the *Proceedings*. If, however, they wish to have the *Journal* as well, with original scientific articles, they must pay £1. 10. 0d more, a total of £3. 0. 0d.

This then is the short eventful history of our British Nutrition Society. We are not just another scientific society with an appeal to a relatively small group of specialist scientists. We offer a forum to all scientists, and to students of science, who are concerned with the future welfare of mankind and of animals. We try to overcome the tendency to divide biological science into smaller and smaller compartments of knowledge. James Lind, who wrote on scurvy, on hygiene and on tropical medicine, would have understood us, would have been of our number. We strive to be worthy of his words:

'I shall propose nothing merely dictated from theory; but shall confirm all by experience and facts, the surest and most unerring guides.'

Ascorbic-acid Deficiency in Experimental and Surgical Subjects*

By John H. Crandon, Stanley Mikal and Bernard R. Landeau,
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Confusion over the significance of ascorbic-acid levels in human blood plasma led in 1940 to a prolonged deficiency experiment on one subject wherein effort was made to correlate blood content of this vitamin with clinical response (Crandon, Lund & Dill, 1940). During the course of this experiment adequate supplements of all other known vitamins were taken daily†. Butler, Cushman & MacLachlan (1943), who had recently developed their method for determination of the ascorbic-acid content of the buffy coat, frequently analysed blood samples. Plasma determinations were performed daily. Diet consisted of bread, well-cooked meat, cake, and butter at first; later, cheese, crackers, eggs, chocolate candy and, occasionally, beer.

The plasma ascorbic acid, as measured by the method of Mindlin & Butler (1938), fell to zero in 41 days, at which time the buffy-coat ascorbic acid was 10 mg/100 g. Thereafter the plasma readings remained at zero, whereas the buffy-coat readings did not reach zero until 121 days had elapsed. Two weeks later small perifollicular hyperkeratotic papules began to appear over the buttocks. Not until after 161 days of the diet, or after the plasma ascorbic acid had been zero for 120 days and the buffy coat zero for 40 days, did the perifollicular haemorrhages so characteristic of scurvy appear over the lower legs. Three weeks later an experimental wound made in the back of the subject showed no healing when biopsied after 10 days. Previously, a similar wound made at the end of 3 months of diet, after the

* This study was made possible by two grants from the Hoffman-LaRoche Company of Nutley, New Jersey, U.S.A.

† Through the kind advice of Dr Arnold Meiklejohn.

plasma had been zero for 44 days and the buffy coat reading was 4 mg/100 g, showed reasonably good healing, both clinically and microscopically.

Although the ultimate failure of wound healing was the more striking result of this experiment, equally significant were the results of fatigue tests performed just before cessation of the diet. In the completely scorbutic state the subject was able to run on a motor-driven tread-mill at a rate of 7 m.p.h. for only 16 sec, at the end of which time he was completely exhausted, with a sensation of impending collapse. Following ascorbic-acid therapy, the subject was able to run for 66 sec, without the sensation of impending disaster experienced in the first test.

The subjective phenomena associated with the ascorbutic state were vague and difficult to describe. There was certainly an increased lassitude and desire for sleep. There was a marked disinclination to exertion. A craving for a variety of fruits and vegetables in the diet disappeared after 3–4 months, but this, of course, may have been the result of factors other than ascorbic-acid deficiency.

From this and other similar experiments (Medical Research Council, Vitamin C Subcommittee of the Accessory Food Factors Committee, 1948) it has been assumed that in true scurvy the blood ascorbic acid must be zero and that the patient whose blood is not close to zero is not very close to scurvy. Some investigators on the basis of this concept have found such variance of blood ascorbic-acid levels as to conclude that they are of little significance. It has been assumed by many, including ourselves, that the buffy coat rather than the plasma ascorbic acid is the better index of body nutrition with respect to this vitamin.

