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Ascorbic Acid and its Deficiency

Choon-Yul Yang
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ASCORBIC ACID AND ITS DEFICIENCY

by

Choon-Yul Yang

Report submitted in partial fulfillment of the requirements for the degree

of

MASTER OF SCIENCE

in

Food and Nutrition

Plan B

UTAH STATE UNIVERSITY
Logan, Utah

1968
The selection of the topic for this paper was influenced by my personal and professional experiences which involved ascorbic acid deficiencies.

My special thanks are due Dr. Ethelwyn B. Wilcox, Head of Food and Nutrition Department at Utah State University, whose persistent encouragement, enthusiasm, faith, and suggestions ensured the completion of this effort.

I would also like to thank Mrs. Ruth Wheeler assistant professor and Mrs. Flora Bardwell, associate professor and extension specialist in the Food and Nutrition Department, of my graduate committee for their critical review and helpful suggestions of the thesis.

Finally, to my husband, Philip Hwang, who provided good advice and understanding in fulfilling this assignment, I extend a wife's gratitude.

Choon-Yul Yang
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>Infantile scurvy</td>
<td>3</td>
</tr>
<tr>
<td>Chemistry</td>
<td>4</td>
</tr>
<tr>
<td>EFFECTS OF DEFICIENCY</td>
<td>7</td>
</tr>
<tr>
<td>Pathology</td>
<td>7</td>
</tr>
<tr>
<td>General appearance</td>
<td>7</td>
</tr>
<tr>
<td>Bones and cartilage</td>
<td>8</td>
</tr>
<tr>
<td>Teeth</td>
<td>8</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>9</td>
</tr>
<tr>
<td>Muscle</td>
<td>9</td>
</tr>
<tr>
<td>Nervous system</td>
<td>10</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>10</td>
</tr>
<tr>
<td>Other organs</td>
<td>10</td>
</tr>
<tr>
<td>METABOLISM</td>
<td>12</td>
</tr>
<tr>
<td>Ascorbic acid metabolism</td>
<td>12</td>
</tr>
<tr>
<td>Function in metabolic system</td>
<td>15</td>
</tr>
<tr>
<td>Cellular respiration</td>
<td>15</td>
</tr>
<tr>
<td>Ascorbic acid and glutathione</td>
<td>17</td>
</tr>
<tr>
<td>Formation of intercellular substance</td>
<td>18</td>
</tr>
<tr>
<td>Ascorbic acid and proline</td>
<td>19</td>
</tr>
<tr>
<td>Development of odontoblasts and bones</td>
<td>22</td>
</tr>
<tr>
<td>Ascorbic acid and calcification</td>
<td>22</td>
</tr>
<tr>
<td>Ascorbic acid and phosphatase</td>
<td>23</td>
</tr>
</tbody>
</table>
TABLE OF CONTENTS CONTINUED

Ascorbic acid and tyrosine metabolism ........ 24
Ascorbic acid and folic acid metabolism ...... 26
Ascorbic acid and iron metabolism .......... 30

Functions that are less well-defined ......... 33
Powers of resistance ....................... 33
Relation to growth .......................... 34
Ascorbic acid and carbohydrate metabolism 36
Ascorbic acid and fat metabolism ............ 37
Ascorbic acid and adrenal glands ............. 37
Ascorbic acid and erythorbic acid metabolism 38

CLINICAL ASPECTS .............................. 40
Causes .......................................... 40
Clinical and biochemical indices of a deficiency in adults 40

Wound healing ............................... 43
Anemia ......................................... 44
Blood coagulation ............................ 46

Clinical and biochemical indices of a deficiency in infants and children 47

Symptoms ......................................... 47
Bone formation ................................. 48
Formation and maintenance on dental structure 48
Anemia ......................................... 49

EDUCATIONAL PROBLEM ...................... 52
Biochemical methods used to measure ascorbic acid nutritional status 52
In blood ......................................... 52
In urine ......................................... 53

Requirements ................................... 53


<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum requirements</td>
<td>54</td>
</tr>
<tr>
<td>Recommended dietary allowances</td>
<td>55</td>
</tr>
<tr>
<td>Infants</td>
<td>56</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>57</td>
</tr>
<tr>
<td>Therapeutic uses</td>
<td>58</td>
</tr>
<tr>
<td>Conservation of ascorbic acid in the preparation and</td>
<td>59</td>
</tr>
<tr>
<td>preservation of goods</td>
<td></td>
</tr>
<tr>
<td>Factors of destruction</td>
<td>59</td>
</tr>
<tr>
<td>Ascorbic acid retention</td>
<td>62</td>
</tr>
<tr>
<td>Effects of radiation</td>
<td>63</td>
</tr>
<tr>
<td>Sources</td>
<td>64</td>
</tr>
<tr>
<td>Prevention of signs of deficiency</td>
<td>65</td>
</tr>
<tr>
<td>Ascorbic acid nutritional status in U.S.A.</td>
<td>65</td>
</tr>
<tr>
<td>Other countries</td>
<td>67</td>
</tr>
<tr>
<td>Solving the problem</td>
<td>67</td>
</tr>
<tr>
<td>Meeting daily ascorbic acid allowances</td>
<td>71</td>
</tr>
<tr>
<td>CONCLUSION AND SUMMARY</td>
<td>74</td>
</tr>
<tr>
<td>LITERATURE CITED</td>
<td>76</td>
</tr>
<tr>
<td>VITA</td>
<td>86</td>
</tr>
<tr>
<td>Table</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1.</td>
<td>Effect of ascorbic acid on mucosal uptake of ferrous and ferric iron by gut sacs from rats</td>
</tr>
<tr>
<td>2.</td>
<td>Summary data of the effects of magnesium, florine, and ascorbic acid on growth, serum magnesium, serum hexosamine, and aorta hydroxyproline</td>
</tr>
<tr>
<td>3.</td>
<td>Mean urinary excretion of total ascorbic acid for 24 hours following ingestion of 300 mg of ascorbic acid or erythorbic acid</td>
</tr>
<tr>
<td>4.</td>
<td>Excretion and plasma levels of ascorbic acid</td>
</tr>
<tr>
<td>5.</td>
<td>Standards and requirement of ascorbic acid for human and guinea pigs</td>
</tr>
<tr>
<td>6.</td>
<td>Food and Nutrition Board, National Research Council Recommended Daily Allowances, Revised 1963</td>
</tr>
<tr>
<td>7.</td>
<td>Comparison of dietary standards for ascorbic acid for selected age groups</td>
</tr>
<tr>
<td>8.</td>
<td>Ascorbic acid content in raw, canned, and cooked food</td>
</tr>
<tr>
<td>9.</td>
<td>Ascorbic acid in raw vegetables and percentage retention after cooking</td>
</tr>
<tr>
<td>10.</td>
<td>A daily basic four food guide used in the United States</td>
</tr>
<tr>
<td>11.</td>
<td>A daily basic five food guide used in Korea</td>
</tr>
<tr>
<td>12.</td>
<td>Fruits and vegetables with serving size needed to meet ascorbic acid ...</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figures</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Representation of the over-all metabolism of ascorbic acid in man</td>
<td>13</td>
</tr>
<tr>
<td>2. Metabolic relationship between L-ascorbic acid and the corresponding sugar acids in rats</td>
<td>14</td>
</tr>
<tr>
<td>3. Relationship of blood ascorbic acid to tensile strength of wounds in guinea pigs</td>
<td>20</td>
</tr>
<tr>
<td>4. Proline and hydroxyproline to collagen synthesis with ascorbic acid</td>
<td>21</td>
</tr>
<tr>
<td>5. Metabolism of phenylalanine and tyrosine in relation of ascorbic acid</td>
<td>25</td>
</tr>
<tr>
<td>6. Conversion of folic acid to folinic acid by ascorbic acid</td>
<td>27</td>
</tr>
<tr>
<td>7. The relationship among various chemical forms of folacin</td>
<td>28</td>
</tr>
<tr>
<td>8. Diagram showing the utilization of iron by the body</td>
<td>29</td>
</tr>
<tr>
<td>9. The role of ferritin in the absorption and storage of iron</td>
<td>32</td>
</tr>
<tr>
<td>10. Representation of the interrelationships of ascorbic acid and vitamin $B_{12}$ to the folic acid coenzymes</td>
<td>45</td>
</tr>
<tr>
<td>11. The mean hemoglobin levels and mean reticulocyte contents with supplement of iron or with supplement of both iron and ascorbic acid</td>
<td>50</td>
</tr>
<tr>
<td>12. Daily ascorbic acid allowances: food plus serving size</td>
<td>71</td>
</tr>
</tbody>
</table>
INTRODUCTION

The purpose of this monograph was to collect into one paper as much as possible of the existing literature on the subject of ascorbic acid, and to present a comprehensive account of the studies on ascorbic acid metabolism which have established the symptoms of the deficiencies and pathology involved, the functions, and methods of prevention or control of these deficiencies.

