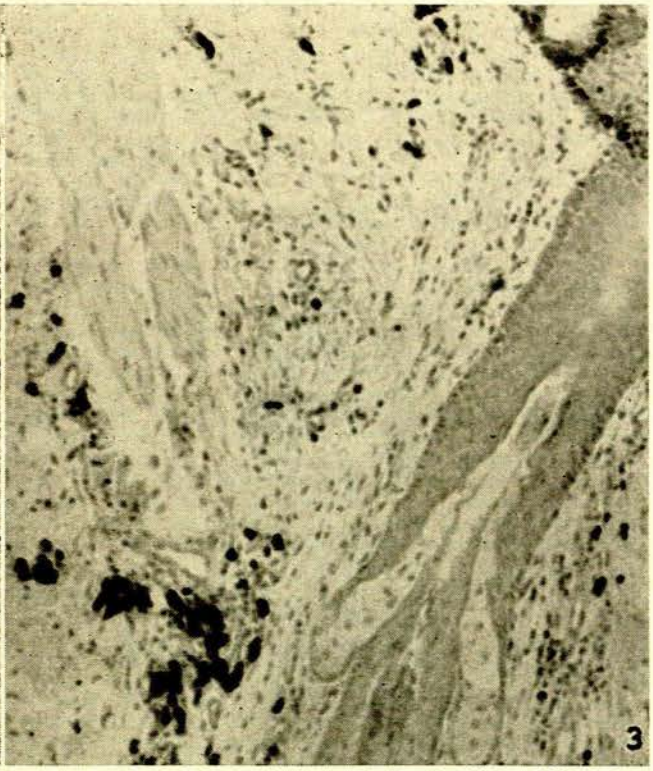

Fig. 3. Iron deposits in dermis (Prussian blue × 1000).

border was normal in outline. There was a marked fibrosis of the whole of the dermis, in which the collagen bundles were denser than normal, thick, wavy and eosinophilic. The sweat glands were embedded in the sclerotic collagen, which proliferated irregularly downwards to enclose islands of adipose tissue in the subcutaneous layer. There was no apparent decrease in the number of fibrocytes (Fig. 2). Large quantities of iron pigment were seen distributed throughout the area of sclerosis and in the adipose tissue (Fig. 3). It was localized mainly in phagocytes, but also occurred independently. The distribution of this iron pigment was predominantly perivascular and, to a lesser extent, peri-adnexal. In the upper dermis occasional, moderately dilated, blood vessels were seen. Small islands of lymphocyte and plasma-cell infiltrate were found in the dermis, predominantly perivascular in arrangement.

Investigations

X-ray of the leg showed marked osteoporosis in the region of the right ankle. A femoral arteriogram (Dr. J. K. Bremer) showed no abnormality. A barium meal revealed no abnormality of the oesophagus, stomach or duodenum. Gastric- and duodenal-juice analysis was normal.

Needle biopsy of the liver showed marked siderosis with hepatofibrosis. The appearance was suggestive of cirrhosis, but the specimen was too small to make a definite diagnosis (Dr. I. W. Simson).

Vitamin-C saturation tests were performed as described in the methods above. Loading doses for the oral test (*a*) varied from 600 to 1,000 mg., and for the intravenous (IV) tests (*b*), from 800 to 1,000 mg. (Table I).

Summary of Results of Saturation Tests

1. After having received 17·7 G. of vitamin C orally and 1·8 G. intravenously within 28 days, the patient excreted negligible amounts of vitamin C in the urine.

2. There was no spill-over of vitamin C into the urine after the first 2 IV injections.

3. A 'normal' degree of saturation was found after the 4th IV injection of vitamin C; 3·8 G., of which 1 G. was the loading dose, had been given intravenously within 40 days.

4. The oral test was followed by normal vitamin-C excretion on the day after the 4th IV injection had been given. Twelve days later it had decreased to below saturation level. After 22 days excretion had dropped to insignificant amounts and remained low until a further IV injection was given.

5. Two days after the 5th IV injection, excretion was again normal, but within 12 days vitamin C had again virtually disappeared from the urine.

