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*

By Robert M. Kark, *Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois, U.S.A.*

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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continued to die miserably of this disease. From 1870 to 1930—when Zilva (1930) produced a potent concentrated canned lemon juice for the British Arctic Air Route Expedition—Polar explorers were sceptical of the antiscorbutic properties of Lind's rob of oranges or lemons, of Curtis's sprouted pulses (Curtis, 1807), and of James Cook's 'inspissated Juice of Wort'* (Cook, 1777). The loss of confidence in these antiscorbutics by explorers has been explained by Chick, Hume, Skelton & Smith (1918). They pointed out that after 1850, for political and economic reasons, the juice of the sour West Indian lime (*Citrus medica*, var. *acida*)—which contains no ascorbic acid—replaced the Royal Navy's traditional ration of 'lime' juice, which had been made, since 1795†, from vitamin C-containing Mediterranean lemons (*Citrus medica*, var. *limonum*). In 1875 the Admiralty supplied large amounts of sour lime juice for Nares's attempt on the North Pole. In retrospect, it is not surprising that an epidemic of scurvy broke out in his men and ruined the expedition.

Following this debacle a distrust in citrus juices as antiscorbutics led Polar explorers to return to their long-standing belief that scurvy was caused by spoiled meat, tainted with ptomaines. At the turn of the century, therefore, medical investigators, such as Jackson & Harley (1900) and Coplans (1904) indicated that scurvy was due to bacterial autointoxication, and as late as 1918, McCollum (1918) stated that chronic constipation was the cause of scurvy in his guinea-pigs. Atkinson, a surgeon and a leader in Scott's tragic last expedition (Scott, 1923) accepted Almroth Wright's (1900, 1908) theory that scurvy was due to an acid intoxication of the blood. But he also believed the age-old notion that 'darkness, cold and hard work were important causes of scurvy' (Cherry-Garrard, 1922).

Scurvy was a disease *par excellence* of the sailor and of the sojourner in high latitudes. From time immemorial, its development has been related to cold, damp, rough seas, fatigue, hard work and the other stresses of sea travel. Lind (1753) also emphasized the importance of cold and its associated stresses as aetiological factors in scurvy, even though he had read Bachstrom (1734), who clearly indicated that cold and allied stresses play no part in producing the disease. Bachstrom had studied and reported an epidemic of scurvy which, appearing in the height of the summer of 1703, decimated 5000 of the besieged inhabitants of Thon, in Prussia.

Stress, adrenal activity, and utilization of ascorbic acid

Rule of thumb and empirical concepts of folk medicine die hard. Despite reports of epidemic scurvy in Africa (Dry, 1933) and other tropical countries (Manson-Bahr, 1925) and despite the epidemic of scurvy in the siege of Kut-al-Amara, Mesopotamia, in 1917 (Great Britain: Mesopotamia Commission, 1917), there

* The common thick syrupy malt of 'cod liver oil and malt' which was introduced as an antiscorbutic into the practice of medicine early in the eighteenth century.

† One is tempted to ask how much freedom from scurvy contributed to the doggedness and fitness of the British tar and his officers during the Napoleonic wars. The Continental Blockade (e.g. Cornwallis off Brest) of necesity kept ships and men at sea for months at a time (Bryant, 1944). This could not have been carried out in an efficient manner with scurvy-ridden crews.

existed during World War II—and there still exists to-day—a belief that, in cold climates, we need more ascorbic acid than usual to maintain health. This is supposed to be particularly true for soldiers living and fighting in the cold. The modern view, which stems from the concepts of Selye (1946) and the observations of Sayers & Sayers (1949), inclines to the belief that ascorbic-acid requirements for man are increased as a result of a variety of stresses which include exposure to cold, burns, severe injuries, operations, infections, rheumatic diseases and other metabolic insults, to describe which Browne, Schenker & Stevenson (1944) chose the apt word, 'damage'.

Between 1941 and 1947, Lund and Levenson and their colleagues studied ascorbic acid in the urine and plasma of patients subjected to surgical stresses of one kind or another (Levenson, Green, Taylor, Robinson, Page, Johnson & Lund, 1946; Lund, Levenson, Green, Page, Robinson, Adams, Macdonald, Taylor & Johnson, 1947). They found that both plasma levels and urinary output of ascorbic acid dropped to low values in their patients during the first week or two after operations, despite treatment with very high doses of ascorbic acid. At about the same time, Sayers & Sayers (1949) working with rats, demonstrated that adrenal ascorbic acid and adrenal cholesterol decreased when the animals were stressed, or when their adrenal cortices were stimulated with corticotrophin (ACTH). These observations on rats led Levinson and Lund to postulate that the increased demand for, and utilization of, ascorbic acid in 'damaged' patients was related to increased consumption of the vitamin by the adrenal gland.