The identification of ascorbic acid as a factor deficient in the diet of man and animals and establishment of its metabolic pathways has grown out of the investigations of a very large number of research workers all over the civilized world, and progress has been due not so much to a few outstanding discoveries as to a great number of advances small in themselves but impressive in their total result.

Ascorbic acid is an important article of commerce today not only for its nutrient and medicinal value but also because it is a powerful antioxidant.

Ascorbic acid research is an active area in chemistry and biology today. We can confidently expect further extensions of our knowledge of what ascorbic acid is and how it works.
Like many other diseases, the history of scurvy shows several distinct phases. Since the end of the last century, it has been discussed more often as a nutritional disturbance. The reference of Hippocrates to a large number of men in the army who suffered from pains in the legs and gangrene of the gums, which was accompanied by loss of teeth, seems sufficiently specific to be identified as this disease. The Greek, Roman, and Arabian writers do not seem to have been acquainted with scurvy (Hess, 1920). An interesting early description of scurvy is that of de Joinville about the middle of the thirteenth century. He refers to the lividity and spongy condition of the gums, and describes how the barber surgeons were forced to cut away the dead flesh from the gums to enable the people to masticate their food (Hess, 1920). Claus Magnus, in his "History of the Northern Nations," published in 1555, described the disease which is now known as scurvy that flourished among the soldiers in the camps and the prisons.

In 1645 the Faculty of Medicine at Copenhagen published a "Consilium," for the benefit of the poor, on treating of causes, prevention, and cure of scurvy, which was prevalent among the Danes and other northern nations (Singer and Underwood, 1962). In an essay published in the eighteenth century (1734), Backstrom described an epidemic of scurvy which occurred in 1703, which caused the death of 5000 men of the garrisons, in addition to a large number of the inhabitants. In the following centuries many descriptions of scurvy are
found in connection with the wars at various periods.

Ascorbic acid's connection with dietary deficiency was established, when James Lind's "Treatise on Scurvy" in 1753 demonstrated the curative effects of lemon juice. Lind's essay on the "Health of Seamen" (1757), an important milestone in the history of naval hygiene, further emphasized this form of treatment. As the result of a regular ration of lemon juice, the incidence of scurvy decreased markedly. It is due largely to the use of lemon juice that between the years 1779 and 1813, according to the statistics of Sir Jay Barrow, the morbidity and the mortality rates in the British Navy were decreased by 75 per cent.

**Infantile Scurvy**

Gilson (1668), who first described rickets, was also the first to recognize scurvy in infants. Gilson's description of infantile scurvy, however, was lost sight of, because it was overshadowed by his description of and work with rickets. This left a period of over two hundred years in which there was no word of infantile scurvy in the scientific literature of England or other countries. There is no doubt that from time to time cases must have occurred, but they were looked upon probably as rickets or as a manifestation of one of the hemorrhagic diseases.

In 1859 Moeller described some cases which evidently were scurvy, but which he termed acute rickets. He was led to this erroneous conclusion chiefly on account of the lack of marked involvement of the gums, which in those days, was considered an essential sign. Another influence was their conception of
adult scurvy. This viewpoint has influenced the German literature even to the present day. However, it has not been clearly established that infantile scurvy in its pathogenesis and pathology is identical with adult scurvy. In 1871 Ingerslev, an assistant of Hirschsprung in Copenhagen wrote a paper on "A Case of Scurvy in a Child," which was quite convincing (Hess, 1920). Two years later Jalland, an English physician, reported a similar case of "Scurvy in a Ten-months Old Infant."

In 1883 Barlow published his paper on scurvy, the first to furnish anatomical proof that this disorder of infants presented the pathological changes characteristic of adult scurvy (Harris and Sebrell, 1954). The work of Barlow was accepted remarkably well in England and in America. This was probably due to the fact that infantile scurvy was occurring far more frequently in these two countries, and that the subject was open therefore to more prompt investigation. In 1894 not less than 106 cases were reported by various physicians, to the Academy of Medicine of New York City. In 1898 the comprehensive investigation of the America Pediatric Society appeared, which was based on 379 cases. It was soon evident that infantile scurvy occurred to a greater or less degree throughout the civilized world. In France, Monfalcon had reported a case in 1820 which is referred to as the earliest case of infantile scurvy mentioned in literature.

Chemistry

A primary requisite for studying the chemical nature of vitamin C was provided by Holst and Froelich in 1907 when they observed that the guinea pig could be used as an experimental animal for study of scurvy. It was suggested
by Drummond in 1918 that the term "water-soluble C" should be applied to the accessory food substance whose connection with the development of scurvy has been proved by many investigators.

The experimental diets and general technic developed by Cohen et al. between 1918 and 1922 (Harris and Sebrell, 1954), made it possible to measure antiscorbutic activity in a satisfactory quantitative manner, free from interference by deficiencies in other essential nutrients. By 1931 many investigators, particularly Zilva, Bezssonoff, and King had succeeded in concentrating the vitamin to such a degree that a daily supplement of approximately 1 to 2 mg of the concentrate, served to protect young guinea pigs from scurvy (Hawke et al., 1954). The report of the isolation of the vitamin from lemons and its identification as hexuronic acid, having a protective level of 0.5 mg a day, by Waugh and King in 1932 was followed within a few weeks by report from Szent-Gyorgyi that 1 mg daily of hexuronic acid prepared from adrenal glands was protective against scurvy.

The compound $C_6H_8O_6$, having the same general form and many properties in common with other hexuronic acid lactones, was prepared from cabbage, oranges, and adrenal glands in 1928 by Szent-Gyorgyi in studying tissue respiration systems. However, there was no knowledge of its antiscorbutic value previous to the work published in 1932. The structural formula of the vitamin was established in 1933, primarily by Haworth and Herst, Karrer, and Klussmann (Isreal and Osten, 1966), using material obtained from adrenal glands and paprika.

The synthesis of the d-ascorbic acid and later the 1-form of the acid was successfully made by Reichstein and coworkers in 1923 (Harris and Sebrel, 1954).
In 1933 Haworth and Szent-Györgyi suggested the name "ascorbic acid" to connote its antiscorbutic nature. This was before the structural formula had been established, so that the acid could be named according to its relationship to known sugars. The American Medical Association introduced the name "Cevitamic acid" expressly to avoid this connotation.
Pathology

Barlow's publication in 1883 (Follis, 1946), establishing the identity of the scurvy of adults and of infants, must be regarded as the modern milestone in the study of the pathology of this disorder. Further studies resulted in an excellent report on the pathology of scurvy by Aschoff and Koch (1919) from Roumania.

General appearance

The skin is usually pale, livid, and dotted with numerous blotches (Beaton and McHenry, 1964). The gums are swollen, particularly in the region of the papilla between the teeth, sometimes producing the appearance of scurvy buds. The first sign of cutaneous bleedings are often to be found on the lower thighs. Before the changes in gums and skin appear, the patient becomes anemic and usually has felt feeble and listless for some weeks or months. General wasting occurs, however, in uncomplicated scurvy due to starvation as the result of lack of appetite or a deficiency of the general food supply. Children are undersized and their bones may be decidedly smaller than normal. Generally there is some edema around the ankles, and in children a somewhat characteristic puffiness around the eyes.
Bones and cartilage

The primary morphologic effects of vitamin C deficiency occur in the intercellular substances of certain mesenchymal derivatives; newly formed fibrous tissue, teeth, growing bones, and blood vessels (Geoffrey, 1956). Microscopic examination reveals a rarefaction of the existing cortex, cessation of bone growth, and replacement of the normal junction by a zone of collagen-poor connective tissue in which are embedded fragments of calcified cartilage matrix, bare of osteoid tissue. The formation of intercellular materials may be completely stopped by a vitamin C deficiency. The formation of intercellular material of bone-osteoid tissue and of teeth may be similarly controlled by withholding or supplying ascorbic acid. The connective tissue cells of marrow are migrated osteoblasts which have reverted to fibroblasts. In the absence of ascorbic acid the osteoblasts, unable to form osteoid tissue, revert to their prototype and attempt to form a fibrous union between the diaphysis and epiphysis.