TABLE I. VITAMIN-C SATURATION TESTS IN CASE 1

Total days	*Total vitamin C received (in G.)*			*Method*	*Vitamin C excreted (in mg.)*
	By mouth	*IM*	*IV*		
1	0·6			Oral method (*a*)	1·04
2	1·2			Oral method (*a*)	1·69
5	3·0			Oral method (*a*)	2·24
6	3·0		0·8	0·8 G. IV 1st 4 hours	3·5
7	3·0		1·8	1 G. IV 1st 3½ hours	9·2
8	4·0		1·8	Oral method (*a*)	2·7
11	6·6		1·8	Oral method (*a*)	3·05
15	9·0		1·8	Oral method (*a*)	8·7
28	17·7		1·8	Oral method (*a*)	5·6
34	20·7		2·8	1 G. IV 2½-5½ hours after injection	14·5
40	24·2		3·8	1 G. IV 1st 6½ hours	465·9
41	25·2		3·8	Oral method (*a*)	47·6
52	27·2		3·8	Oral method (*a*)	29·1
62	29·2		3·8	Oral method (*a*)	2·66
73	35·2		3·8	Oral method (*a*)	3·9
86	42·8		4·8	1 G. IV 1st 2½ hours	248·0
88	43·8		4·8	Oral method (*a*)	50·4
98	47·6		4·8	Oral method (*a*)	2·9
102	50·0		4·8	24-hour specimen. No loading ..	20·9
104	51·0		4·8	24-hour specimen. 1 G. by mouth	18·0
105	52·0		4·8	24-hour specimen. 1 G. through Ryle's tube	17·9
111	52·0		5·8	24-hour specimen. 1 G. IV drip in 45 minutes	131·0
113	52·0		5·8	24-hour specimen. No loading ..	16·2
116	52·0		6·8	24-hour specimen. 1 G. IV in 5 minutes	143·3
122	52·0	1·0	6·8	24-hour specimen. 1 G. IM ..	91·1

IM = intramuscularly, IV = intravenously.

6. The daily excretion of reducing substances in the urine, after the patient had received 50 G. of vitamin C by mouth and 4·8 G. intravenously within 102 days, was low (20·9 mg.). It did not increase after 1 G. of vitamin C was given by mouth, nor when the same amount was introduced directly into the duodenum through a Ryle's tube. It should also be remembered that these low amounts in the single 24-hour specimens (20·9 mg., 18·0 mg., and 17·9 mg.), as determined by the simple dye-titration method, do not represent vitamin-C excretion alone. The Medical Research Council[13] found the daily output of inactive reducing substances in the urine to average about 24 mg. in their experiments.

7. Increased excretion during a 24-hour period was found after IV administration, and to a lesser degree after intramuscular administration. When this increase is compared with that obtained in urine specimens collected over shorter periods of time (2½ - 6½ hours), it can be seen that the preservation of vitamin C in a 24-hour specimen is inadequate.

From these results it was concluded that it was impossible to saturate the patient with oral vitamin C alone, even when massive doses had been given over a considerable period.

It was interesting to note, however, that by the 11th day (when he had received 1·8 G. intravenously) the affected leg showed considerable improvement, being no longer warm and painful. Several months later, when the patient had received vitamin C injections at irregular intervals, the sclerotic tissues were found to be distinctly softer in texture.

CASE 2

This patient was a 40-year-old Msuto male. He had been healthy until the year before admission, when he developed a painful swelling of his right lower leg. Several months later, i.e. 8 months before admission, he developed a pain in the middle of his back. This improved, but 2 months later he again developed backache, this time after lifting a heavy weight. At about the same time his left lower leg and knee became swollen. When the swelling subsided the leg was 'shrunken'.

He had suffered from bleeding gums and bad teeth for the previous 10 years, resulting in the extraction of all his upper teeth 8 months before admission.

On examination his left lower leg was thinner than the right. The skin was sclerotic and pigmented around the ankle, and the calf muscles were atrophic. The same scleroderma-like changes described in case 1 were found. The liver was not palpable and no other abnormalities were noted.

Investigations

X-rays of the lumbar spine showed wedge formation of the 2nd lumbar vertebral body, owing to an old collapse. There was bony destruction of the anterior superior corner of the 4th lumbar vertebral body, very suggestive of tuberculosis.

Biopsy of the 5th lumbar vertebral body (Dr. I. Henkel) showed haemosiderosis of the bone marrow and osteoporosis, and the 4th lumbar vertebral body showed a haemosiderosis of the marrow with the formation of granulation tissue, osteoporosis and areas of new-bone formation.