Since then there has been a general acceptance of Levenson and Lund's observations of, and speculations on, ascorbic-acid requirements in states of 'damage' or physiological stress, such as exposure to cold. Thus, there exists at present a strong belief, among surgeons and physicians, that large amounts of ascorbic acid are consumed by the adrenal gland during illness in its synthesis of cortical hormones from cholesterol. Conversely, many accept the thesis that adrenal activity will be sharply reduced when ascorbic-acid supplies are curtailed. They believe that patients with low plasma levels of ascorbic acid, or with inadequate supplies of ascorbic acid, may develop adrenal insufficiency when they are stressed by surgical treatment or illness. These concepts have been tested experimentally during the past few years by a number of investigators, including ourselves, and are now known to be erroneous. In the light of data now at hand, our ideas of the interrelationships between ascorbic-acid metabolism and adrenocortical activity need reorientation, at least with regard to guinea-pigs, monkeys and man, who unlike the rat, do not synthesize ascorbic acid in their adrenals.

Effect of cold on ascorbic-acid metabolism and adrenal activity in man

Very few investigations have been reported on the effects of cold on ascorbic-acid metabolism in man. My colleagues and I carried out three series of investigations in Canada on soldiers exposed to severe cold (Fig. 1). The first (in February 1943) was made on hardened troops at Prince Albert, Saskatchewan (Kark, McCreary, Johnson, Melson & Richardson, 1944). The second study was made on

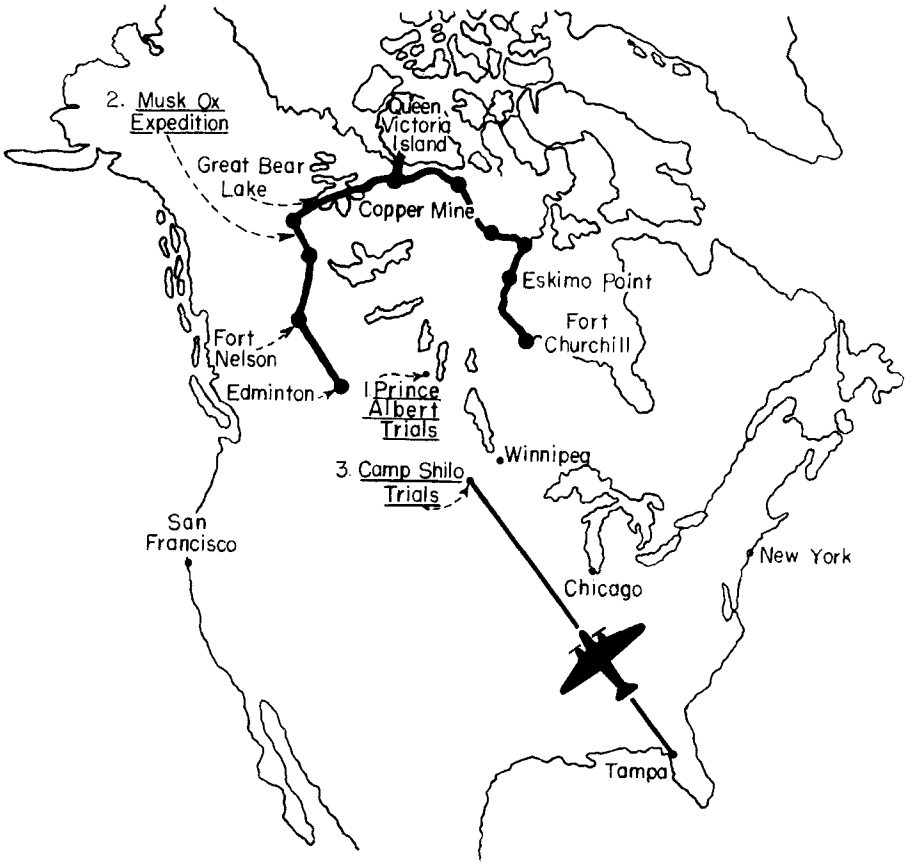

Fig. 1. Map of North America showing location of tests of army rations in cold climates in which studies of vitamin C metabolism were made: 1. The Prince Albert Trials. 2. The Musk Ox Expedition. 3. The Camp Shilo Trials held in the winter of 1947–8.

the men of the 'Musk Ox' Expedition, on fifty men who travelled 3000 miles through the Canadian barren lands in the winter of 1945–6 (Kark, Croome, Cawthorpe, Bell, Bryans, MacBeth, Johnson, Consolazio, Poulin, Taylor & Cogswell, 1948–9) and the third study was made at Camp Shilo, Manitoba on thirty-two men, acclimatized to a hot climate (Bly, Johnson, Kark, Consolazio, Swain, Landeni, Maloney, Figueroa & Imperiale, 1950; Anonymous, 1948). In February 1947 these thirty-two volunteers were flown overnight from Florida (75°F.) and were left to fend for themselves in the middle of a Canadian prairie, with the temperature at 40°F. below zero. Plasma and urinary ascorbic-acid studies were made on all these men and compared with data collected by us on thousands of soldiers acclimatized to tropical and temperate climates (Kark, Aiton & Pease, 1946; Kark, Aiton, Pease, Bean, Henderson, Johnson & Richardson, 1947).