Lack of ascorbic acid produces a pathological condition at the growing ends of the bones characterized by a disorderly organization of the cells and a resulting weakness. The significant losses of collagen from bones and teeth occur in scurvy (Geoffrey, 1956).

Teeth

Zilva and Wells in 1934 (Harris and Sebrell, 1954) showed that pathological changes in the odontoblasts and dentine occur in scurvy. The growth and arrangement of the odontoblasts is directly related to the ascorbic acid intake. In the guinea pigs partial deficiency results in the formation of osteodentin, and complete
deficiency is undifferentiated matrix. The teeth become loose and fall out or may be easily pulled out by the patient himself.

**Connective tissue**

The role of the mesenchymal cells and the stimulating effect upon them of ascorbic acid in the formation of connective tissue fibers has been developed and elucidated largely from studies made with tissue cultures, inflammatory reactions, and in healing experimentally induced wounds (Beaton and McHenry). In wounds produced in scorbutic animals a pink-staining fluid-like material surrounds immature proliferating connective tissue cells. The hemorrhage, which occurs as a result of the incision, is observed and may never completely disappear. The strength of a scar is dependent on the intercellular substances laid down by the fibroblasts. Within certain limits a quantitative relation exists between the amounts of ascorbic acid available and the amounts of intercellular materials produced. However, increasing the intake above the normal daily requirement does not produce greater than normal tensile strength of wounds.

**Muscle**

Ascorbic acid is of special importance in maintaining the integrity of both structure and function of muscle tissue, although it is present in low concentration when compared to the content of many other tissues. The differences in the types of change in the muscles in acute and chronic scurvy in guinea pigs were identified by Boyle and Irving in 1951 (Bourne and Kidder, 1953). In the acute form, degeneration of the muscles around the knee joint, ribs, scapulas, and trachea was much less common and the finer structure of the muscle became more prominent.
Nervous system

The nervous system is considerably affected in scurvy. In 1938, Meyer found hemorrhage in the brain, spinal cord, posterior root ganglia, and nerve trunk of scorbutic in guinea pigs. He also observed degenerative changes other than fatty which resulted in complete loss of substances in the central, peripheral, and sympathetic nervous system. The brains of scorbutic guinea pigs contained significantly more cerebroside and less sphingomyelin than did the brains of normal animals (Sadhu, 1952).

Circulatory system

There are numerous reports of increased capillary fragility in scurvy. The chief lesion in scurvy is a swelling and degeneration of the capillary endothelium resulting in stagnation of the blood in the capillaries (Walter and Dalldorf, 1944).

Other organs

The most notable gross symptoms of ascorbic acid deficiency in the liver are paleness and a tendency to fatty infiltration. The cells are reduced in volume, the cytoplasm stained only faintly and appeared to be homogenized, and the cell boundaries are indistinct, with a tendency for diminution of parenchyma cells. The lack of the ascorbic acid causes a decrease in the amount of the bile and in the pigment-secreting function of the liver. Pancreatic islands are larger than normal and are hypoplastic (Harris and Sebrell, 1954).

The enlargement of the adrenal glands in scurvy appeared to be a result of simple swelling. However, the most characteristic lesion in the adrenals of scorbutic guinea pigs, as described by Bessey in 1934 (Harris and Sebrell, 1954),
was the depletion of fat and cholesterol from the cortex in the final stages of the disease with little reduction the fat content until several days before death.

The water content of skin increases in scurvy. The skin is of particular interest because of the frequency of signs of the skin diseases and the clue it gives to easily, observable lesions and thus to the general status of the patient. The lesion of the skin that is characteristic of scurvy is the perifollicular of petechial hemorrhage. Frequently dark, grayish pigmentation also was described.
Ascorbic acid is highly soluble in water and readily absorbed from the gastrointestinal tract. There is no evidence that its absorption is impaired by achlorhydria or bacterial destruction in the gut. The oxidized form of the vitamin, dehydroascorbic acid, is readily converted to the reduced form, L-ascorbic acid, in the human body (Baker, 1964).

When ascorbic acid is injected into guinea pigs, about one-third is not recoverable in the form of its products of decomposition. The greater part is excreted as CO$_2$ in the breath. Some appears as oxalate in the urine, about 60 per cent. Ascorbic acid is catabolized to yield oxalate from carbon atoms in human (Figure 1). About half the daily turnover of ascorbic acid occurs by oxalate formation or the excretion of ascorbic acid, dehydroascorbic acid, and 2,3-diketogulonic acid in the urine and the remainder is metabolized to CO$_2$ (Atkins et al., 1964). In the rats, the ascorbic acid can be synthesized from glucose, therefore, their metabolic pathway is quite different from humans (Figure 2).
Metabolic precursor of ascorbic acid, e.g. D-glucuronic acid and ascorbic acid

Figure 1. Representation of the over-all metabolism of ascorbic acid in man.\(^a\)

\(^a\)From Baker et al., 1966, p. 13.
Figure 2. Metabolic relationship between L-ascorbic acid and the corresponding sugar acids in rats.\textsuperscript{a}

\textsuperscript{a}From Ashwell et al., 1961, p. 106.
Function in Metabolic Systems

Ascorbic acid has been shown to have a number of functions in the body which are characterized by specific symptoms when a deficiency of the vitamin occurs.

The metabolic systems in which ascorbic acid has a role include (NBC Bulletin):

1. Regulation of the respiratory cycle of mitochondria and microsomes
2. Formation of intercellular substance
3. Development of odontoblasts and bones
4. Oxidation of phenylalanine and tyrosine
5. Conversion of folacin to folinic acid
6. Conversion of ferric to ferrous iron

Cellular respiration

The ascorbic acid is a hexose derivative. In the rat, glucose is converted into correspondingly labeled ascorbic acid.

The most obvious property of ascorbic acid is the reversible oxidation and reduction capacity. Much speculation and experimental work arose from the idea of correlating this behavior with the mechanism of the vitamin action.
From the fact that both the reduced and the oxidized forms are usually found in animal and plant tissues and their occurrence coincides generally with tissues possessing high metabolic activity it appears that ascorbic acid must play an important role in respiration (Meiklejohn, 1953). Thus its role in tissue oxidation would be that of a hydrogen acceptor. However, only the oxidized form, dehydroascorbic acid, is capable of accepting hydrogen. It was found that in the body only a small part of the vitamin was in this form; the largest part was present as reduced ascorbic acid or the L-form. The reduced form can also act as hydrogen donor.

The demonstration by Szent-Gyorgyi in 1931 (Meiklejohn, 1953), and since then by many other investigators, that an enzyme, ascorbic oxidase, is capable of catalyzing direct reaction between ascorbic and molecular oxygen indicates that it is a respiratory catalyst, acting in a similar capacity to that of cytochrome. In animal tissues there is no specific oxidase catalyzing the direct oxidation of ascorbic acid. Glutathione has been shown to be the most effective reductant and protective agent for ascorbic acid in the living animals and in the plant cells. Glutathione is present in many body tissues and fluids. It was at first thought to be an important oxidation-reduction agent. At the present time its role is quite uncertain. Ascorbic acid takes part in a respiratory system, involving the following reactions (Szent-Gyorgyi, 1938):

\[
\text{Ascorbic acid} + O_2 \xrightarrow{\text{Cu}^{++} \text{Hexoxidase}} \text{Dehydroascorbic acid} + H_2O_2
\]

\[
\text{Flavone} + H_2O_2 \xrightarrow{\text{Peroxidase}} \text{Oxidized flavone} + H_2O
\]
Flavone-oxide + Ascorbic acid $\rightarrow$ Dehydroascorbic acid + Flavone

Dehydroascorbic acid + glutathione $\rightarrow$ Ascorbic acid + Oxidized Glutathione

Oxidized glutathione + Glucose phosphate $\rightarrow$ glutathione + CO$_2$ + H$_2$O

Ascorbic acid and glutathione. The ascorbic acid in the blood is present in the plasma and in the reduced state. Plasma alone is incapable of reducing dehydroascorbic acid so that the red cells are probably responsible for keeping the ascorbic acid reduced in the presence of glutathione. Hopkins in 1921 discovered glutathione and later identified it as a tripeptide of glutamic acid, cysteine, and glycine. The relationship between ascorbic acid and glutathione was first observed by Szent-Györgyi in 1928 in his early work on hexuronic acid (Hartman and Brownell, 1949). In the course of the enzymatic oxidation of ascorbic acid, the oxidation product, dehydroascorbic acid, was readily reduced to ascorbic acid by various tissue preparations which contained glutathione. These oxidation products disappeared during the reaction. Glutathione protects ascorbic acid from oxidation in plants so that no dehydroascorbic acid was formed until all the glutathione was converted to its oxidized form. Glutathione also was responsible for maintaining ascorbic acid in the reduced state in animal tissues.

