

The Pathophysiology of Scurvy*

A Report of Seven Cases

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SCURVY is seen rarely today, and few clinical reviews of scurvy have appeared in the literature in the past twenty years [7-6]. However, patients with scurvy still are found in most city and county hospitals. An unusual opportunity to observe seven patients admitted to the Tufts (I and III) Medical Service at the Boston City Hospital occurred during the year ending May 1961. These seven patients form the basis of this report.

Moderate anemia commonly is found in patients with scurvy and is often megaloblastic in nature [7-17]. The clinical features of the seven patients observed and the pathophysiology of the features of scurvy and the associated anemia will be discussed.

CASE REPORTS

CASE I. A sixty-nine year old white single man (F. P., No. 1711142) was brought to the hospital on June 24, 1960, in a debilitated state after having been found in an attic by the police. He complained of having had dyspnea on exertion and weakness for two months and of red spots on the extremities and two episodes of severe epistaxis over the same period. He had lost approximately 12 pounds during the preceding six months. He was not an alcoholic. For several years his diet had consisted of soups, cereal, bread and butter because he could not afford to purchase fruit, meat or vegetables.

The patient was pale, slightly icteric and showed evidence of weight loss. Extensive petechiae, perifollicular hemorrhages with hyperkeratoses and "corkscrew hairs" were noted on the abdomen, chest and extensor surfaces of both arms and legs. Small reddish blue masses situated at the interdental papillae of the lower set of teeth were seen, and the teeth were in an advanced state of decay. He had extensive ecchymoses over the posterior surface of the left thigh and calf. There was no evidence of cardiac

enlargement or failure; the blood pressure was 100/60 mm. Hg, and the pulse 84 beats per minute. The results of a capillary fragility test were negative.

The hematocrit was 23 per cent, reticulocyte count 4.2 per cent and white blood cell count 7,200 per cu. mm., with a normal differential count. The platelets were normal, and the red blood cells were normochromic normocytic with marked polychromasia. The bone marrow showed normoblastic maturation with erythroid hyperplasia. The serum bilirubin was 3.3 mg. per cent, stools were negative for occult blood on three occasions; liver function test results were normal and the urine was negative for bile and red blood cells but positive for urobilinogen (1:32).

During the patient's period in the hospital he became disoriented and confused, with neurologic signs consistent with thrombosis of the middle cerebral artery. He was given ascorbic acid and 2 units of whole blood and was transferred to the Neurological Service twenty-four hours after admission. The patient made an uneventful recovery after being treated with a "house diet" and supplemental multiple vitamins. He was discharged six weeks later, much improved with only a slight residual hemiparesis.

CASE II. A sixty-six year old white man (C. S., No. 1714116) was admitted to the hospital on August 3, 1960, with a history of painful bleeding gums and red spots on his arms and legs of two months' duration. He had noted progressive weakness and fatigue for eight months and watery diarrhea for six weeks prior to hospitalization. The patient was not an alcoholic. His dietary intake was limited to coffee, doughnuts, frankfurters and hamburgers.

He appeared chronically ill and pale, with ecchymoses bilaterally over the malar regions of the face, right arm and popliteal fossae. Purpuric areas and perifollicular hemorrhages were noted, accompanied by many broken "corkscrew hairs" over the anterior portion of the chest and legs. The teeth were markedly

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decayed, with reddish blue friable masses in the interdental papillae. Pneumonic signs were evident in the upper left lung, and a roentgenogram revealed diffuse infiltration of the upper lobe of the left lung consistent with tuberculosis. The blood pressure was 110/55 mm. Hg and pulse rate 110 beats per minute. There was no evidence of cardiac enlargement or failure. The results of a capillary fragility test were positive.

The urine was orange in color but negative for bile and red blood cells. The hematocrit was 18 per cent; white blood cell count 3,000 per cu. mm., with 19 per cent monocytes; reticulocyte count 0.1 per cent; platelets were adequate, and the red blood cells were hypochromic and normocytic. The bone marrow was normoblastic. Stool was negative for occult blood on three occasions. The serum bilirubin was 2.2 mg. per cent. Acid-fast bacilli were seen in the sputum. The prothrombin time was normal. The patient was transferred to a sanatorium one day after admission, where he was treated with isoniazid, streptomycin and supplemental vitamins. He responded to medical therapy and was asymptomatic one year later.

CASE III. A fifty-five year old slightly demented white woman (I. F., No. 1731540) was admitted to the hospital on February 18, 1961, with symptoms of osteoarthritis of her right knee. She also complained of weakness, lassitude, anorexia and diarrhea for several weeks prior to admission.

The patient had ecchymoses of the arms, chest, abdomen and thighs. There were no changes in her gums or hair, and perifollicular hemorrhages were not present. The blood pressure was 130/70 mm. Hg and pulse rate 84 beats per minute. There was no evidence of cardiac enlargement. The results of a capillary fragility test were negative.

The urine was yellow in color and negative for red blood cells. Hematocrit was 32 per cent; white blood cell count 5,200 per cu. mm., with a normal differential; platelets were normal; the red blood cells were normochromic with macro-ovalocytes and hypersegmented polymorphonuclear leukocytes. Reticulocyte count was 0.3 per cent. The bone marrow was megaloblastic. Three stools were examined for occult blood and were negative. The prothrombin time was normal.