At Prince Albert, soldiers testing allied rations did hard work, through simulated battle activities, in a series of eleven 10-day manoeuvres in the frozen brush. Data from 280 measurements of urinary ascorbic-acid output show a normal distribution curve before and after each test with a mean of 0·6 mg/h before the test

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and a mean of 0·7 mg/h after the test (Fig. 2), there being no significant increase in urinary output. In one test, soldiers lived and worked hard on a pemmican ration devised by V. Steffanson (Kark, Johnson & Lewis, 1945). After 3 days they

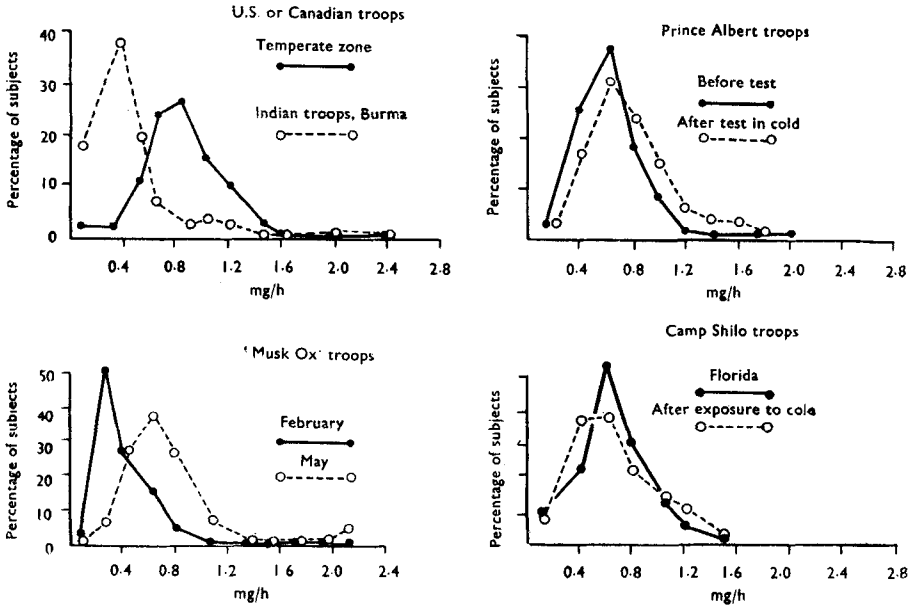

Fig. 2. Percentage distribution of urinary ascorbic acid excreted by soldiers in various environments while living on different rations. Data plotted from observations reported in detail elsewhere (see text p. 282 and Kark, McCreary, Johnson, Melson & Richardson, 1944; Kark, Croome, Cawthorpe, Bell, Bryans, MacBeth, Johnson, Consolazio, Poulin, Taylor & Cogswell, 1948–9; Bly, Johnson, Kark, Consolazio, Swain, Landeni, Maloney, Figueroa & Imperiale, 1950; Kark, Aiton & Pease, 1946; Kark, Aiton, Pease, Bean, Henderson, Johnson & Richardson, 1947; Kark, Johnson & Lewis, 1945).

collapsed as a result of severe ketosis with involuntary dehydration. A sharp and significant drop in urinary ascorbic-acid output was found (Table 1) but there was no change in output of thiamine, riboflavin or N-methylnicotinamide. These

Table 1. *Nutritional status of seventeen soldiers, before and after 3 days of military operations in the cold, during which they subsisted on pemmican as an army ration (Kark, Johnson & Lewis, 1945)*

Measurement	Before test	After 3 days of pemmican
Body-weight before breakfast (lb.)	156	149
Physical fitness (Harvard pack test scores)	80	36
Haemoglobin (g/100 ml.)	16·2	17·1
Total protein (g/100 ml.)	6·1	6·7
Fasting urinary vitamin C (mg/h)	0·7	0·4
Fasting urinary thiamine (mg/h)	3·0	3·0
Fasting urinary riboflavin (mg/h)	58	55
Urinary N-methylnicotinamide (mg/h, fasting)	3·0	5·0

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findings in our pemmican trial were confirmed by Consolazio & Forbes (1946) and lend strength to our observations that pemmican should not be used as a ration for troops. We also made a thorough search of the literature on Polar explorations and found no authentic examples of exploring parties thriving when pemmican was the sole, or major, component of their rations. It is conceivable that consumption of pemmican as the main source of food by Polar explorers may have hastened the appearance of scurvy in them, not only because ascorbic acid was absent from such diets, but also because the metabolic disturbance it produces may consume body stores of ascorbic acid at a more rapid rate than usual.

The fifty men of the Musk Ox Expedition travelled in ski-mobiles, and were supplied with food and fuel by air-drop. Plasma and urinary ascorbic-acid values at Fort Churchill, Manitoba (December 1945, temperature −40°F.) fell within the normal range for North American troops. We examined them again in April 1946 at the time of the spring break-up after they had moved rapidly from the cold of the Great Bear Lake (temperature −10°F.) to the comparative warmth of Fort Nelson, British Columbia (temperature 38°F.). Although there was no change in the plasma level of ascorbic acid, urinary output of the vitamin was found to