Dehydroascorbic acid + 2 glutathione + ascorbic acid + oxidized glutathione

(Colowick et al., 1954). Dehydroascorbic acid was reduced by a mixture of cysteine with fresh potato juice. Fresh cabbage and cauliflower juice could catalyze the oxidation of glutathione by dehydroascorbic acid known as dehydroascorbic acid reductase (Kleiner and Orten, 1966). The Mitochondria catalyzed oxidation
of ascorbic acid by oxygen and glutathione was also oxidized by oxygen when a trace of ascorbic acid was added to the particles.

Formation of intercellular substance

Ascorbic acid is concerned fundamentally with the formation of intercellular substances, including the collagen of fibrous tissue structure, the matrix of bone, cartilage, and dentin, and all nonepiendothelium cells. In the absence of the protection afforded by this vitamin, the condition known as scurvy develops. The onset of the disease is gradual in humans, a period of indolence, fleeting pains in the joints, and shortness of breath being followed by decline in weight and anemia. Soon the complexion becomes sallow, subcutaneous hemorrhages occur upon slight injury, the gums become spongy and bleed easily, the teeth become loose and fragile, and often there is marked edema of the extremities.

Ascorbic acid was suggested as essential for the maintenance of collagen by the work of Hoejer in 1923. More recently Abt et al., (1960) investigated the ascorbic acid, collagen, and hexosamine distribution in scars produced in guinea pigs, wounding by abdominal incision, that were maintained on various dietary levels of ascorbic acid. Fractionation of tissues that compose the scar revealed that the highest concentration of ascorbic acid was present in the connective tissue.
The rate of production of intercellular material had a quantitative relationship to the amount of ascorbic acid administered. Bourne in 1944 and later Abt et al. in 1960 showed that in the animals receiving the lowest level of ascorbic acid there was a greater amount of reticular (precollagen) fibers than in those receiving the highest level. This finding was correlated with the tensile strength of the wounds (Figure 3). In ascorbic acid deficiency, cartilage cells failed to produce matrix, developed an abnormal appearance, and became shrunken and irregular. The cells were separated from each other by small quantities of material which did not give the normal staining reaction for matrix. In animals fed a basal semi-synthetic diet supplemented with a low level of ascorbic acid, severe alteration in structure of dentine was observed. Mild alteration occurred in the normal pattern of bone deposition and resorption in the jaws.

Hemorrhage occurred in both the pulp and periodental membrane. There was a failure in the formation of collagen fibers, cementum, dentine, and bone.

**Ascorbic acid and proline.** Many research groups found that the hydroxylation of proline to hydroxyproline is decreased in scorbutic tissue (Robertson, 1961; Stone et al., 1962; Ross et al., 1964; and Hurych et al., 1963). In the absence of ascorbic acid there is an apparent accumulation of hydroxyproline-free precursor of collagen (Figure 4). The hydroxylation step occurs an early stage of collagen biosynthesis, before completion of the collagen chain, possibly at the proline activation of sRNA (transfer RNA). Hydroxylation of proline may occur beyond the terminal stage of the biosynthesis
Figure 3. Relationship of blood ascorbic acid to tensile strength of wounds in guinea pigs.\(^a\)

\(^a\)From Bourne, 1944, p. 690
Intracellular reactions

Proline $\rightarrow$ Active proline $\rightarrow$ Tropocollagen $\rightarrow$ Soluble collagen $\rightarrow$ Insoluble collagen

$\rightarrow$ Noncollagen protein

Active hydroxyproline $\rightarrow$ Peptides

Hydroxyproline

Extracellular reactions

Proline $\rightarrow$ Active proline $\rightarrow$ Tropocollagen $\rightarrow$ Soluble collagen $\rightarrow$ Insoluble collagen

$\rightarrow$ Noncollagen protein

Active hydroxyproline $\rightarrow$ Peptides

Hydroxyproline

Figure 4. Proline and hydroxyproline to collagen synthesis with ascorbic acid. $^b$

$^a$ The possible sites of blockage in collagen synthesis because of ascorbic acid deficiency.

$^b$ From Robertson, 1961, p. 165.
of a proline polypeptide on polysomal RNA, when the final polypeptide esterified through its terminal carboxyl group to the last RNA remaining attached to the RNA (messenger RNA) is formed (Fitton et al., 1965).

A deficiency of ascorbic acid causes intracellular changes mainly in the microsomes and endoplasmic reticulum and this could result in an alteration of protein synthesis. On microsomal electron transport and hydroxylation reactions the presence of ascorbic acid gave the most consistent approach to elucidate the mode of action of the vitamin (Staudinger et al., 1961). One of the hypotheses for the formation of collagen fibers from a procollagen is that ascorbic acid is required for the formation of hydroxyproline from the bound proline in a procollagen peptide, and that it is involved in the synthesis of new collagen or results in its destruction as it is formed.

Under scorbutic conditions the incorporation into collagen of both proline and hydroxyproline is decreased while the hydroxylation of proline appears to be unaffected (Robertson et al., 1959). However, the specific activities of the gelatin amino acids indicated that the incorporation of proline as well as hydroxyproline is affected by ascorbic acid deficiency.

**Development of odontoblasts and bones**

**Ascorbic acid and calcification.** Ascorbic acid is important for the functional activity of the formative cells. Dietary deficiency in ascorbic acid during the period of tooth development causes impairment of the odontoblasts, leading to defective calcification of the dentin accompanied by hemorrhagic and degenerative lesions in the pulp tissues. In scurvy, bone formation stops, but resorption continues so that there is a resultant atrophy
and bone fragility. Skeletal defects are demonstrated first at the costochondral junctions, where the lesions are similar to those of rickets. Bone lesions appear mainly at the joints and are particularly severe in infants and children.

Histological evidence of bone repair may be observed within a few hours after administration of ascorbic acid, and signs of connective tissue regeneration in 24 hours. These findings in humans by Bourne (1949) indicated that an optimal level of ascorbic acid favored rapid repair of tissues in wounds and bone fractures, and is an important factor in determining resistance to infection. The disappearance of the ascorbic acid is greater during periods of rapid growth. The younger the animal and the more rapidly it grows, the smaller the amount excreted.

Ascorbic acid and phosphatase. As early as 1932, Smith observed that the alkaline phosphatase activity of the plasma of infants and young children suffering from scurvy was low and that enzymic activity was restored to normal on treatment with ascorbic acid (Harris and Sebrell, 1954). Whenever blood phosphatase decreases, there is a stoppage of growth accompanied by loss of weight. How much the reduction of phosphatase activity is related specifically to a deficiency of ascorbic acid remains in doubt. Evidence was obtained by Perkins and Zilva, (1950) indicating that the fall in the phosphatase content of the serum and in the zone of provisional calcification of the costochondral junctions is caused by the scorbutic condition (Harris and Sebrell, 1954).

The fall in the phosphatase of bone may be due to a disturbance in the function of the osteoblasts caused by local scorbutic lesions. It is possible that the low phosphatase content of bone may be due to poor synthesis,
and the low content in serum to a redistribution of the enzyme between blood
and other tissues (Bourne, 1956).