Biopsy of the skin of the left lower leg showed changes identical with those found in case 1, viz. fibrosis in the dermis and subcutaneous tissue with widespread deposits of haemosiderin pigment.

Similar osteoporotic changes in the vertebral bodies have been seen in cases of Bantu siderosis in Johannesburg.[1,7] They may easily be diagnosed and treated in error as tuberculous disease of the spine.

Vitamin-C Tests (Table II)

Vitamin C was given by mouth only for the first 56 days, during which time the patient received a total of 45·4 G. Tests were performed with 2-hour specimens of urine as described in method (*a*) above, but a loading dose of 1·0 G. was given in each case. Although there was a rise in excretion between the 23rd and 31st days, it was not maintained and again fell to very low levels even after 45·4 G. of vitamin C had been ingested over a period of 56 days.

The patient was then given vitamin C by daily intramuscular injection (100 mg. once or twice daily) and intravenous tests [method (*b*) (*i*)] were repeated at intervals. Excretion was inadequate and did not reach normal levels even after 50 days in which a total of 10·6 G. of vitamin C had been given parenterally. It appeared therefore to be impossible to saturate case 2 either by oral or parenteral vitamin-C administration.

TABLE II. VITAMIN-C SATURATION TESTS IN CASE 2

Total days	Total vitamin C received (in G.) By mouth	IM	IV	Method	Vitamin C excreted (in mg.)
2	2·0			Oral. 4-hour urine	0·97
8	8·0			Oral method (*a*)	4·32
9	9·0			Oral method (*a*)	3·01
16	16·0			Oral method (*a*)	1·52
23	23·0			Oral method (*a*)	71·4
31	31·0			Oral method (*a*)	31·5
38	38·0			Oral method (*a*)	4·76
50	42·6			Oral method (*a*)	13·87
56	45·4			Oral method (*a*)	11·4
59	45·4		0·3	—	—
69	45·4	1·0	0·3	—	—
70	45·4	1·0	0·8	0·5 G. IV 1st 4 hours	91·0
77	45·4	1·7	1·3	0·5 G. IV 1st 4 hours	47·2
80	45·4	2·3	1·8	0·5 G. IV 1st 4 hours	43·4
87	45·4	2·6	2·3	0·5 G. IV 1st 4 hours	28·5
94	45·4	4·0	2·8	0·5 G. IV 1st 4 hours	86·6
101	45·4	5·4	3·3	0·5 G. IV 1st 4 hours	78·5
108	45·4	6·8	3·8	0·5 G. IV 1st 4 hours	35·6

CASE 3

This patient was a Nyasa male, about 50 years old. Ten months before admission his left leg had become painful and swollen after a trivial injury. On examination he was found to have lower-leg changes identical with those found in the previous 2 cases, viz. atrophy of the calf, and hard sclerodermatous texture of the skin and subcutaneous tissues with a fairly well-defined edge below the popliteal fossa. There was a marked generalized darkening of the skin, particularly on the face and limbs. The liver was enlarged and hard.

The diagnosis of chronic scurvy was made on histological examination of the skin of the affected leg. Vitamin-C saturation tests were not done.

His condition did not respond at all to vitamin-C administration and he later developed the picture of a cor pulmonale and died.

Postmortem Examination (Dr. I. W. Simson)

There was a marked subcutaneous fibrosis of the left lower leg. All the tissues of the calf were sclerotic, and macroscopically there was a brown discoloration of the fat, muscle and ligaments. Microscopically there was fibrosis and haemosiderin deposition in all the affected tissues of the leg.

The following organs were found on histological examination to be siderotic — liver (severe siderosis with a concomitant fine cirrhosis), duodenum, jejunum, mesenteric lymph glands, thyroid, pancreas, adrenal and pituitary glands, spleen, and cardiac muscle. There was a marked interstitial fibrosis of the thyroid and pancreas.

CONTROL STUDIES

Samples of various brands of vitamin C used in the saturation tests were examined for potency and were found to conform to their specifications. In addition we were able to demonstrate that Bantu subjects, not known to be suffering from siderosis, were readily saturated with vitamin C given by mouth. Twenty-two patients in the skin and medical wards were given vitamin C daily and saturation tests were done at irregular intervals. In each case a loading dose of 800 mg. was given by mouth and a 2-hour specimen of urine was collected.