During the past $2\frac{1}{2}$ years study has been made of ascorbic acid in 1136 blood samples of 561 different selected surgical patients at the Boston City Hospital. Both buffy coat and plasma were analysed by the method of Roe & Kuether (1943), whereby dehydroascorbic acid rather than ascorbic acid is measured. The results have forced a revision of some of the concepts arrived at from observation of the experimental deficiency.

For a base-line in these studies blood analyses were made on all patients who showed clinical scurvy during this period. Seven frankly scorbutic patients, four of whom suffered no surgical disease, were encountered (Table 1). Four of these patients were known to have received small amounts of ascorbic acid in some form before blood sampling, but all seven showed small amounts of the vitamin in their blood buffy coat and five showed traces in their plasma as well. In this regard it is pertinent to speculate that an individual showing 5 mg ascorbic acid /100 g in his buffy coat will have in fact in the order of magnitude of only 1 mg of this vitamin in his entire circulating white cells and platelets. It is not surprising, therefore, that a sick, markedly deficient patient with this level in his buffy coat may show a zero reading within a day or so thereafter.

The finding of traces of ascorbic acid in scorbutic patients suggests a thesis consistent with the observations of Lind in 1753 and postulated by Hess in 1920, but little emphasized: that clinical scurvy is the result not of ascorbic-acid deficiency alone, but of ascorbic-acid deficiency plus local tissue stress.

This finding also raises a question regarding the method of blood analysis. That

Table 1. *Blood ascorbic acid in seven cases of clinical scurvy in the course of 2½ years*

Patient: Name	Hospital no.	Age (years)	Diagnosis	Known intake before and after sampling	Date of sampling	White blood cells (mg/100 g)	Whole blood (mg/100 ml.)	Plasma (mg/100 ml.)	Improved on vitamin C
J.C. (11.ix.50 to 3.x.50)	1372567	82	Essential hypertension ? Carcinoma of stomach Benign prostatic hypertrophy Scurvy	Received one small glass fruit juice/day for 4 days before first sampling and thereafter 1000 mg vitamin C intravenously ——→ Commenced on 200 mg/day	14.ix.50	4.75	0.06	0.14	
					18.ix.50	9.00	0.04	0.06	
					1½ h	2.10	0.64	0.60	
					5 h	Clot	0.30	0.29	
					19.ix.50	5.30	0.30	0.18	
					21.ix.50	15.00	0.35	0.25	
					25.ix.50	15.00	0.38	0.32	
					28.ix.50	11.00	0.48	0.43	
					2.x.50	26.00	0.70	0.60	Yes
C.C. (19.vii.52 to 28.viii.52)	1443334	71	Scurvy Developed carcinoma of buccal mucosa 4 months later	No vitamin C Commenced on 100 mg ——→ vitamin C/day (intramuscularly) All signs of scurvy ——→ gone; vitamin C discontinued	24.vii.52	few red cells 5.10	0.00	0.00	
					26.vii.52				
					30.vii.52	0.00	0.00	0.00	
					6.viii.52	5.69	0.41	0.12	
					12.viii.52	19.00	0.67	0.40	
					20.viii.52	8.75	0.39	0.12	Yes
W.W. (9.ix.52 to 15.x.52	1448340	64	Scurvy	No vitamin C Commenced on 50 mg ——→ vitamin C/day	9.ix.52	3.40	0.03	0.00	
					17.ix.52	4.46	0.01	0.00	
					23.ix.52	3.57	0.12	0.00	
					30.ix.52	6.12	0.04	0.01	
					14.x.52	5.00	0.47	0.01	Yes
J.K. (17.vii.50 to 8.viii.51)	1404920	54	Strangulated hernia with intestinal obstruction Chronic alcoholism Psychosis Cirrhosis	May have received ascorbic acid in some form during week before sampling After operation 500 mg vitamin C/day	17.vii.51	7.50	0.21	0.09	Yes
O.J. (7.xi.51 to 15.i.52)	1416577	69	Pernicious anaemia Pulmonary tuberculosis Cold abcess of caecum	Received 50 mg ascorbic acid/day for 4 weeks before sampling Ileotransverse colostomy Femoral vein ligation Placed on 200 mg ascorbic acid /day	6.xii.51	3.40	0.14	0.09	Yes
					10.xii.51	0.00	0.12	0.09	Died shortly after leaving hospital
					17.xii.51	3.70	0.39	0.09	
					20.xii.51	5.30	0.23	0.14	
					3.i.52	10.20	0.47	0.35	
E.C. (7.iii.52 to 27.iii.52)	1429475	91	? Acute cholecystitis Generalized arteriosclerosis Diaphragmatic hernia Postphlebitic dermatitis of lower legs	Received one small glass fruit juice/day for 1 week before sampling Commenced on 100 mg vitamin C/day	20.iii.52	6.70	0.34	0.15	
					24.iii.52	5.80	0.55	0.46	Yes, but died. ? cerebro-vascular accident
					26.iii.52	9.20	0.37	0.27	
L.J. (29.v.52 to 21.viii.52)	1438146	72	Scurvy Cirrhosis	No vitamin C Commenced on 100 mg vitamin C/day	29.v.52	5.35	0.09	0.06	Yes