**Ascorbic acid and tyrosine metabolism.** Ascorbic acid plays an
important role in intermediate protein metabolism, particularly with respect
to the oxidation of the aromatic amino acid, tyrosine and phenylalanine. Ap­
parently the first biochemical evidence of abnormal metabolism in scurvy was
the demonstration by Sealock and Silberstein in 1940 (LaDu and Zannoni, 1961)
of an abnormality of tyrosine metabolism in scorbutic guinea pigs (Figure 5).
They demonstrated in the urine of these animals the appearance of hydroxy­
phenyllactic and hydroxyphenylpyruvic acids, presumably derived from the
deamination of tryosine which thereafter failed to undergo further catabolism.
When aromatic amino acids are fed in large amounts to premature infants
subsisting on cow's milk or to guinea pigs on a diet lacking ascorbic acid,
there is an excretion of abnormal metabolities in the urine. Of a large series
of phenylalanine and tyrosine derivatives only L-phenylalanine, L-tyrosine,
and phenylpyruvic acid showed any dependence on the intake of ascorbic acid.
The oxidized form, dehydroascorbic acid, of vitamin behaved as a coenzyme
to the reaction by acting as a hydrogen acceptor.

The action of ascorbic acid appeared to be chiefly one of continuing
the oxidation of tyrosine to the formation of aceto-acetate. Important con­
tributions to the understanding of the mechanism involved in this effect have
Pathway of tyrosine metabolism in liver

Tyrosine

\[
\begin{align*}
\text{Transaminase} & : \text{Tyrosine} + \text{KG B}_6\text{PO}_4 \\
\text{p-hydroxyphenylpyruvate (pHPP)} & : \text{OH} \\
\text{HGA oxidase} & : \text{++} + 2(O) \text{Fe}^{2+} \\
\text{Homogentisate (HGA)} & : \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Maleylacetoacetate (MAA)} & : \text{H - C} - \text{COOH} \\
\text{Fumarylacetoacetate (FAA)} & : \text{HOOC} - \text{C} - \text{OH} - \text{COOH} \\
\text{Acetoacetate} & : \text{CH}_3\text{C} - \text{CH}_2\text{COOH}
\end{align*}
\]

TCA cycle

Figure 5. Metabolism of phenylalanine and tyrosine in relation of ascorbic acid.\(^a\)

\(^a\)La Du and Zannoni, 1961, p. 177.
been made by Knox and Goswami (1960), and LaDu and Zannoni in 1960. Tyrosine administration causes the excretion of p-hydroxyphenylpyruvic acid by increasing the activity of tyrosine and decreasing that of p-hydroxyphenyl-pyruvic acid oxidase.

The inhibition of the oxidase can be prevented by administration of ascorbic acid and by other compounds, such as 2,6-dichlorophenolindophenol, D-isoascorbic acid, and D-gluco-ascorbic acid.

**Ascorbic acid and folic acid metabolism.** Folic acid is present in natural materials in the form of folinic acid, and it has been demonstrated that ascorbic acid enhances the conversion of folic to folinic acid (Wohl and Goodhart, 1964). This conversion is shown in Figure 6.

The suggestion has been advanced that the change from folic to folinic acid is associated with the transfer of single carbon units (Figure 7, Guthrie, 1967). The exact role of ascorbic acid in the folic-folinic acid relation is not known, but is possible that it has a stabilizing effect on folinic acid, owing to its antioxidant action. A megaloblastic anemia which responded to ascorbic acid, and which occurred in association with clinical scurvy in man is described by Brown in 1955 (Greenberg, 1957). The explanation that the anemia was due in part to ascorbic acid deficiency and in part to an abnormal folic acid metabolism as a result of liver disease appears logical in view of the known interrelationship between folic acid and ascorbic acid.
Figure 6. Conversion of folic acid to folinic acid by ascorbic acid.\textsuperscript{a}

\textsuperscript{a}From Wohl and Goodhart, 1964, p. 413.
Figure 7. The relationship among various chemical forms of folacin.

---

a Indicates the site of action of folic acid antagonist.

b From Guthrie, 1967, p. 255.
Iron in foods (mostly organic compounds) → Excretion in feces (major portion)

Alimentary tract

Fe

Ascorbic acid
Dinitrophenol or maleimide

Fe

Mucosa cell

++

Fe

Apoferitin

Ferritin

Destruction

++

Plasma iron

Fe

Siderophilin (iron-protein complex)

Fe

Muscle

Myoglobin

Functional tissue

Enzyme systems containing iron (cytochromes)

Liver

(storage ferritin)

Bone marrow

(ferritin storage)

Hematopoietic organs

Hemoglobin

Destruction

Gestational loss → Intestine

Bile

Urinary excretion

Figure 8. Diagram showing the utilization of iron by the body.

aMetabolic inhibitor of iron absorption.

Chronic ascorbic acid deficiency leads to a deficiency of folic acid or a disturbance in the metabolism of folic acid or related compounds, and thus results in megaloblastosis.

Hemorrhagic tendencies of folic acid deficient rats have been beneficially influenced and normal white cell and normoblast counts restored by administration of ascorbic acid (Vitler et al., 1963). The effect on liver ascorbic acid may be attributed to intestinal bacteriostasis, resulting in inhibition of production of one or more substances needed by the rat for the synthesis of ascorbic acid.

Ascorbic acid and iron metabolism. Iron is absorbed in an ionized form (Figure 8). It has been shown that ferrous iron is much more efficiently absorbed than is ferric iron (Pearson and Reich, 1965). In all probability the ferric form must be reduced to ferrous before absorption. However, when ascorbic acid is given along with ferric iron, absorption is significantly enhanced, because of the reducing properties of ascorbic acid, but a similar effect is not obtained with ferrous salts (Table 1).

The addition of large amounts of ascorbic acid to foods causes absorption of iron to be considerably increased. When transferrin-bound iron is incubated with liver slices, adenosine triphosphate (ATF) and ascorbic acid mediate the transfer of iron to ferritin (Kleiner and Orten, 1966). The suggested mechanism is as follows (Figure 9).
Table 1. Effect of ascorbic acid on mucosal uptake of ferrous and ferric iron by gut sacs from rats

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Index of mucosal uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no ascorbic acid</td>
</tr>
<tr>
<td>Ferric chloride (ferric iron conc. 0.004 g/ml)</td>
<td>13.2 ± 0.8</td>
</tr>
<tr>
<td>Ferrous sulfate (ferrous iron conc. 0.004 g/ml)</td>
<td>13.8 ± 1.3</td>
</tr>
</tbody>
</table>

*aPearson and Reich, 1965, p. 121.

A complex is formed involving two moles of ATP, 1 mole of ascorbic acid, and iron-transferrin; ATP is thought to stimulate the oxidation of ascorbic acid in the presence of iron; this reaction reduced the plasma-bound ferric iron to the ferrous state, thus releasing the iron from the protein and making it available for incorporation into ferritin (Mazur, 1961).

In case of chronic ascorbic acid deficiency, the serum iron fell to about one third of normal and the animal became anemia (Snell and Metzer, 1956). The combined therapy with iron and ascorbic acid markedly increased both serum iron and hemoglobin levels. The release of iron from its linkage to the plasma iron-binding protein, transferrin, and its subsequent incorporation into hepatic ferritin is dependent on oxidative metabolism of the liver cell, specifically for the continued synthesis of ATP and also the presence of ascorbic acid (Mazur et al., 1960).

In the hydrogen peroxide system, it is proposed that ascorbic acid functions to reduce the ferric iron produced by interaction of hydrogen...
Figure 9. The role of ferritin in the absorption and storage of iron.

\[ \text{From Kleiner and Ortén, 1966, p. 638.} \]
peroxide with ferrous iron; in the oxygen system, ascorbic acid serves in
addition as the source of the required hydrogen peroxide via an iron-
catalyzed auto-oxidation (Pearson and Reich, 1965).

**Functions That are Less Well Defined**

Other uses of ascorbic acid are less well defined and the symptoms
of a deficiency may be indistinguishable from deficiencies of other vitamins
or nutrients.

Ascorbic acid also aids in maintaining other functions such as resistance
to common stresses, normal growth, moderate exposure to bacterial toxin,
low temperatures, wound healing, enzyme activity, and cellular proliferation.