The patient's condition improved on a "house diet" with vitamin supplements, and she was discharged much improved one month later.

CASE IV. A sixty year old white single man (C. R., No. 1733067) was admitted to the hospital on March 6, 1961, with profound weakness and syncope. He had noted "red spots" on his arms and legs for several months and a painless swelling with discoloration of the right leg for two weeks. He also complained of having experienced weakness, fatigue and dizzy spells for several months. He was not an

alcoholic. His dietary intake consisted of coffee, doughnuts, frankfurters and hamburgers, and he had not eaten any fruit or vegetables during the past year.

He was pale and showed evidence of weight loss. Petechiae, perifollicular hemorrhages and broken, brittle "corkscrew hairs" were noted over the anterior portion of the chest and extensor surfaces of the extremities. Large ecchymoses were present over the posterior aspects of both thighs. The gums were hypertrophic with bluish red lesions in the interdental papillae, and the teeth were carious. There was no cardiac enlargement or failure; the blood pressure was 110/60 mm. Hg and the pulse rate 80 beats per minute. The results of a capillary fragility test were negative.

The urine was orange in color, urobilinogen was present in a dilution of 1:16, and bile and red blood cells were absent. The hematocrit was 16 per cent; white blood cell count 5,500 per cu. mm., with a normal differential; reticulocyte count 5.5 per cent. The red blood cells were normochromic, normo-macrocytic with macro-ovalocytes and hypersegmented polymorphonuclear leukocytes. The platelets were normal. Three stools were negative for occult blood, the serum bilirubin was 1.6 mg. per cent and liver function test results were normal. The initial bone marrow aspiration showed giant metamyelocytes and many early red blood cell precursors. A subsequent examination showed the bone marrow to be overtly megaloblastic.

The patient responded to therapy with ascorbic acid, folic acid and a high calorie diet. He soon became asymptomatic and was discharged six weeks after admission. (This case has been reported in detail elsewhere [72].)

CASE V. A fifty-five year old white man (J. C., No. 173711) a chronic alcoholic, was admitted to the hospital on April 27, 1961, with confusion, weakness and postalcoholic seizures. He was cachectic and poorly nourished. Perifollicular hemorrhages, petechiae and hyperkeratosis were seen on the extensor surfaces of all limbs, more marked on the lower extremities. The patient dated the onset of the "red spots" to two months prior to admission. Large ecchymotic areas were not seen, but purpuric areas were noted on the skin of the thighs, knees, legs and forearms. The gums were pale and edematous, with ecchymosis about the margins of a few remaining carious teeth. The heart was not enlarged clinically. The blood pressure was 104/70 mm. Hg and pulse rate 80 beats per minute. There was no evidence of heart failure. The results of a capillary fragility test were negative.

The urine was yellow and negative for red blood cells. The hematocrit was 36 per cent; white blood cell count 6,400 per cu. mm., with a normal differential; and reticulocytes 0.2 per cent. The red blood cells were normochromic with macro-ovalocytes and hypersegmented polymorphonuclear leukocytes; the

platelets were normal. The bone marrow aspiration showed giant metamyelocytes, erythroid hyperplasia and megaloblastic changes in the red blood cell series. Three stools were negative for occult blood.

Two days after admission hypotension developed suddenly and the patient died sixteen hours later, despite the administration of ascorbic acid and vasopressor agents. In addition to the clinical findings, postmortem examination revealed cardiomegaly, congestion of the lungs, liver and spleen, and a normal central nervous system. Superficial mildly hemorrhagic gastritis was found also. The immediate cause of death was not readily apparent.

CASE VI. A seventy-three year old, single, non-alcoholic white man (J. B., No. 1739527) was admitted to the hospital on May 17, 1961, complaining of a cough productive of yellowish sputum. He had also noted increasing weakness, fatigue and weight loss during the previous six months. Anorexia was an outstanding symptom. His food intake was limited to coffee in the morning and a single hamburger for supper.

He was cyanotic and dyspneic, with clinical and roentgenologic signs of extensive bilateral bronchopneumonia. He had perifollicular hemorrhages with hyperkeratosis and broken "corkscrew hairs" on the chest, lower part of the abdomen and arms. There were no ecchymoses. The rectal temperature was 101.8°F., blood pressure 110/60 mm. Hg and pulse 78 beats per minute. There was not any evidence of cardiac failure or enlargement. The results of a capillary fragility test were negative.

The urine was dark yellow in color and was negative for red blood cells. The hematocrit was 36 per cent, white blood cell count 6,100 per cu. mm. with a normal differential and reticulocyte count 2.8 per cent. The platelets were normal, and the red blood cells were normocytic normochromic with hypersegmented polymorphonuclear leukocytes. Stools were negative for occult blood on three occasions. A bone marrow aspiration was not obtained.

The patient was treated with ascorbic acid, multiple vitamins and a "house diet." The sputum revealed *Diplococcus pneumoniae*, and a course of penicillin therapy was begun. The patient rapidly improved, and he was discharged asymptomatic on the fourteenth hospital day.