zero readings can be obtained by the method is attested by the fact that of approximately 1000 patients sampled, nineteen were found with no ascorbic acid in the blood buffy coat and for the most part with only a trace in their blood plasma, none of whom showed any clinical evidence of scurvy at the time of blood sampling. Eight of these nineteen were subjected to laparotomy, and of these, four had evisceration of their abdominal wounds requiring resuture between the 9th and 12th postoperative days and one other developed a persistent draining sinus in her wound (Table 2). This group showed no bleeding gums or perifollicular haemorrhages, perhaps because of lack of stress in these areas, but when subjected to local tissue stress in the form of a laparotomy wound, five of the eight showed wound

Table 2. *Information about surgical patients with no ascorbic acid in blood buffy coat but without manifestation of clinical scurvy*

Total, of 561 different patients (1136 samples)	19
Followed up	16
Subjected to laparotomy	8
Eviscerated between 9th and 12th postoperative day*	4
Developed persistent draining sinus in wound†	1
Dead within 2 years	9

* None of these patients are duplicated in the fascia low-level group (see text below).

† This patient is included in fascia low-level group (see text below).

disturbance consistent with scurvy. However, since no wound biopsies were obtainable in any of these patients, proof of a causal relationship of ascorbic-acid deficiency is lacking. Nine of the sixteen patients followed in this group were dead within 2 years.

In seventy patients analyses were made of fascia (generally anterior rectus sheath) and muscle, as well as blood, at time of operation, in an effort to correlate blood and tissue ascorbic-acid with clinical response. When the data from this group were assembled, it was found that these patients could be divided into a low group and a remaining group which was arbitrarily divided into a medium and a high group. The low group had fascia ascorbic acid ranging between zero and 1·4 mg/100 g, the medium group levels between 1·5 and 5, and the high group levels above 6. In the low group, totalling twenty-four patients, the plasma ascorbic acid was consistently low, being under 0·2 mg/100 ml. in all but three, each of whom had been receiving ascorbic-acid supplement (Fig. 1)*. There was thus some correlation between plasma and static-tissue ascorbic acid in this group. On the other hand, the buffy-coat ascorbic acid showed considerable variation in this group (Fig. 2)*. In the medium and high groups no correlation whatsoever could be found between plasma, buffy-coat, and tissue ascorbic acid. The question arises as to whether in surgical patients, a plasma ascorbic-acid level of below 0·2

* The blood ascorbic acid of twenty patients ranged beyond the area included in this graph.