**Powers of resistance**

Of particular interest is the reaction of the human organism toward
ascorbic acid administration in cases of various poisonings. The reaction
of ascorbic acid to resistance of certain toxins, for example, diphtheria,
was reported by King and Menten in 1955 (Greenberg, 1957). In human beings
beneficial effects of large doses of ascorbic acid have been recorded in
cases in which toxic doses of drugs, for example, L-tyrosine, lead, arsenic
compounds, benzene, virus, and substances producing anaphylaxis, have
had no toxic effect when administered simultaneously with ascorbic acid.

Ascorbic acid is often credited with assisting the body to resist
infection, particularly with respect to those diseases which are associated
with an elevation of body temperature. Among the diseases in which the
requirement of the vitamin appears to be increased are tuberculosis, rheumatic fever, and pneumonia. If ascorbic acid does have a beneficial influence on the course of certain types of infection in animals, the effect may presumably result from an increase in the formation of, or availability of, immune bodies; detoxification of harmful products of bacterial action; altered permeability of membranes; or increased phagocytic activity. The speculation is that the production of the antibody is impaired if ascorbic acid is lacking and that there is failure of the formative cells to produce new body tissue. A suggestion has been made that activity of white blood cells can be stimulated by ascorbic acid (Dodds, 1959).

Relation to growth

In the absence of ascorbic acid in the diet, the young guinea pigs succumb so suddenly that a retarding effect on growth is often not observable. Anderson and Smith in 1924 (Bourne, 1956) were the first investigators to eliminate inanition as a factor in the weight differences of animals receiving ascorbic acid. They demonstrated that with a deficiency of ascorbic acid in the diet of guinea pigs there is first either a loss in weight or a failure to increase in length, and finally a failure to reach maturity. Since the differences in food consumption, the suggestion was made that the lack of ascorbic acid had caused alterations in metabolism, water balance, and food absorption. The lack of ascorbic acid caused a diminished retention of water, which largely accounted for the observed differences in body weight. There is little evidence that a direct relation occurs between ascorbic acid
and growth of cells in animal tissues. However, a marked depression in growth rate resulted from a low ascorbic acid intake. The growth rate was retarded within the first week and in the second week a very marked reduction in growth rate occurred (Thompson, Heintz, and Philips, 1964).

Blood serum magnesium levels were reduced in scurvy but serum hexosamine was significantly increased (Table 2). The elevated serum hexosamine is produced or its incorporation in the form of new connective tissue may have been blocked. When the diet was low in ascorbic acid, the aorta hydroxyproline levels also were decreased (Woessner, 1961).

Table 2. Summary data of the effects of magnesium, florine, and ascorbic acid on growth, serum magnesium, serum hexosamine, and aorta hydroxyproline

<table>
<thead>
<tr>
<th></th>
<th>Avg. gain/week</th>
<th>Serum Mg.</th>
<th>Serum hexosamine</th>
<th>Aorta hydroxyproline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>week 1</td>
<td>week 2</td>
<td>mg/100 ml</td>
<td>mg/100 ml</td>
</tr>
<tr>
<td>Control</td>
<td>46</td>
<td>36</td>
<td>3.17 ± 0.44</td>
<td>100 ± 12</td>
</tr>
<tr>
<td>Low magnesium</td>
<td>35</td>
<td>4</td>
<td>0.55 ± 0.29</td>
<td>102 ± 13</td>
</tr>
<tr>
<td>(96 ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ascorbic a.</td>
<td>36</td>
<td>23</td>
<td>2.59 ± 0.57</td>
<td>144 ± 7**</td>
</tr>
<tr>
<td>High florine</td>
<td>27</td>
<td>11</td>
<td>2.88 ± 0.60</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>(450 ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High F. and low Mg.</td>
<td>27</td>
<td>7</td>
<td>1.25 ± 0.29</td>
<td>144 ± 7**</td>
</tr>
<tr>
<td>Low ascorbic acid</td>
<td>39</td>
<td>6</td>
<td>0.70 ± 0.28</td>
<td>134 ± 17**</td>
</tr>
<tr>
<td>and low Mg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a From Thompson et al., 1964, p. 28.
b SD

**Significantly different at 1 per cent level from control.
Ascorbic acid and carbohydrate metabolism

There has been no clear indication of a disturbance in the oxidation of carbohydrates in scurvy (Meiklejohn, 1953). The successive stages of ascorbic acid deficiency resulted in corresponding rises in the fasting blood sugar level and a decrease in glucose tolerance. The exact role of insulin in carbohydrate metabolism has not been determined. The insulin content of pancreas of the scorbutic animals was reduced to about one-eighth the normal value. The glycogen deposition is decreased in the livers of guinea pigs and muscle glycogen on a scorbutic diet. Administration of ascorbic acid to deficient animals caused a prompt storage of glycogen. The complete relationship of ascorbic acid to glucose tolerance has not been elucidated.

The activities of the enzymes of the glycogen cycle were studied in liver tissue preparations from scorbutic guinea pigs (Barnerjee and Ganguli, 1962). The activities of uridine diphosphate glucose pyrophosphorylase, glycogen synthetase, and phosphorylase were found to be unaffected in scurvy.

Hepatic glycogen synthesis from glucose, glucose-1-phosphate, and glucose-6-phosphate were diminished in vitro as a result of scurvy. The incorporation of uniformly labeled glucose-$^{14}$C by liver tissue into glycogen was less in scorbutic guinea pigs.
Ascorbic acid and fat metabolism

It is reported that the fat content of tissues is decreased in experimen­tal scurvy in guinea pigs, particularly in the muscles and adrenals by several workers. The marked decrease of cholesterol content in the adrenals and lungs was shown in scorbutic animals. The most characteristic lesion in the organs of scorbutic guinea pigs was the depletion of fat and cholesterol from the cortex of the adrenals (Meiklejohn, 1953).

Later Bronte et al., in 1963 suggested that the release of adrenal cortical hormone may be involved in lowering the content of ascorbic acid and cholesterol in adrenals.

Ascorbic acid and adrenal glands

The hypertrophy of the adrenal in scurvy has directed attention to a possible relationship between the adrenals and ascorbic acid. Ascorbic acid was first isolated as a crystalline compound from the adrenal by Szent-Györgyi in 1928 as hexuronic acid. The amounts of ascorbic acid in the adrenal of the female is significantly greater than in the male of most species (Meiklejohn, 1953).

The adrenal content of ascorbic acid as well as liver and kidney decreases with age. The following the injection of adrenocorticotropic homone (ACTH), there occurred a sharp drop in ascorbic acid content of this gland (Sayers et al., 1945). The biological role of ascorbic acid in adrenocortical physiology has not been solved. The recognized
marked depletion of adrenal ascorbic acid which accompanies discharge of the adrenal cortex raises the possibility that this vitamin participates directly or indirectly in steroidogenesis (Meiklejohn, 1953).

Ascorbic acid and erythorbic acid metabolism

Erythorbic acid, a stereoisomer of L-ascorbic acid which differed from L-ascorbic acid only in the spatial configuration of its five C atoms, has little or no antiscorbutic activity, but it is fully as active as the vitamin in several cell-free enzyme reactions. Erythorbic acid and L-ascorbic acid, when given in load doses to human subject, produce comparable elevations in plasma ascorbic acid concentration for periods of 3 to 4 hours. However, erythorbic acid supplementation to low ascorbic acid diets would not maintain fasting plasma ascorbic acid concentration in human subjects (Wang et al., 1962; Kadin et al., 1959).

The plasma was the first to be depleted in progressive ascorbic acid deficiency and with supplementation plasma concentration remained very low until the tissues had taken up their required amounts. The ascorbic acid supplementation did not increase urinary ascorbic acid significantly. The decline in white cell ascorbic acid concentration with erythorbic acid supplementation showed that the intake or tissue fixation of ascorbic acid by white cells was specific for the configuration of the five C. The rejection of erythorbic acid by white cells and the decrease in the rate of white cell depletion with the increase in the erythorbic acid supplement shown
in this study indicate that the action of erythorbic acid is due to its protection of ascorbic acid (Rivers et al., 1963).

The antiscorbutic activity of erythorbic acid based on guinea pigs experiments suggested that its behavior might show deviation from that of ascorbic acid (Table 3).