CASE VII. A seventy-seven year old white, single, non-alcoholic man (H. C., No. 1740025) was admitted to the hospital on May 23, 1961, with a history of progressive weakness, fatigue, dizziness, anorexia and weight loss of three months' duration. His presenting complaint was painful swelling and discoloration over the right leg. He had also noted red spots on the extremities for one month. His dietary intake consisted of toast, coffee, doughnuts and hamburgers, and he could not recall having eaten fresh

fruits or vegetables for the past twelve months.

He was alert and oriented; there was marked pallor of the skin and mucous membranes. There were perifollicular hemorrhages, "corkscrew hairs" and hyperkeratosis of the hair follicles on the extensor surfaces of the left arm, hips, anterior portion of the chest and abdomen. Massive ecchymosis of the right thigh was present. He was edentulous, and the gums were normal. There was no evidence of cardiac enlargement or failure. The blood pressure was 115/70 mm. Hg and the pulse rate 88 beats per minute. The results of a capillary fragility test were positive.

The urine was light brown in color, positive for urobilinogen in a 1:64 dilution and negative for bile and red blood cells. Serum bilirubin was 2.4 mg. per cent, and liver function test results were normal. The hematocrit was nineteen per cent; white blood cell count 3,500 per cu. mm., with a normal differential; and reticulocytes 4 per cent. The platelets were normal, and the red blood cells were normochromic with macro-ovalocytes and hypersegmented polymorphonuclear leukocytes. Bone marrow aspiration revealed giant metamyelocytes and increased erythroid activity with megaloblastic changes.

During the first three days the patient's hematocrit fell, the reticulocyte count rose and the hematoma in the right thigh enlarged. Then the patient was given ascorbic acid intravenously; this therapy was accompanied by a stable hematocrit and a falling reticulocyte count. On the ninth hospital day bronchopneumonia developed and the patient suddenly went into peripheral vascular collapse. He was treated with antibiotics, vasopressor agents and whole blood. Despite this therapy, the patient remained in shock. He died on the fourteenth hospital day. Autopsy was not performed.

SUMMARY OF CLINICAL AND LABORATORY DATA

The average age of the seven patients was sixty-five years (range: fifty-five to seventy-seven). Six of the seven were single men or widowers who lived alone. All the patients gave a history of poor dietary intake, none could recall having eaten fresh fruit or vegetables for at least six months prior to admission. In only two patients (Cases III and V) could the inadequate diet be explained on the basis of alcoholism or dementia; the remainder ate poorly because of limited funds.

All the patients complained of severe weakness and fatigue. Most were anorectic, had marked weight loss and noted "red spots" on the arms and legs. A huge ecchymotic area on a lower limb was the outstanding presenting symptom in three instances (Cases II, IV and VII). The other less frequent symptoms were

TABLE I
SUMMARY OF THE PRESENTING SYMPTOMS

| Case No. | Weakness and Lassitude | Weight Loss | Anorexia | "Red Spots" on Arms and Legs | Swelling and Ecchymosis of Extremities | Syncope or Dizzy Spells | Painful Gums |
|----------|------------------------|-------------|----------|------------------------------|--|-------------------------|--------------|
| I | + | + | + | + | + | 0 | 0 |
| II | + | + | + | + | + | 0 | + |
| III | + | 0 | + | 0 | + | 0 | 0 |
| IV | + | + | 0 | + | + | + | 0 |
| V | + | + | 0 | + | 0 | 0 | 0 |
| VI | + | + | + | + | 0 | 0 | 0 |
| VII | + | + | + | + | + | + | 0 |

NOTE: + = present; 0 = absent.

TABLE II
SUMMARY OF THE PHYSICAL FINDINGS ON ADMISSION

| Case No. | Pulse (beats/min.) | Blood Pressure (mm. Hg) | "Corkscrew Hairs" | Peri-follicular Hemorrhages | Hyperkeratosis of Hair Follicles | Gum Changes | Ecchymoses | Capillary Fragility Test | Infection |
|----------|--------------------|-------------------------|-------------------|-----------------------------|----------------------------------|-------------|------------|--------------------------|--------------|
| I | 84 | 100/60 | + | + | + | + | + | 0 | 0 |
| II | 110 | 110/55 | + | + | + | + | + | + | Tuberculosis |
| III | 84 | 130/70 | 0 | 0 | 0 | 0 | + | 0 | 0 |
| IV | 80 | 110/60 | + | + | + | + | + | 0 | 0 |
| V | 80 | 104/70 | + | + | + | + | 0 | 0 | 0 |
| VI | 78 | 110/60 | + | + | + | Edentia | 0 | 0 | Pneumonia |
| VII | 88 | 115/70 | + | + | + | Edentia | + | + | 0 |

syncope, painful gums, epistaxis, dyspnea and diarrhea. (Table I.)

The average blood pressure was 110 mm. Hg systolic (range: 100 to 130 mm. Hg) and 65 mm. Hg diastolic (range: 55 to 70 mm. Hg). Despite the "low" average blood pressure for patients in this age group, tachycardia was noted in only one patient, and in no instance was there evidence of cardiac failure. Hemorrhages and hyperkeratosis of hair follicles were seen in all but one of the patients; "corkscrew," brittle, broken hairs commonly were found on the extensor surface of the extremities and the anterior chest wall.