We did not attempt to ascertain exactly how much vitamin C or how many days were necessary, but merely whether these patients could be saturated or not. The results are summarized in Table III.

It can be seen that in at least 5 cases it was necessary to repeat the test after 3 weeks of vitamin-C intake before saturation levels were reached. This long period of time makes the test cumbersome and perhaps explains why more extensive use of saturation tests was not made by previous investigators of scurvy in this country.

TABLE III. VITAMIN-C SATURATION TESTS IN CONTROLS

Patient	Diagnosis	Total days	Total vitamin C received (in G.)	Vitamin C excreted (in mg.)
1	Pellagra	20	6·8	22·4
		27	9·7	60·75
2	Seborrhoeic dermatitis	7	2·9	17·76
		27	6·8	26·01
		34	9·7	36·75
3	Ecthyma	7	2·9	35·28
		33	8·6	55·0
4	Hodgkin's disease	6	4·4	0
		26	16·2	23·0
		32	20·6	112·5
5	Erythema multiforme	7	2·9	37·6
6	Seborrhoeic dermatitis	5	2·3	1·9
		11	4·9	11·4
		18	7·8	67·8
7	Seborrhoeic dermatitis	7	2·9	20·7
		27	9·7	19·47
		34	12·6	40·2
8	Traumatic ulcers	3	2·0	72·9
9	Seborrhoeic dermatitis	1	0·8	0
		27	1·6	8·34
		34	6·6	119·39
10	Pellagra	13	16·4	57·07
11	Splenomegaly	28	10·7	114·14
12	Tuberculosis	15	7·55	4·1
		21	11·5	38·9
13	Plantar warts	12	4·4	14·9
		21	7·3	105·5
14	Seborrhoeic dermatitis	2	2·0	16·5
		9	5·0	60·1
15	Eczema	4	3·2	66·6
16	Eczema	4	2·0	48·4
17	Eczema	2	1·1	6·6
		8	4·0	133·8
18	Tuberculosis	21	9·45	13·8
		25	11·3	127·0
19	Tuberculosis	17	7·65	27·5
		31	15·55	54·0
20	Nevus verrucosus	1	0·8	7·5
		10	7·6	99·9
21	Eczema	1	0·8	7·0
		8	3·7	14·6
		15	6·6	78·4
22	Sporotrichosis	4	1·9	89·7

DISCUSSION

The first problem arising from a study of our 3 patients and from previous observations in the literature, is the hitherto little recognized relationship between scurvy and Bantu siderosis. The simultaneous occurrence of lower-leg scurvy and siderosis has been found in Grusin's 1 postmortem report,[1] in our 3 patients, and in at least 3 postmortem examinations by Simson.[7]

Simson has in addition seen 10 cases of idiopathic haemothorax or haemopericardium in patients with severe siderosis having a haemochromatotic distribution.[7] It was suggested by Grusin that some of these otherwise unexplained haemorrhages may be due to scurvy.[1] Subsequently he described one patient with spontaneous haemopericardium, who also had spongy gums and haematuria, all of which healed after 10 days of intramuscular vitamin-C therapy.[15]

Another link between scurvy and siderosis is supplied by the occurrence of osteoporosis in both conditions. Grusin and Samuel[16] found the incidence of osteoporosis in 48 patients with classical acute scurvy to be 18·7%. They investigated 16 Bantu patients suffering from collapsed vertebrae caused by osteoporosis of the spine, of whom 11 had evidence of scurvy. In all the 9 patients in whom the condition was looked for, siderosis was found. In addition, 2 of Grusin's earlier patients with scurvy[1] had osteoporosis of the spine and collapse of several vertebrae, as did case 2 in our series.

Grusin and Samuel[16] postulated that the vitamin-C deficiency, owing to its effect on ground substance, was the cause of osteoporosis, and not the siderosis. This view is supported by the investigations of Walker *et al.*[17] who could find no correlation between iron concentration and mineral density in even severely siderotic vertebral bodies.

Association of Siderosis and Scurvy

As a result of our finding an abnormal vitamin-C metabolism in cases of scurvy associated with Bantu siderosis, we wish to postulate that the association between the 2 conditions is not fortuitous, and that the one condition (siderosis) in fact gives rise to the other (scurvy). The fact that scurvy in the South African adult Bantu usually occurs in subjects with iron overload has already been tentatively suggested by Bothwell *et al.*,[18] who considered ascorbic acid to be concerned in the transport of iron across reticulo-endothelial cells.