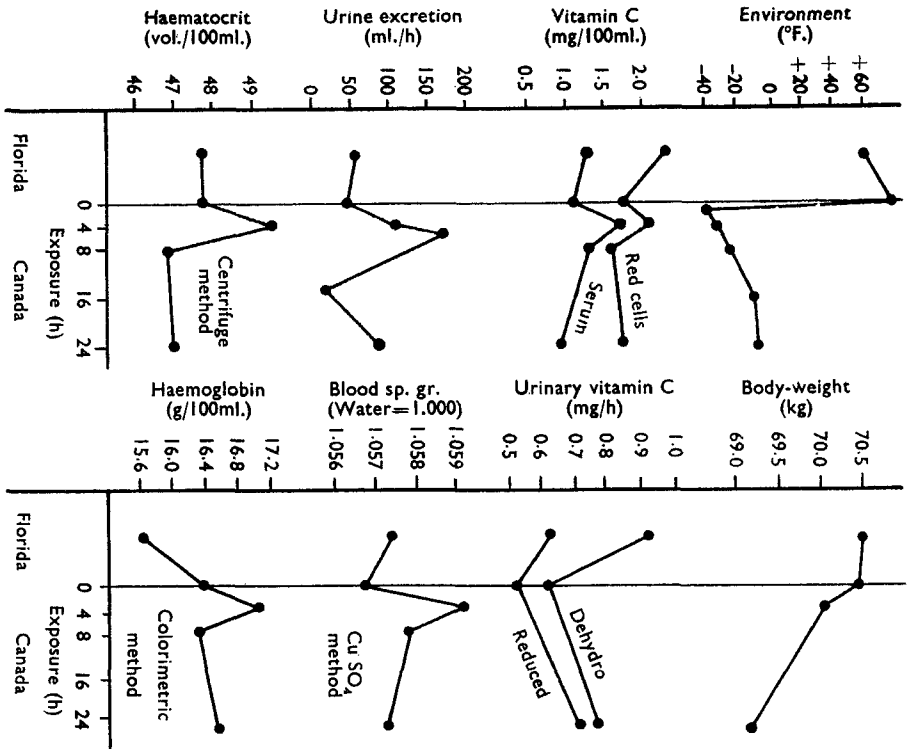

Fig. 3. Effects of acute exposure to cold in men acclimatized to heat (average data for 30 men). Note:
1. Diuresis associated with drop in weight and haemoconcentration, i.e. increase in plasma specific gravity, haematocrit and haemoglobulin level.
2. Transitory alterations in vitamin C metabolism are related to the cold diuresis.

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be reduced at Fort Nelson; we interpreted this as being due to a 50°F. rise in temperature and 'acclimatization to heat' (Fig. 2).

In the soldiers exposed suddenly to bitter cold in bivouacs at Camp Shilo (temperature −40°F.) we found, on the 1st day, a diminution of ascorbic-acid levels in the blood with an increase in the urine output of the vitamin. This occurred coincidently with a cold diuresis of urine, which manifested itself both clinically and biochemically (Fig. 3). Thereafter, plasma ascorbic-acid levels and daily urinary excretion of the vitamin returned to the Florida values (Fig. 2). The serum total ascorbic acid and similarly the whole-blood total ascorbic-acid level fell slightly between Florida and Shilo measurements, rose sharply during the 4 h period of exposure to cold, fell sharply by 8 h of exposure, remained low for the first 48 h, then returned to and remained at approximately Florida levels throughout the rest of the bivouac period and the recovery period. The urinary excretion of ascorbic acid (total, reduced and, by difference, dehydroascorbic) was measured in daily fasting-hour urine samples. The excretions of total, reduced, and dehydroascorbic acid (mg/h) during the Florida period were relatively constant. During the bivouac period these three substances were excreted steadily at Florida levels by those on normal rations and at increasingly high levels by those on experimental rations—the total amounts of ascorbic acid excreted in the 12 bivouac days were roughly proportional to the vitamin C intakes in the rations. Calculation of metabolic balances for ascorbic acid showed the men to be in balance with a daily intake of from 30 to 40 mg of vitamin C (Bly *et al.* 1950).

None of these three field studies, nor the laboratory studies made by Glickman, Keeton, Mitchell & Fahnestock (1946) or by Stein, Eliot & Bader (1948–9) indicate any remarkable change in ascorbic-acid metabolism in man due to exposure to cold. Moreover, the stress of cold, though it seems to stimulate adrenal activity in the rat does not seem to affect, significantly or consistently, the output of adrenal hormone in man (Stein, Bader, Eliot & Bass, 1949; Anonymous, 1948). It is true that during the Shilo investigation we believed that cold had stimulated adrenocortical activity in some of the men but we have since recognized that many things besides cortical activity may cause eosinopenia (Kark & Muehrcke, 1952; Best, Muehrcke & Kark, 1952; Best, Kark, Muehrcke & Samter, 1953) and change uric acid : creatinine ratios (Taussky, Swan & Schorr, 1951).

Adrenal activity in scurvy

Even though present data indicate that exposure to cold does not seem to stimulate the adrenal cortex in man, it is quite likely that new techniques may prove this to be wrong. The precipitation of scurvy in Arctic explorers could then be explained on the basis of the work of Sayers & Sayers (1949). That is, we could speculate that explorers, stressed by cold, used up their body stores of ascorbic acid to supply the adrenal gland with sufficient vitamin C to convert cholesterol to adrenal hormones. Moreover, if the adrenal gland needs to draw large amounts of ascorbic acid from body stores to function properly, we could expect little or no response by the gland to stimulation by corticotrophin in patients whose bodily stores of