The ecchymoses varied in size from several centimeters to massive involvement of an entire limb and commonly were found in the area of the hamstring muscles and popliteal fossae.

The gum changes consisted of small reddish blue, shiny, friable, tumor-like masses situated in the interdental papillae and were more

pronounced about the more carious teeth. The two edentulous patients had normal gums. (Table II.)

Anemia was found in all seven patients and was severe in four. Tissue bleeding was a factor common to all. The white blood cell counts tended to be in the low normal range (5,200 to 7,200 per cu. mm.) and were abnormally low in two patients (3,000 and 3,500 per cu. mm.). In Case VI extensive pneumococcal pneumonia was unaccompanied by leukocytosis. (Table III.)

Results of repeated stool examinations for occult blood and microscopic examination of urine for red blood cells were negative. Increased serum bilirubin was associated with urine which contained no bile but increased amounts of urobilinogen. The results of liver function tests performed were within normal limits. (Table IV.)

Plasma ascorbic acid concentrations were below 0.2 mg. per cent in all cases, and it has

TABLE III
SUMMARY OF HEMATOLOGICAL DATA

| Case No. | Hematocrit (%) | White Blood Cell Count (cu. mm.) | Reticulocyte Count (%) | Platelets by Smear | Normochromic Normocytic Smear | Hypochromic Normocytic Smear | Normochromic Normomaerocytic Smear with Macro-ovalocytes | Per cent Hypersegmented Polymorphonuclear Leukocytes per 100 Polymorphonuclear Leukocytes | Normoblastic Bone Marrow | Megaloblastic Bone Marrow |
|----------|----------------|----------------------------------|------------------------|--------------------|-------------------------------|------------------------------|--|---|--------------------------|---------------------------|
| I | 23 | 7,200 | 4.2 | Normal | + | ... | ... | 0 | + | ... |
| II | 18 | 3,000 | 0.1 | Normal | ... | + | ... | 0 | + | ... |
| III | 32 | 5,200 | 0.3 | Normal | ... | ... | + | 42 | ... | + |
| IV | 16 | 5,500 | 5.5 | Normal | ... | ... | + | 42 | ... | + |
| V | 36 | 6,400 | 0.2 | Normal | ... | ... | + | 25 | ... | + |
| VI | 36 | 6,100 | 2.8 | Normal | + | ... | ... | 3 | Not performed | Not performed |
| VII | 19 | 3,500 | 4.0 | Normal | ... | ... | + | 6 | ... | + |

TABLE IV
BIOCHEMICAL DATA

| Case No. | Plasma Ascorbic Acid (mg. %)* | Serum Folic Acid ($\mu\text{mg.}/\text{ml.}$) † | Serum Vitamin B ₁₂ Levels ($\mu\text{mg.}/\text{ml.}$) † | Serum Iron Level ($\mu\text{g. %}$) ‡ | Serum Bilirubin (mg. %) | Urine Urobilinogen | Stool Guaiac Test for Occult Blood |
|----------|-------------------------------|---|---|---|-------------------------|--------------------|------------------------------------|
| I | 0.03 | 5.0 | 539 | 64 | 3.3 | 1:32 | 0 |
| II | 0.00 | ... | ... | 29 | 2.2 | ... | 0 |
| III | 0.18 | 3.6 | 400 | 66 | ... | ... | 0 |
| IV | 0.12 | 1.5 | 160 | 75 | 1.6 | 1:16 | 0 |
| V | 0.05 | 1.5 | 2,027 | 174 | ... | ... | 0 |
| VI | 0.00 | ... | ... | 67 | ... | ... | 0 |
| VII | 0.05 | 2.7 | 170 | 81 | 2.4 | 1:64 | 0 |

* Plasma ascorbic acid levels estimated by Dr. J. H. Crandon [13,14] (normal 0.20 to 1.50 mg. per cent).

† Serum vitamin B₁₂ and folic acid levels were determined in the laboratory of Dr. Victor Herbert. The normal level of "folic acid" (*L. casei*) is 7 $\mu\text{g.}$ per ml.; 5 to 7 $\mu\text{g.}$ per ml. is diagnostically indeterminate, 3 to 4.9 $\mu\text{g.}$ per ml. is strongly suggestive of deficiency [77,78]. The normal range of serum vitamin B₁₂ levels (*E. gracilis*) is 200 to 900 $\mu\text{g.}$ per ml.; 100 to 200 $\mu\text{g.}$ per ml. being diagnostically indeterminate and below 100 $\mu\text{g.}$ per ml. representing deficiency.

‡ Serum iron levels were determined by the Tufts Hematology Laboratory using the method described by T. Peters et al. [19]. The normal for this laboratory is 60 to 160 $\mu\text{g.}$ per cent.

been shown that these values are indicative of a marked tissue ascorbic acid deficiency [14-16]. There were no abnormally low serum vitamin B₁₂ levels. However, the serum folic acid levels were low in the four patients with megaloblastic anemias. (Table iv.)