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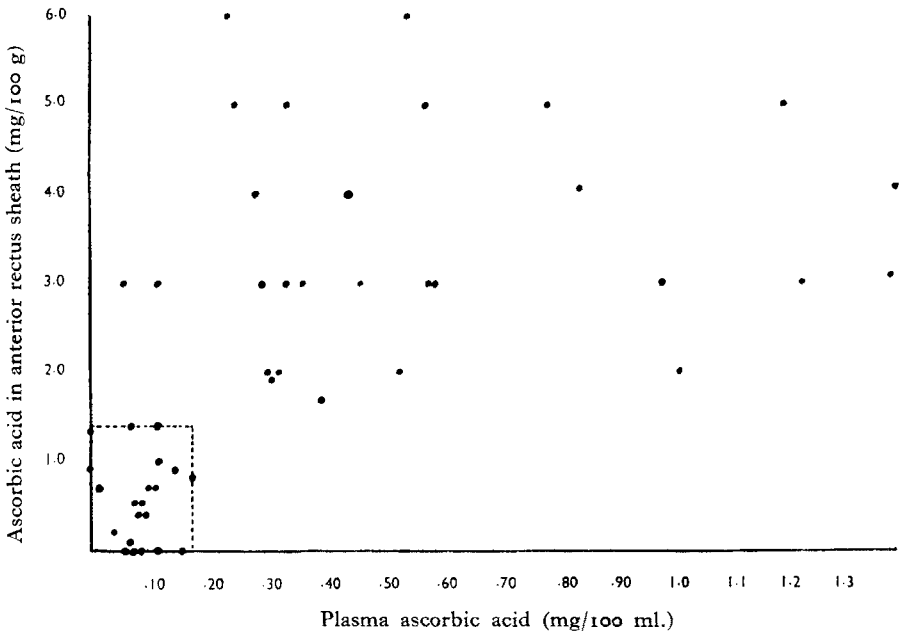

Fig. 1. *Plasma and rectus-sheath ascorbic acid (fifty cases).*

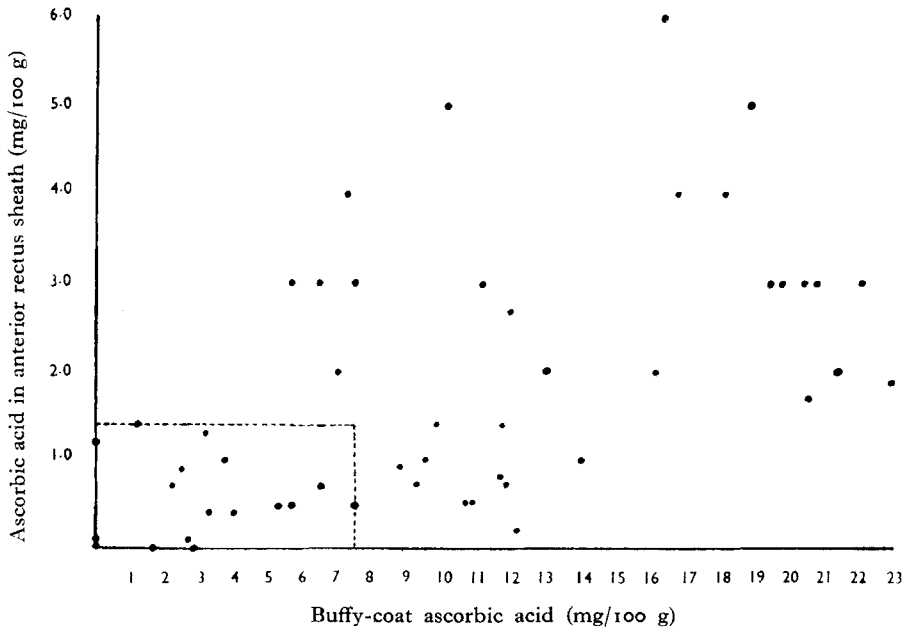

Fig. 2. *Buffy-coat and rectus-sheath ascorbic acid (fifty cases).*

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mg/100 ml. is reasonably a good index of deficiency. Farmer & Abt (1938) postulated that the fasting plasma ascorbic acid was a good reflection of vitamin C nutrition but considered much higher levels to be indicative of deficiency. It is probable that our figures are not absolute, that values will vary with the laboratory and method, and that each laboratory should correlate its own results with clinical deficiencies.