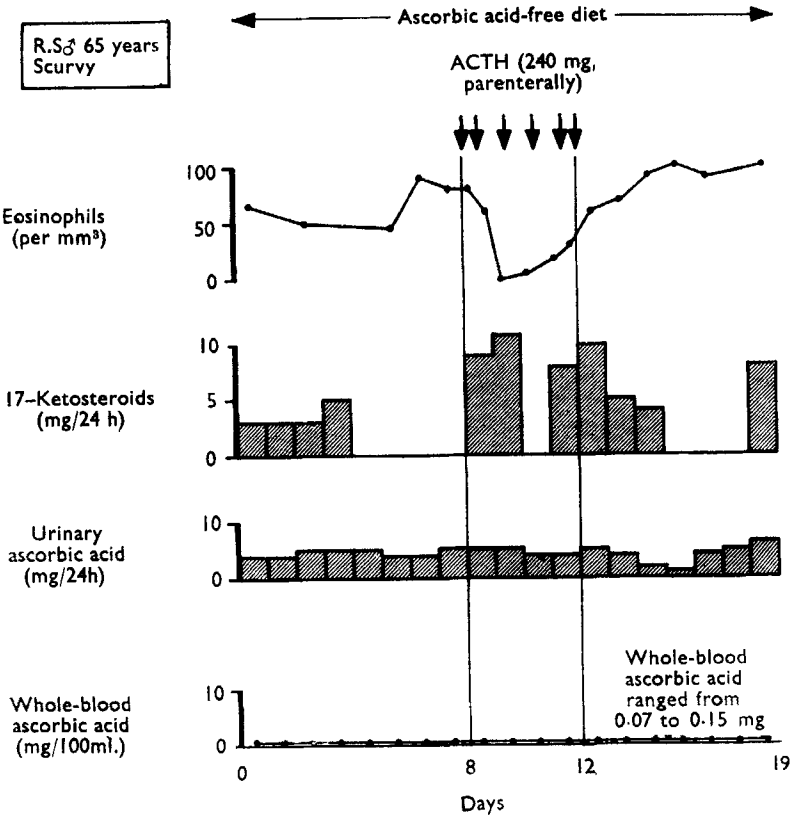

Fig. 4. Effects of parenteral injection of ACTH in patient R.S., aged 65, an alcoholic widower ill with scurvy. He subsisted on an ascorbic acid-free diet during the study. Note: drop in eosinophils and increased excretion of 17-ketosteriods with rebound after ACTH injections were stopped. There is no change in urinary or whole-blood vitamin C levels.

ascorbic acid were depleted. That this is not the case is shown in Fig. 4, which describes a study of R.S., aged 65 years. He was a lonely and retired widower living in Chicago, who despised vegetables and fruit and solaced his old age with whisky. He came to the hospital complaining of bleeding gums and bruises. Physical examination revealed full-blown scurvy and clinical and laboratory studies confirmed the diagnosis. He was, therefore, admitted to the metabolic unit where he lived on a diet that contained no ascorbic acid. After a suitable control period, 240 units of corticotrophin gel were injected intramuscularly over a period of 3 days. This caused a drop in eosinophils and an increase in adrenocortical activity with no change in serum or urinary ascorbic acid. When the corticotrophin injections were stopped, there was a rebound rise in eosinophils and a fall in ketosteroids. A second patient, P.T., ill with scurvy, also responded in a normal manner to injection of corticotrophin (Kark, Chapman & Consolazio, 1952). Beck, Browne & Mackenzie (1951), Gardiner (1953), and Eisenstein (1953) have also made similar observations on urinary hormone excretion and eosinophil counts in patients ill with scurvy who were tested with corticotrophin. Treager, Gabuzda, Zamencheck

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& Davidson (1951) studied five patients who had clinical and laboratory evidence of scurvy. In these five individuals the response to corticotrophin (as measured by eosinophil counts) was normal and was not affected by repletion of ascorbic acid.

Experimental studies on guinea-pigs and monkeys confirm and extend these observations in man. Clayton & Prunty (1951) and Nadel & Schneider (1951) found an increased excretion of urinary 17-ketosteroids, or urinary formaldehydogenic substances by scorbutic guinea-pigs, and Long (1947) noted that the adrenals of scorbutic guinea-pigs could respond normally to stimulation with corticotrophin. Stewart, Salmon & May (1952) studied the eosinophils, urinary 17-ketosteroid output and the ascorbic-acid content of the adrenal glands in eighteen monkeys in whom scurvy or ascorbic-acid deficiency was produced by a diet completely free of ascorbic acid. The data were compared with observations on control animals, some of whom had had their adrenal glands removed. In the deficient or scorbutic monkeys the ascorbic acid in the adrenals—as in other tissues—fell to low levels (i.e. from 50 to 3 mg/100 g adrenal gland). Despite this wasting of tissue and glandular ascorbic acid, the 17-ketosteroid output remained normal and even increased in some of the animals. Whenever the scorbutic animals were stimulated with corticotrophin there was a marked increase in 17-ketosteroid excretion.

These experiments on animals and man demonstrate quite clearly that the adrenal cortex functions actively during scurvy or severe ascorbic-acid depletion and responds in a normal manner to repeated stimuli by corticotrophin. Thus, the adrenal gland cannot consume or waste much ascorbic acid in the synthesis of cortical hormone. Its activity in the cold cannot be a cause of scurvy in explorers, unless some other mechanism exists whereby excess circulating adrenal hormones either increase the utilization of, or loss of, ascorbic acid.