COMMENTS

The clinical diagnosis of scurvy is not difficult when a patient has a combination of perifollicular hemorrhages, "corkscrew hairs," hyperkeratosis of hair follicles, ecchymoses, typical gum changes and a poor dietary history. However, in one instance (Case III) the only clinical findings were generalized ecchymotic areas, and in another (Case VI), perifollicular hemorrhages

and hair changes were the only signs of scurvy. Awareness that scurvy still exists and the availability of methods for the measurement of plasma ascorbic acid concentrations will lead to the diagnosis in early or atypical cases.

Predisposing Factors. Social and economic factors determined the dietary habits in these patients. The patients lived alone in single rooms without cooking facilities and ate their meals in restaurants. The average diet was restricted to hamburgers, frankfurters, doughnuts, bread, milk and coffee because of limited funds.

The estimated vitamin content of this diet reveals only small amounts of folic acid (4 $\mu\text{g.}$) and no ascorbic acid [20,21]. There was no evi-

dence of malabsorption in any of the patients, and it appears that the low serum folic acid concentration and associated megaloblastic anemia were the result of inadequate folic acid intake.

Clinical evidence of beriberi, ariboflavinosis, pellagra, peripheral neuropathy or avitaminosis A was not found; this lack of associated vitamin deficiency may be due to suboptimal but apparently adequate amounts of the corresponding vitamins in the diet.

Despite the high incidence of alcoholism among the patients admitted to the Boston City Hospital [22], alcoholism was a factor in only one case. The complications of alcoholism necessitate frequent admission or visits to the hospital when the patients routinely are given vitamin supplements. These supplements may account for the apparent low incidence of scurvy in the alcoholic.

Symptoms and Signs. Although non-specific symptoms such as fatigue, weakness, anorexia and weight loss were common to all patients, the outstanding symptom was tissue bleeding. Some patients had bleeding into the thighs, others had "red spots" on the extremities. Only two patients complained of syncope, although relatively low blood pressure was a feature in all patients. Despite weight loss, anemia and the presence of scurvy, infection was a complicating factor in only two cases.

Tissue Bleeding. Ascorbic acid is necessary for maintenance of the integrity of ground substance. In the absence of ascorbic acid there is depolymerization of collagen with resulting defects in connective tissue [23]. In the small venules there is little muscle, and the endothelial cells are separated only by large amounts of collagen. These areas of defective collagen may allow the extravasation of blood. It also has been shown in scorbutic animals that there is diminished tone and decreased contractability of the smooth muscle in the blood vessel walls [24]. This decrease of tone associated with a defect in the connective tissue may be the explanation for the tissue bleeding in scurvy.

In this series the tissue bleeding varied from minor petechiae and perifollicular hemorrhages to severe purpura and massive ecchymoses. The petechiae characteristically occurred around the hair follicles on the extensor surfaces of the limbs, anterior chest wall and abdomen. Although most of the petechiae were perifollicular in distribution, some were not. The large ecchymoses most commonly were seen

in the dependent areas of the lower limbs. In some cases bed rest alone without ascorbic acid in the diet resulted in regression of these ecchymoses. This phenomenon has been observed in the past [1,2].

Capillary Fragility. Scurvy is characterized by spontaneous tissue bleeding, but in most patients the capillary fragility test results are negative [2,4,25]. Increased capillary fragility could not be demonstrated in experimental human scurvy even when the blood ascorbic acid content fell to zero [25]. On the other hand, positive capillary fragility test results can occur in patients who have normal or low ascorbic acid concentrations [1,4,25,26]. It had been suggested that a lack of vitamin P (flavonoids) resulted in the increased capillary fragility in scurvy, but the evidence is not conclusive [23,26-28].

In five of the seven patients the results of capillary fragility tests were negative, and in the two patients who had positive results the petechiae occurred on the extensor surface of the arms around hair follicles.

Gums and Teeth. The typical gum changes seen in scurvy are characterized by large, reddish blue, friable, tumor-like masses situated at the interdental papillae. The gums are usually diffusely hypertrophied and edematous. The only change directly associated with ascorbic acid deficiency is hemorrhage into the gums [29]. All other changes may be due to a combination of pre-existing or superimposed gingivitis and dental caries. Ascorbic acid is required for dentinogenesis, and in its absence odontoblasts produce a modified, weakened, osteodentine [29] which may lead to softening, decay and loss of teeth. In human experimental scurvy, when good oral hygiene was maintained no changes developed in the gums or teeth [25].

In this series the gum changes were limited to small bluish red masses on the interdental papillae. The gums were friable but were not spongy or hypertrophied, and markedly decayed and necrotic teeth were common. There were no changes in the gums of the edentulous patients.

Hair Changes. Follicular hyperkeratosis* appears to be the earliest sign of scurvy [4,25], and is usually associated with characteristic broken, brittle, "corkscrew hairs."

* These hyperkeratoses are similar to the changes seen in avitaminosis A [25,30,31,32], but in human experimental scurvy hyperkeratosis is accompanied by normal vitamin A concentrations and disappears soon after ascorbic acid therapy [25].