The mechanism by which iron deposits in the body cells may give rise to an ascorbic-acid deficiency is, at the moment, a matter for speculation. Under normal circumstances, vitamin C, which is very soluble, is readily absorbed from the alimentary tract. It has been seen that in Bantu siderosis massive haemosiderin deposits are found in the jejunal and duodenal mucosa,[3,4] thus greatly increasing the available amount of ferric iron in the cells. Using a non-enzymatic hydroxylating system, Breslow and Lukens[19] have demonstrated that ferric iron oxidizes ascorbic acid to dehydroascorbic acid. Above pH5 dehydroascorbic acid itself undergoes further oxidation to the biologically inactive substance diketogulonic acid.[9] It may be possible, therefore, for the excess ferric iron in the cells of the small intestine to decrease the amount of ascorbic acid being absorbed by catalyzing its initial conversion to an inactive form. A similar and further reduction in available ascorbic acid could occur in the other siderotic tissues.

Pseudoscleroderma and Scurvy

The second problem arising from our observations was why some patients develop chronic scleroderma-like

changes following an acute haemorrhage in scurvy, while others recover. In most of Grusin's patients[1] the extravasated blood became absorbed in 4 - 6 weeks, leaving no scar. All 3 of our patients with chronic scurvy had evidence of siderosis, and in the 2 in whom prolonged vitamin-C saturation tests were carried out, it was apparent that vitamin C given by mouth was not being absorbed. It would appear then that *chronic* tissue changes in the form of fibrosis occur in those patients in whom there is a *chronic* vitamin-C lack. In these patients it is hardly possible to reverse their deficiency state, even if the intake of vitamin C by diet or oral medication is adequate.

It is generally agreed, and has recently been histologically confirmed by Abt *et al.*,[20] that the rate of collagen formation in the connective tissues is markedly diminished in the scorbutic state. It was therefore all the more unexpected to find that a chronic deficiency of vitamin C led to an excess formation of fibrous tissue in our cases. The initial haemorrhage alone was apparently not the cause, since in most cases it is resorbed and leaves no sequelae.

A possible explanation is that the chronic vitamin-C lack (here perhaps secondary to siderosis) gives rise to repeated small haemorrhages following the initial one. This extravasated blood, or the resultant excessive deposition of haemosiderin pigment, then acts in some way to stimulate fibroblast activity. That this is not due to a foreign-body reaction alone, is indicated by the finding that values for collagen (calculated as hydroxyproline) were found to be lower in carrageenin granuloma tissue than in scar wound muscle in experiments done on normal and scorbutic guinea-pigs by Abt *et al.*[20]

Direct evidence that iron may cause fibrosis in the skin and subcutaneous tissues following repeated intramuscular injections of iron-dextran (which undergoes rapid intracellular conversion to ferritin) was found by Golberg *et al.*[21] in experimental studies on mice. 'In the tissues overlying the sites of injection of heavy doses of iron-dextran, there was always an accumulation of siderophages owing to diffusion of the excess of injected material. These siderophages promoted, in the dermis and subcutaneous tissue, an extensive fibrosis, which often extended through the adnexal structures to the base of the epidermis; these consequently showed atrophic changes.'[21] The close parallel presented by our findings in chronic haemorrhagic scurvy and those provoked by ferritin in mice, would seem to justify the title scorbutic pseudoscleroderma, by which we have described the condition.

SUMMARY

Three patients are described in whom an initial acute attack of scurvy led, after a period of several months, to scleroderma-like changes in the affected limb. All patients were found to be suffering from Bantu siderosis. Vitamin-C saturation tests were performed on 2 patients and a disturbance of vitamin-C metabolism was found to exist. Neither patient could be saturated by oral vitamin C, and 1 of them could not be saturated by parenteral vitamin-C administration as well.

Attention is drawn to the concomitant occurrence of siderosis and scurvy in our patients and in patients described in the literature. It is postulated that the excessive iron deposits found in siderosis give rise to a sometimes refractory vitamin-C deficiency, and also that the iron may be the cause of the unexpected fibrosis found in chronic scurvy.

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