Effects of corticotrophin, adrenal steroids and adrenal activity on excretion of ascorbic acid

Both Beck *et al.* (1951) and my colleagues and myself (Kark, Chapman & Consolazio, 1952, 1953) have reported that following injection of corticotrophin there is increased output of urinary ascorbic acid in man. Fig. 5 shows the effect of injecting corticotrophin on urinary excretion of ascorbic acid in three healthy men. The rise in ascorbic acid when the corticotrophin was injected and the rebound some days after withdrawal of corticotrophin suggest strongly that the ascorbic-acid excretion is related to adrenal activity and is not a direct effect of the pituitary hormone on ascorbic-acid metabolism. Since patients with Addison's disease (Kark, Chapman & Consolazio, 1953; Beck *et al.* 1951) do not excrete more ascorbic acid than usual when corticotrophin is injected into them, it seems more than likely that adrenal activity is responsible for increasing ascorbic-acid excretion. Yet this explanation is not entirely satisfactory because we have noted that the diuresis does not appear constantly in people who are unsaturated with respect to vitamin C. In both our data and in the charts published by Beck *et al.* (1951) we can find

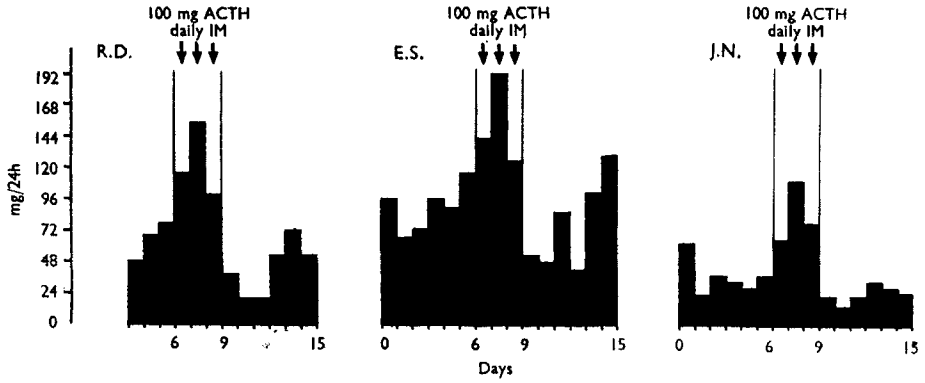

Fig. 5. Effect of intramuscular administration of ACTH on the urinary excretion of total ascorbic acid in three healthy young men, R.D., E.S., and J.N., who were saturated with ascorbic acid at the time of injection. Note rebound drop in excretion after ACTH administration was stopped. IM, intramuscularly.

a peak excretion of ascorbic acid after a few days of corticotrophin therapy and thereafter in many patients there is a tapering off of the diuretic effect. During corticotrophin therapy balance studies of food, urine and stool ascorbic acid were made. In our studies we found that, despite a large increase in urinary total ascorbic acid, the balances remained positive. Similar effects were seen when cortisone was given intramuscularly (Chapman, Kark, Keeton, Calloway, Consolazio, Weigend, Dyniewicz & Kyle, 1952) (Fig. 6). In this regard we should note that in six out of nine patients treated with cortisone, Beck *et al.* (1951) observed no effect on ascorbic-acid metabolism.

We do not know, as yet, exactly how adrenal activity increases the output of urinary total ascorbic acid. C. P. Stewart and his colleagues (Stewart, Horn & Robson, 1953) have found that administration of corticotrophin to man causes a rise in plasma levels of total and reduced ascorbic acid and a diminution of dehydro-ascorbic acid. Studies of the renal clearance of ascorbic acid in man by the method of Homer Smith are being carried out in my laboratory by my colleagues (Schoenberger, Dyniewicz, Rix, Nesby & Kark, 1953). Our observations confirm the findings of Stewart *et al.* (1953), for our data show that plasma reduced ascorbic acid increased by 11% to 28% after injection of corticotrophin. However, renal clearance data are as yet incomplete. For example, in two subjects increases in tubular reabsorption of total ascorbic acid of 65% and 83% were found! So far other renal functions such as glomerular filtration rate and effective renal plasma-flow showed insignificant changes.

By now many thousands, perhaps hundreds of thousands, of patients have been treated for long periods of time with corticotrophin or synthetic adrenal hormones. The only reports of scurvy appearing in patients after prolonged corticotrophin administration were made by Holley & McLester (1951) and by Stefanini & Rosenthal (1950). It is quite possible that scurvy was precipitated in their five patients as a result of excess renal loss of ascorbic acid but in view of our observations on