TABLE V
AVERAGE BLOOD PRESSURE RECORDINGS (MM. HG)
BEFORE AND AFTER ASCORBIC ACID THERAPY

| Case No. | Blood Pressure on Admission* | Blood Pressure Following Ascorbic Acid Therapy† |
|----------|------------------------------|---|
| I | 100/60 | 120/75 |
| II | 110/55 | 124/76 |
| IV | 110/60 | 140/80 |
| VI | 110/60 | 150/72 |

* These values are the average of at least twenty observations recorded for several days prior to the administration of ascorbic acid.

† These values represent many observations recorded one to three weeks after therapy with ascorbic acid.

Hair protein is composed of keratin, a protein containing many disulfide cross linkages. Contraction or curling of hair results when these cross linkages are broken [33]. Ascorbic acid is important for maintaining disulfide bonds in a reduced form, and in the absence of ascorbic acid the arrangement of the protein chains may be altered. This alteration may account for the abnormal hairs seen in patients with scurvy.

In this series, six of the seven patients had follicular hyperkeratosis and abnormal hairs. These changes usually were found on the anterior chest wall and extensor surfaces of the extremities, and they disappeared following the administration of ascorbic acid.

Blood Pressure. The presence of low blood pressure in patients with scurvy has been noted in the past [1,2,25]. In human experimental scurvy the low blood pressure was not due to blood loss or reduction in blood volume but rose to normal levels after treatment with ascorbic acid [25]. Although the evidence from animal experiments suggests that relative adrenal insufficiency may be responsible for this hypotension [33-37], this observation has not been substantiated in man. In this series, repeated blood pressure recordings before the administration of ascorbic acid were low. (Table v.) In the four patients followed up after treatment with ascorbic acid there was a marked rise in both systolic and diastolic blood pressure.

Hypotension and sudden death have been described in patients with scurvy [7,2] and also have been noted in scorbutic guinea pigs [24]. The arterioles of these scorbutic animals are less responsive to epinephrine than the arterioles of

normal animals. Furthermore, the scorbutic animals do not tolerate blood loss or hypotension well and are more likely to die from this combination than are normal animals. Two patients (Cases v and vii) in this series had sudden, profound hypotension, did not respond to therapy with either vasopressors or ascorbic acid and died. Postmortem examination in one (Case v) did not reveal an immediate cause of death. It may be postulated that the peripheral vascular system in these patients was less responsive to epinephrine and thus more prone to vascular collapse and shock. However, the exact nature of the shock and sudden death that occurs in patients with scurvy still remains obscure.

The Anemia of Scurvy. Moderate anemia often occurs in scurvy, although reduction in hemoglobin concentrations was not encountered in human experimental scurvy [4,25]. The anemia has been attributed to blood loss and iron deficiency [2,6,38], hemolysis (intravascular [2,6,39] and extravascular [2,40]), ascorbic acid deficiency *per se* [6,17] or folic acid deficiency [7-11,47]. These etiologic factors will be discussed with particular reference to the patients in this series.

Blood loss: Tissue bleeding occurs in all patients with scurvy and may be partly responsible for the anemia. In this series, tissue bleeding was present in all patients, and in one (Case i) with massive ecchymoses, skin bleeding appeared to be entirely responsible for the anemia. In another patient (Case vii) the bleeding apparently stopped after the administration of ascorbic acid. Bleeding in the gastrointestinal or genitourinary tract (common in scorbutic infants) was not seen in these patients and does not appear to be an important feature of scurvy in adults [32].

Hemolysis: The combination of elevated reticulocyte count, increased serum bilirubin and excessive amounts of urobilinogen in the urine commonly seen in scorbutic patients has led to the diagnosis of a hemolytic anemia [2,6,39]. In one series of patients with scurvy, the red blood cell survival time was shown to be reduced greatly [39]. However, this decreased survival time may have been the result of active tissue bleeding. Increased serum bilirubin and urine urobilinogen may result from breakdown and resorption of blood products from the hematomas. Since all these findings may be explained by tissue bleeding and resorption of

blood products, it seems unnecessary to invoke intravascular hemolysis.

Iron deficiency: Although ascorbic acid increases the absorption of iron from the gastrointestinal tract [42-46], there is no evidence that impaired iron absorption occurs in patients with scurvy. Low serum iron concentrations have been reported both in patients with scurvy [6,42] and in scorbutic animals [8,9,43], but these were due to external blood loss. In experimental human scurvy [4,25], as in six of the seven patients in this series, iron deficiency anemia did not occur. There was no evidence of external blood loss in any of these patients, and the one patient who had a low serum iron level (Case II) had pulmonary tuberculosis. It appears that when serum iron is low in scurvy, it is most likely due to external blood loss or superimposed infection.

Megaloblastic anemia: A megaloblastic anemia is often seen in patients with scurvy [7-11,41] and has been variously attributed to deficiency of ascorbic acid [6,11] or folic acid [7-11,41]. Ascorbic acid may enhance the conversion of folic acid to a more physiologically active form (folinic acid) both *in vivo* and *in vitro* [10,41,47], but this simply may be a reflection of the assay method [17]. Folic acid can be utilized in man [7] and animals [8-10] without the presence of ascorbic acid.