When, after 2 years, follow-up study was made of this low group, eighteen patients could be traced. Of these, twelve had suffered wound complications of one kind or another (Table 3). Eleven were now dead. It cannot be assumed that, in either this or the totally deficient group, lack of ascorbic acid was directly the cause of the

Table 3. *Information about surgical patients with low fascia and blood ascorbic acid at operation (Roe-Kuether method)*

Total in low group		24
Followed up		18
Total wound complications		12
Undergoing laparotomy		13
Eviscerated	1	
Massive bleeding into wound	1	
Dehisced down to peritoneum	2	9
Developed incisional hernia	3	
Developed persistent draining sinus	2	
Herniorrhaphy, amputation, or sympathectomy		5
Poor or no healing	2	3
Draining sinus lasting 2 years	1	
Of eighteen, total dead within 2 years		11

high rate of wound complications. That the general physical state of the patients was poor is indicated by the high mortality rate in both groups. Nevertheless the association of low blood ascorbic acid and high wound complication rate in the two groups would seem to be more than coincidental.

In this entire series, no increased incidence of wound complications was observed among those patients having a deficient plasma but a buffy-coat ascorbic acid consistently above 8 mg/100 g, provided there existed no wound infection or other increased local tissue stress. However, among patients with almost totally deficient plasma who were receiving no vitamin C, a precipitous drop in buffy-coat ascorbic acid was frequently noted, with onset of infection, evisceration, or other complication. Patients were observed with plasma of less than 0·2 mg/100 ml. and buffy-coat ascorbic acid as high as 13 mg/100 g. On the other hand, where no ascorbic acid had been recently given, buffy-coat levels below 8 mg/100 g were rarely found with plasma levels above 0·2 mg/100 ml. Repeated low buffy-coat levels accompanied by plasma levels above 0·2 mg/100 ml. were associated not only with some ascorbic-acid intake but also with conditions compatible with increased utilization of the vitamin. Beyond the foregoing general rules, no correlation between plasma and buffy-coat ascorbic acid could be found.

Summary and conclusions

From analyses of blood and tissues in surgical patients it appears that blood ascorbic-acid levels are of value in estimating deficiency of this vitamin. The more or less predictable relationships between blood and tissue ascorbic acid seen in acute deprivation experiments in otherwise normal individuals are not found in the sick patient. The dissimilarities of blood findings in experimental subjects and sick patients are at least partially the result of local tissue stress and variable, small, uncontrolled intake in the latter.

In the surgical patient plasma ascorbic acid below 0·2 mg/100 ml., as determined by the Roe & Kuether (1943) method in our laboratory, is suggestive of serious ascorbic-acid deficiency. Nevertheless, with plasma ascorbic acid below this level, wound healing has been observed to occur, provided the buffy-coat ascorbic acid remained above 8 mg/100 g and provided there was no wound infection or other increased local tissue stress.

Taking into consideration the relative difficulty of method, limit of error, and safety factors involved, the plasma determination must be considered of more value than the buffy-coat determination in assessing ascorbic-acid nutrition in surgical patients.

Scurvy, in many cases, appears to be a manifestation not of complete absence of ascorbic acid alone, but of marked ascorbic-acid deficiency plus local tissue stress. Surgical patients having a deficient plasma and buffy coat are frequently very ill, have a relatively poor prognosis, and have a high incidence of evisceration, incisional hernias, and draining wound sinuses postoperatively.

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Ascorbic Acid in Relation to Cold, Scurvy, ACTH and Surgery*

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It is extraordinary that in 1913, some 160 years after Lind's (1753) discovery of the treatment and prevention of scurvy, Arctic and Antarctic explorers, like Scott,

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