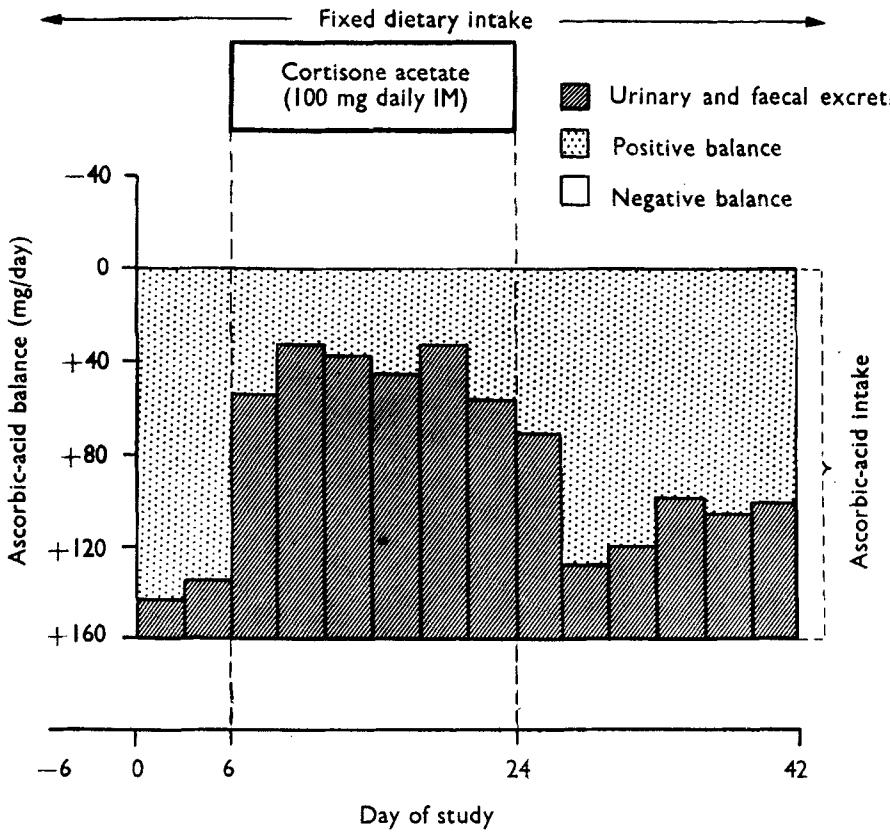

Fig. 6. Effects of daily intramuscular injection of 100 mg cortisone acetate on total ascorbic-acid balance in J.N., ill with Laennec's cirrhosis and living on a fixed dietary intake in a metabolic unit. The data in this figure are arranged according to the scheme of Dr Fuller Albright. Ascorbic-acid intake is charted on a reverse scale downwards from the baseline; the faecal and urinary excretions are then measured from the intake line upwards towards the base-line. If the output (faeces and urine) exceeds the intake, the final level will be above the base-line; if it does not, the final level will be below the base-line. Thus, a positive balance will be indicated by a speckled area below the base-line; a negative balance by a clear area above the base-line. Note the increase in output of ascorbic acid during therapy with cortisone. However, the ascorbic-acid balance was positive throughout the study. IM, intramuscularly.

ascorbic-acid balances it is unlikely that renal loss due to corticotrophin could have been the sole cause of the deficiency.

Postoperative metabolism of adrenal and ascorbic acid

It is also possible that stress or adrenal activity in man may increase utilization or storage of ascorbic acid in the tissues. Levenson *et al.* (1946) and Lund *et al.* (1947) and Andrae & Browne (1946) were the first to demonstrate retention of ascorbic acid in patients after surgical operations. Later, adrenocortical activity (Browne *et al.* 1944; Forbes, Donaldson, Reifenstein & Albright, 1947; Dao & Shank, 1951) was found to accompany the acute postoperative phase of elective operations. The data presented above indicate clearly that the postoperative

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retention of ascorbic acid described by Levenson *et al.* (1946) and Lund *et al.* (1947) could not be related to increased consumption of vitamin C by the adrenal gland.

In order to test the hypothesis that adrenal activity might increase the demand for, and utilization of, ascorbic acid in the patients' tissues we repeated Levenson and Lund's experiments but made one change, that is, we injected corticotrophin into the patients during the immediate postoperative period of study to stimulate adrenocortical activity. Eighteen patients have been studied to date in cooperation with Professor Freemont Chandler (Kark, Chandler, Lemmens, Lewis & Nesby, 1953). They were chosen for observation because of serious orthopaedic disease which could be corrected only by rather prolonged and traumatic operations. Two typical studies are shown in Fig. 7. They show quite clearly that administration of rather small amounts of corticotrophin in the postoperative period not only stimulated the adrenal cortex but also caused a diuresis of ascorbic acid similar to