When patients with scurvy and megaloblastic anemia are treated with small doses of folic acid alone, they have an increased reticulocyte count, build blood and revert to a normoblastic marrow. However, when these patients are first given ascorbic acid alone, reticulocytosis does not occur and there is no change in the megaloblastic anemia. These observations suggest that folic acid deficiency is responsible for the megaloblastic anemia [12].

In the present series, serum folic acid concentrations in the four patients with megaloblastic anemia were significantly lower than normal, indicating the presence of folic acid deficiency.*

There was no evidence of malabsorption or faulty folic acid metabolism in any of these patients. From the dietary history it would appear that the folic acid deficiency was on the basis of inadequate intake. It seems that the megaloblastic anemia often seen in patients with scurvy is due to folic acid deficiency based on inadequate dietary intake.

* It should be noted that the serum vitamin B₁₂ levels were normal in these four patients.

SUMMARY AND CONCLUSIONS

Adults with scurvy still turn up in large city and county hospitals. Seven patients observed during a one year period are described. The diagnosis in all patients was based on the classic signs and symptoms of scurvy, supported by low blood ascorbic acid levels. The patients all ate poorly because of economic factors; their diet contained no ascorbic acid and was markedly deficient in folic acid.

The pathogenesis of the tissue bleeding, dental pathology and hair changes so frequently seen in scurvy is discussed.

Relatively low blood pressure was observed in several patients. Blood pressure levels rose after the administration of ascorbic acid. It is postulated that the vascular system is less responsive to epinephrine in the absence of ascorbic acid. Moderate to marked anemia was present in all patients. There was no evidence for blood loss or intravascular hemolysis. It appears that the megaloblastosis and low folic acid concentrations seen in four patients were due to inadequate folic acid in the diet.

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REFERENCES

1. RALLI, E. P. and SHERRY, S. Adult scurvy and the metabolism of vitamin C. *Medicine*, 20: 251, 1941.
2. VILTER, W. R., WOOLFORD, P. and SPIES, T. Severe scurvy. A clinical and hematologic study. *J. Lab. & Clin. Med.*, 31: 609, 1946.
3. McMILLAN, R. B. and INGLIS, J. C. Scurvy; a survey of 53 cases. *Brit. M. J.*, 2: 233, 1944.
4. Vitamin C, Subcommittee of the Accessory Food Factors Committee, Medical Research Council. Vitamin C requirement of human adults. *Lancet*, 1: 853, 1948.
5. CUTFORTH, R. H. Adult scurvy. *Lancet*, 1: 454, 1958.
6. BRONTE-STEWART, B. The anemia of adult scurvy. *Quart. J. Med.*, 22: 309, 1953.
7. MAY, C. D., NELSON, E. N., LOWE, C. U. and SALMON, R. J. Pathogenesis of megaloblastic anemia in infancy; interrelationship between pteroylglutamic acid and ascorbic acid. *Am. J. Dis. Child.*, 80: 191, 1950.
8. PROEHL, E. G. and MAY, C. D. Experimental