Table 3. Mean urinary excretion of total ascorbic acid for 24 hours following ingestion of 300 mg of ascorbic acid or erythorbic acid

<table>
<thead>
<tr>
<th>Collection period</th>
<th>Excretion of total ascorbic acid</th>
<th>Excretion of total ascorbic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythorbic acid</td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td></td>
<td>mg</td>
<td>% of intake mg               % of intake</td>
</tr>
<tr>
<td>0 - 6</td>
<td>96.0 ± 22.8</td>
<td>32.0</td>
</tr>
<tr>
<td>7 - 12</td>
<td>37.8 ± 11.4</td>
<td>12.6</td>
</tr>
<tr>
<td>13 - 24</td>
<td>27.1 ± 0.8</td>
<td>9.0</td>
</tr>
<tr>
<td>0 - 24 Total</td>
<td>160 ± 37.2</td>
<td>53.6</td>
</tr>
</tbody>
</table>

a From Wang et al., 1962, p. 445.
CLINICAL ASPECTS

Causes

Though there is undoubtedly a great deal of subclinical ascorbic acid deficiency, clinical scurvy is a rare disease in most of the civilized world today. However, patients with scurvy can still be found in many city and country hospitals (Chazan and Mistilis, 1962). Their diagnosis in all patients was based on the classic signs and symptoms of scurvy, supported by low blood ascorbic acid levels. One peak of high incidence ascorbic acid deficiency occurred between the ages of 6 and 12 months in infants whose processed milk formulas are unsupplemented with citrus fruits or vegetables, or because they refused or spit out the orange juice offered them. Breast-fed infants are protected if their mothers are well nourished. Another time in the life cycle when deficiencies are apt to occur is in the middle and old age groups who live alone, cook for themselves, or eat alone in restaurants. The deficiency occurs because of a primary dietary inadequacy in ascorbic acid or in conditions of the increased requirement for the vitamin imposed by hypermetabolism, chronic infection, or the increased loss accompanying chronic diarrhea.

**Clinical and chemical indices of a deficiency in adults**

The chemical means of estimating tissue levels and nutritional status for ascorbic acid of human beings include measurement of the ascorbic
acid in plasma, whole blood, white blood cells, platelets, and urine. The white blood cell and platelet levels show a straight-line relationship to the intake of ascorbic acid but the serum levels do not follow a linear relation­ship with intake and are not a function of the white cell ascorbic acid level. With serum values below 0.4 mg per cent, white cell ascorbic acid is diminished (Lowry et al., 1946).

During realimentation of volunteers depleted of ascorbic acid, the rise in white blood cell ascorbic acid was parallel to the amount of the ascorbic acid retained in the body (Lowry et al., 1946). Low levels of ascorbic acid in white cells have been found in cancer patients and in chronic non-cancer disease. These findings are indicative of low body stores. The body pool of ascorbic acid for guinea pigs was 54 mg per g which is very close to the quantity 50 mg per g estimated for saturation of human tissues (Hellman and Burns, 1958).

The conversion of ascorbic acid to oxalate did not increase at an intake of 4 gm of ascorbic acid per day. Rapid urinary excretion of the ascorbic acid could account for this limited conversion to oxalate (Baker et al., 1962). In contrast to that in human beings, the chief metabolic product of L-ascorbic acid in the guinea pigs is respiratory CO₂ and only a small fraction is excreted as oxalate. For nutritional survey purposes, serum levels are useful. Combination of measurement of serum levels, urinary excretion, white cell levels, and evidence of tissue deficiency will effectively determine the range of ascorbic acid nutrition from the state of abundant
supply to severe deficiency. If the white blood cells are 27 to 30 mg per cent, the tissues are saturated; the body will contain about 50 mg of ascorbic acid per kilogram (Burch, 1961). Urinary excretion will effectively measure intake with 60 to 80 per cent recovery of a large dose; serum levels will be above 1 mg per cent and will indicate an adequate intake. In Table 4 are shown the excretion and plasma levels of ascorbic acid (Vilter et al., 1954).

Table 4. Excretion and plasma levels of ascorbic acid

<table>
<thead>
<tr>
<th>Intake</th>
<th>Urinary exc.</th>
<th>Amount retained</th>
<th>Plasma level</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg %</td>
</tr>
<tr>
<td>50</td>
<td>11</td>
<td>39</td>
<td>0.85</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>80</td>
<td>1.12</td>
</tr>
<tr>
<td>200</td>
<td>109</td>
<td>91</td>
<td>1.14</td>
</tr>
<tr>
<td>350</td>
<td>259</td>
<td>91</td>
<td>1.15</td>
</tr>
</tbody>
</table>

aFrom Viter et al., 1954, p. 910.

Detection of the first stage of ascorbic acid tissue depletion accompanied by the deleterious effect is hard to identify (Crandon et al., 1941). Chronic gingivitis, pyorrhea, and bleeding gums occur as the result of chronic, mild ascorbic acid depletion based on low plasma ascorbic acid levels and tissues half saturated with the vitamin in many of the affected persons. In experimental ascorbic acid depletion, gum lesions did not occur, or occurred only after the tissue stores of ascorbic acid were exhausted and other scorbutic lesions had been present for many weeks. In
a human subject on a diet free of ascorbic acid but adequate in other nutrients, fatigue and poor performance appeared after 90 days. At this time the white blood cell ascorbic acid level had reached 4 mg per cent.

**Wound healing.** Wounds do not heal satisfactorily in clinical scurvy. Ascorbic acid is important to surgical patients; new wounds fail to heal or break open with stretching when apparently healed. The tissues depleted of ascorbic acid need to accumulate and store ascorbic acid in order to recover normal functions as the depleted animals do not systemically metabolize ascorbic acid more rapidly than the animal on adequate ascorbic acid intake.

More recently the surgical requirements for ascorbic acid has demanded even further re-evaluation in view of the suggestion that stress accentuates the need for the ascorbic acid and that the seriously injured human behaves physiologically like the scorbutic (Levenson et al., 1957).

Blood ascorbic acid can be maintained adequately on 100 to 300 mg of ascorbic acid per day for the majority of surgical patients. When such supplements are given, the plasma ascorbic acid level may be high relative to the body status of the vitamin (Crandon et al., 1961). Surgical patients with biochemical evidence of low serum and white blood cell-platelet ascorbic acid concentrations have a rate of breaking open of the wound eight times greater than that of patients with higher values of the vitamin. The concentration of ascorbic acid in the wound tissue in recently healed wounds rose above the concentration in distant tissue in the scar which persists for long intervals after healing (Abt et al., 1960).
Anemia. The first detailed description of an anemia of scurvy was published by Mettier et al. in 1930 (Robert Gould Research Foundation, 1947). They reported that the erythrocytes were normocytic or moderately macrocytic hyperchromic. After the administration of orange juice, there was a further increase in normoblasts in the bone marrow and a rapid rise in erythrocytes in the peripheral blood, which could not be shown by the administration of liver extract or iron preparation free of ascorbic acid.

The anemia in adults with scurvy is probably not due to ascorbic acid deficiency alone, but due to blood loss, iron deficiency, infections, and a B-complex deficiency state. A state of chronic iron deficiency could not be established, since the serum iron values were within normal limits (Wintrobe, 1946). After administration of ascorbic acid without any other change in regime, blood regeneration was rapid and the bone marrow returned to a normal state. Anemia has been defined as a reduction below normal in the number of red corpuscles, the quantity of hemoglobin, and the volume of packed red cells.

Macrocytic megaloblastic anemia occurs because of a deficiency of vitamin $B_{12}$ or folic acid and sometimes is combined with a deficiency of ascorbic acid. Combined deficiencies of folic acid and ascorbic acid cause the megaloblastic anemia of infancy and of scurvy (Vilter et al., 1963). In both conditions, ascorbic acid deficiency interferes with the mechanism necessary for the protection of the folic acid coenzymes and, when dietary folic acid is marginal, a severe deficiency of these enzymes occur (Figure 10).
Figure 10. Representation of the interrelationships of ascorbic acid and vitamin B₁₂ to the folic acid coenzymes. \(^a\)

\(^a\)From Vilter et al., 1963, p. 138.
Blood coagulation. The hemorrhagic symptoms of scurvy have been known for centuries. Early work showed that the fundamental lesion of scurvy is loss of vascular integrity. The influence of factors involved in clotting of blood and vascular integrity was studied by Dayton and Weiner (1961). Alteration in a nutritional factor, such as ascorbic acid or its biosynthesis mechanism, may influence clotting factors in many different ways. Even when altered coagulability was not found, the possibility remained that a coagulation factor change at the tissue or cellular level was influencing vascular integrity.