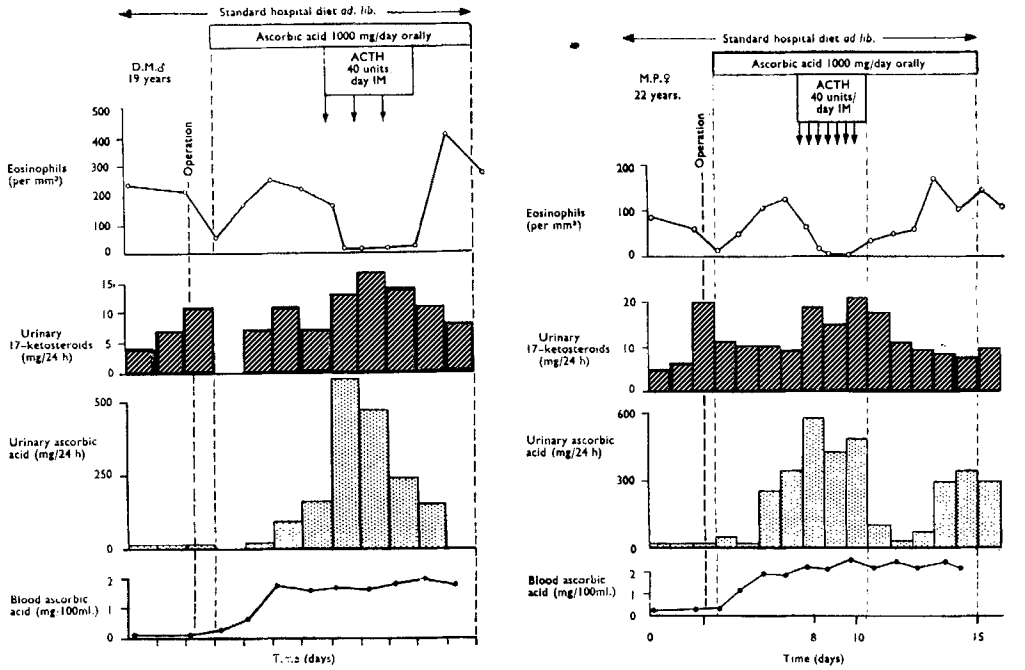

Fig. 7. Effects of injection of ACTH on eosinophil counts, urinary 17-ketosteroid excretions and whole-blood levels and urinary excretion of total ascorbic acid in patient M.P. (F) before and after operation for a fractured femur and pelvis, and in D.M. (M.) before and after operation for fracture of the head of the femur. The hospital diet was supplemented daily with 1 g ascorbic acid after the operation. IM, intramuscularly.

that produced in healthy undamaged individuals stimulated by corticotrophin. These data clearly indicated that adrenal activity was not responsible for postoperative ascorbic-acid retention and confirm similar observations made by Dao & Shank (1951). The best explanation for postoperative retention of ascorbic acid is given by Lauber & Rosenfeld (1938) and by Bartlett, Jones & Ryan (1942*a*,*b*) They

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studied the ascorbic-acid content of healing wounds and scars produced experimentally in healthy and in scorbutic guinea-pigs. They showed that ascorbic acid was mobilized from the tissues and organs of the body and selectively concentrated in the traumatized area. Whether an excess of ascorbic acid does any good there is doubtful and must remain a subject for speculation until further data are at hand.

Recapitulation

Because of the high incidence of scurvy in Polar explorers and seamen, exposed to cold and the hard life and stresses of travel, there has been handed down to us a tradition that scurvy can be precipitated by stress. Our generation inclines to the belief that stress stimulates adrenocortical activity and the opinion has been expressed that this glandular excitation destroys or consumes vitamin C. From this hypothesis some corrolaries have been formulated. These postulate that ascorbic-acid requirements in man are increased as a result of a variety of bodily insults, including exposure to cold, and they assume that adrenal activity will be sharply reduced when ascorbic-acid supplies are curtailed. The evidence presented here, not only from human experiments, would indicate that, as far as man is concerned, there is no evidence that the stress of cold increases significantly ascorbic-acid requirements; there is no evidence that adrenal function is curtailed as a result of ascorbic-acid deficiency; and there is no evidence that the ascorbic-acid retention seen after operation is due to adrenal activity.

A natural experiment in man gives us convincing evidence that adrenocortical activity does not increase ascorbic-acid requirements to any significant degree, at least from a practical point of view. We have made a search of the literature and have not found any reports of the coexistence of scurvy and Cushing's syndrome. None of our patients with Cushing's syndrome have ever shown any clinical or laboratory evidence of scurvy, nor have blood or urine studies indicated depletion of ascorbic-acid stores. The patients eat the usual North American diet which supplies ample vitamin C, and biochemical analysis of urine and blood reflects their intake. A questionnaire was sent to a number of endocrinologists but none of them had seen scurvy in patients with Cushing's syndrome. The Clinical Sections on Endocrinology at the Mayo Clinic have had the largest experience with this disease and have seen over 100 patients with Cushing's syndrome. Dr E. H. Rynearson (1953), reporting on behalf of his colleagues, writes as follows: 'First, we have not observed frank scurvy in patients with Cushing's syndrome; second, we have administered large doses of ascorbic acid to a number of patients with Cushing's syndrome without any apparent modification of the condition; and third, a few determinations of blood ascorbic acid have not revealed any significant abnormalities'.

In this age of synthetic vitamins it is popular to flood our patients with all sorts of vitamins. The observations reported here on the effects of cold and cortical activity on ascorbic-acid metabolism indicate that 'enough is as good as a feast'.

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Aminoaciduria in Infancy and Ascorbic-acid Deficiency*

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It has been reported from various laboratories that free amino-acids are found in the urine of newborn infants, in relatively larger amounts than in urines of children or adults, and even more so in prematurity. According to Dent's major contribution to the subject of aminoaciduria in general, a distinction should be made between aminoaciduria resulting from a raised blood level ('overflow mechanism') and from a defect of kidney function ('renal mechanism') (Crumpler, Dent, Harris, & Westall, 1951). He has also recognized various patterns of aminoaciduria in adults, involving eventually genetic factors.

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