- nutritional megaloblastic anemia and scurvy in the monkey. *Blood*, 7: 671, 1952.
9. MAY, C. D., HAMILTON, A. and STEWART, C. T. Experimental megaloblastic anemia and scurvy in the monkey. *Blood*, 7: 978, 1952.
 10. JANDL, J. H. and GABUZDA, G. J. Potentiation of pteroylglutamic acid by ascorbic acid in anemia of scurvy. *Proc. Soc. Exper. Biol. & Med.*, 84: 452, 1953.
 11. BROWN, A. Megaloblastic anemia associated with adult scurvy: report of a case which responded to synthetic ascorbic acid alone. *Brit. J. Haemat.*, 1: 345, 1955.
 12. HERBERT, V. and ZALUSKY, R. Megaloblastic anemia in scurvy with response to 50 micrograms of folic acid daily. *New England J. Med.*, 265: 1033, 1961.
 13. ROE, J. H. and OESTERLING, M. J. The determination of dehydroascorbic acid and ascorbic acid in plant tissues by the 2,4-dinitrophenylhydrazine method. *J. Biol. Chem.*, 152: 511, 1944.
 14. MAHONEY, N. and REIF, A. E. Unpublished data.
 15. CRANDON, J. H., MIKAL, S. and LANDAU, B. S. Ascorbic acid in surgical patients with particular references to the blood buffy layer. *Surg. Gynec. & Obst.*, 95: 274, 1952.
 16. CRANDON, J. H., LANDAU, B. S., MIKAL, S., BALMANN, J., JEFFERSON, M. and MAHONEY, N. Ascorbic acid economy in surgical patients as indicated by blood ascorbic acid levels. *New England J. Med.*, 258: 105, 1958.
 17. HERBERT, V. The assay and nature of folic acid activity in human serum. *J. Clin. Invest.*, 40: 81, 1961.
 18. HERBERT, V. and ZALUSKY, R. Folic acid deficiency in alcoholic cirrhosis. (Abstract.) *Am. J. Clin. Nutrition*, 9: 246, 1961.
 19. PETERS, T., GIOVANNIELLO, T. J., APT, L. and ROSS, J. F. A simple improved method for the determination of serum iron. *J. Lab. & Clin. Med.*, 48: 280, 1956.
 20. TOEFFER, E. N., ZOOK, E. G. and ORR, M. L. Folic acid content of food. In: U. S. D. A. Handbook, no. 29. Washington, D. C., 1951. U. S. Department of Agriculture.
 21. COOPER, L. F., BARBER, F. M., MITCHELL, H. S. and RYNBERGEN, H. J. Nutrition in Health and Disease, p. 628. Philadelphia, 1957. J. B. Lippincott Co.
 22. ADAMS, R. Nutritional diseases of the nervous system in the alcoholic patient. *Tr. Am. Clin. & Climatol. A.*, 71: 59, 1959.
 23. GOODMAN, L. S. and GILMAN, A. The Pharmacological Basis of Therapeutics, p. 1721. New York, 1956. The Macmillan Co.
 24. LEE, R. E. Ascorbic acid and the peripheral vascular system. *Ann. New York Acad. Sc.*, 92: 295, 1961.
 25. CRANDON, J. H., LUND, C. C. and DILL, D. B. Experimental human scurvy. *New England J. Med.*, 223: 353, 1940.
 26. LIEBMANN, J., WORTIS, H. and WORTIS, E. Note on the lack of correlation of capillary fragility with vitamin C content of blood, spinal fluid and urine. *Am. J. M. Sc.*, 196: 388, 1938.
 27. AMBROSE, A. M. and DEEDS, F. Further observations on the effect of rutin and related compounds on cutaneous capillaries. *J. Pharmacol. & Exper. Therap.*, 97: 115, 1949.
 28. FREDERICKS, C. T., TILLOTSON, I. G. and HAYMAN, J. M., JR. The effect of rutin on capillary fragility and permeability. *J. Lab. & Clin. Med.*, 35: 933, 1950.
 29. FULLMER, N. M., MARTIN, G. R. and BURNS, J. J. Role of ascorbic acid in the formation and maintenance of dental structures. *Ann. New York Acad. Sc.*, 92: 286, 1961.
 30. KEIL, H. The follicular lesions of vitamin A and C deficiencies: a critical survey. *Am. J. Digest. Dis.*, 5: 40, 1938.
 31. HUME, E. M. and KREB, H. A. Medical Research Council Special Report Series, p. 264. London, 1949. His Majesty's Stationary Office.
 32. DUNGAN, C. F. Diseases of Metabolism, pp. 378, 469. Philadelphia, 1959. W. B. Saunders Co.
 33. SPEAKMAN, P. T. Permanent set, super-contraction, urea bisulphite solubility—the proton-transfer nature of some changes in keratin and the analogy with muscle contraction. *Nature, London*, 184: 339, 1959.
 34. RONDINI, P. Remarks on the pathogenesis of deficiency diseases and on pellagra. *Brit. M. J.*, 1: 542, 1919.
 35. HOWARD, A. N. and CARTER, D. B. Adrenal cortex and the effect of ACTH and cortisone in scorbutic guinea pigs. *J. Endocrinol.*, 18: 175, 1959.
 36. HYMAN, G. A., RAGAN, C. and TURNER, J. C. Effect of cortisone and ACTH on experimental scurvy in the guinea pig. *Proc. Soc. Exper. Biol. & Med.*, 75: 470, 1950.
 37. HERRICK, E. H., MEAD, E. R., EGERTON, B. W. and HUGHES, J. S. Some effects of cortisone on vitamin C deficient guinea pigs. *Endocrinology*, 50: 259, 1952.
 38. BARNES, A. E. A case of scurvy. *Brit. M. J.*, 1: 338, 1947.
 39. MERSKY, C. Survival of transfused red cells in scurvy. *Brit. M. J.*, 2: 1353, 1953.
 40. WINTROBE, M. Clinical Hematology, p. 153. Philadelphia, 1957. Lea & Febiger.
 41. GABUZDA, C. J., JR., PHILLIPS, G. B., SCHILLING, R. F. and DAVIDSON, C. J. Metabolism of pteroylglutamic acid and the citrovorum factor in patients with scurvy. *J. Clin. Invest.*, 31: 756, 1952.
 42. Utilization of iron compounds in enriched bread. *Nutritional Rev.*, 13: 165, 1955.
 43. GREENBERG, L. D. and RINEHART, J. F. Serum iron levels in Rhesus monkeys with chronic vitamin C deficiency. *Proc. Soc. Exper. Biol. & Med.*, 88: 325, 1955.
 44. MOORE, C. V. and DUBACH, R. Observations on the absorption of iron from food tagged with radioactive iron. *Tr. A. Am. Physicians*, 64: 245, 1961.
 45. GORTEN, M. K. and BRADLEY, J. E. The treatment of nutritional anemia in infancy and childhood with oral iron and ascorbic acid. *J. Pediat.*, 45: 1, 1954.
 46. STEINKAMP, R., DUBACH, R. and MOORE, C. V. Studies on iron transport and metabolism. Absorption of radioactive iron from iron-enriched bread. *Arch. Int. Med.*, 95: 181, 1955.
 47. NICHOL, C. A. and WELCH, A. D. Synthesis of citrovorum factor from folic acid by liver slices; augmentation by ascorbic acid. *Proc. Soc. Exper. Biol. & Med.*, 74: 52, 1950.