Ascorbic acid shortens clotting time in man and rabbit, and can cause changes in platelets, prothrombin complex, and thromboplastin complex (Constable, 1960). Hemorrhage into extravascular spaces of any etiology may initiate a chain of reactions involving clotting factors, which would result in an alteration in the coagulation properties of circulating blood.

The prolonged clotting times of plasma from scorbutic animals might be caused by a condition deficiency of vitamin K, if the intestinal absorption of vitamin K is impaired. All scorbutic animals examined had hemorrhages in the muscles adjacent to the knees and some also in the viscera but it has not been established whether they were casually related to the coagulation defects (Barkham and Howard, 1958).
Clinical and biochemical indices of a deficiency in infants and children

Infantile scurvy differs from the disease in adult persons because the growing bones of infants react differently to ascorbic acid deficiency. Breast-fed infants never develop scurvy, unless the nursing mother is extremely depleted of ascorbic acid. Consequently scurvy is a disease of artificially fed infants or infants past the age of breast feeding. The fresh cow's milk supplies enough ascorbic acid to prevent the clinical disease but pasteurization or boiling reduces ascorbic acid by 50 per cent or more. Further processing such as spray drying or evaporation with terminal sterilization reduces the ascorbic acid concentration of the formula partially to zero. Hydrogen peroxide, once used as a preservative for milk, was a flagrant cause of scurvy. Scurvy is often associated with rickets since defective diets are responsible for both diseases. Many cases of infantile scurvy have been reported recently for several countries of the world, especially from China, India, Africa, and Spain.

Symptoms. The first symptom to attract attention is usually tenderness of the legs. At first it may be so slight as only to cause the infant to cry upon being handled; in other cases there is a sudden refusal to sit or stand (Grewar, 1965). Changes in the gums and hemorrhage are commonly found in the early stage. The swelling of the joints, particularly the knee, may be so great that the limb is almost twice the size of its fellow. The gums are swollen, livid, and bleed easily. Irritability, anorexia, and low-grade fever may occur and are often accompanied by mild diarrhea.
Bone formation. The earliest manifestations of scurvy in the infant appear in bones and can be demonstrated by X-ray techniques. These lesions do not occur in the adult patient, therefore, the X-ray is of little help in the diagnosis of adult scurvy. A defect appears at the anterior corner of the tibia or at the outer corner of the lower end of the radius. The most distinctive X-ray sign of scurvy is the dense white line lying across the end of the shaft. It is composed of calcified cartilage matrix which is not destroyed in the normal fashion.

The costochondral junctions become broader and the lattice is irregular. The cortex is normally thinned which may be completely absent in radiographs. The changes characteristic of early scurvy are (Beaton and McHenry, 1964):

1. A ground-glass appearance of the shaft, due to atrophy of the trabeculae.
2. A broadened epiphyseal line is conspicuous.
3. A zone of rarefaction is observed beneath the broad epiphyseal line.

Formation and maintenance on dental structures. Zilva and Wells in 1919 and Jackson and Moore in 1916 were apparently the first to examine dental structure of scorbutic animals microscopically (Holt, 1936). Zilva and Wells noted fibrosis and the formation of osteoid-like deposits in the pulps of teeth, while Jackson and Moore reported hemorrhages. During the development of the scorbutic state the odontoblasts produced either a
modified product designated osteodentin or a liquid substance which accumulated between the odontoblasts and dentin (Fullmer, 1961). The daily administration of 12 mg of D-ascorbic acid to scorbutic guinea pigs did not prevent hemorrhages, but it did permit survival, a normal weight gain, and dentinogenesis (Burns et al., 1959).

In animals receiving the optimum amount of ascorbic acid the characteristic reaction of the pulp to cavity preparation was a greatly increased amount of dentin formation. When animals received only enough ascorbic acid to produce chronic scurvy, the characteristic osteodentin formation was produced (Mohammed and Mardfin, 1961). The guinea pigs with acute scurvy showed almost a complete cessation of dentin deposition, no recognizable odontoblasts, and a decrease in pulpal cell population. Growing children deficient in ascorbic acid have shown identical dentin formation as is characteristic of scorbutic guinea pigs.

Anemia. The basic etiological factor in hypochronic anemia which develops in a large number of young children is the depletion or inadequacy of the body's iron stores. Since iron is most efficiently absorbed in the ferrous state and adequate conversion of ferric iron in foods to ferrous iron, is aided by the presence of ascorbic acid, cysteine- and sulfhydryl-containing compounds, and the gastric hydrochloric acid, the hypochromic anemia of iron deficiency may be closely related to ascorbic acid intake (Figure 11). Iron absorption is decreased significantly by a high phosphate content in food, such as, phytates in oatmeal and brown bread,
Figures 11. The mean hemoglobin levels and mean reticulocyte contents with supplement of both iron and ascorbic acid.  

\textsuperscript{a} From Gorton and Bradley, 1954, p. 5.
alkaline foods, certain medications, an excess of calcium, and to a minor
degree, achlorhydria (Comar, 1961).

Megaloblastic anemia which is common and occurs predominately in the first year of life has occasionally been found in association
with steatorrhea and other disorders interfering with the ingestion,
absorption, or utilization of essential nutrients such as ascorbic acid,
folic acid, and vitamin B₁₂ (Vilter et al., 1963). Clinical signs of scurvy were
present in 25 per cent of the patients with megaloblastic anemia. There
were several reasons which led these workers to recognize that ascorbic
acid is a factor in the pathogenesis of megaloblastic anemia (Gorton and
Bradley, 1954):

1. Neither folic acid or ascorbic acid relieved the tyrosyluria
induced in scorbutic guinea pigs by feeding excessive tyrosine.

2. Megaloblastic anemia was reported frequently as a complication
of scurvy.

3. Megaloblastic anemia was not produced by feeding a variety
of diets to species which are able to synthesize ascorbic acid.

A deficiency of ascorbic acid is characteristic in infants in whom
megaloblastic anemia developed. A chronic deficiency of ascorbic acid
leads to a deficiency of folic acid or some difficulty in the metabolism of
folic acid which results in a megabloblastic pattern in bone marrow (May et
al., 1950). The megaloblastic anemia has disappeared among those infants
being fed milks which supply adequate ascorbic acid.
EDUCATIONAL PROBLEM

Biochemical Methods Used to Measure Ascorbic Acid

Nutritional Status

In blood

One of the methods of biochemical estimation of ascorbic acid intake is the serum or plasma ascorbic acid level. If an adult consumes an ascorbic acid free diet, his serum level approaches zero in 4 to 6 weeks but the clinical signs of scurvy do not appear until after 4 to 6 months of deprivation (Pearson, 1966).

In adults plasma ascorbic acid levels of 0.6 to 1.4 mg per 100 ml indicate a daily intake of 70 mg or more, and levels of less than 0.2 mg per 100 ml indicate intake of less than 25 mg (Davey et al., 1952).

The ICNND (Interdepartmental Committee on Nutritional Defense) in 1963 has classified serum ascorbic acid levels (in milligrams per 100 ml) as follows; less than 0.10, "deficient;" 0.10 to 0.19, "low;" 0.2 to 0.4, "acceptable," and over 0.4, "high."

The white cell-blood platelet ascorbic acid concentration is more closely related to tissue stores. In well-nourished adult the white cell-blood platelet ascorbic acid level averages 20 to 30 mg per 100 ml but it will decrease to 0 to 2 mg per 100 ml in 3 to 5 months in case of an ascorbic acid free diet. Clinical scurvy will usually appear shortly thereafter (Pearson, 1966).
In urine

A close correlation between the daily intake of ascorbic acid and the ascorbic acid content of an early morning fasting urine sample was examined by Johnson et al., in 1945 (Pearson, 1966). The average 24 hours ascorbic acid excretion of the well-nourished adult ranged from 8 to 25 mg. In human beings where it is of importance to determine the tissue ascorbic acid deficit, urinary excretions after ascorbic acid administration are informative. About 40 per cent of the test dose of ascorbic acid is excreted in the urine, with less than 5 per cent appearing as respiratory CO2. The urinary products excreted are primarily oxalate (44 per cent), ascorbic acid (20 per cent), 2,3-diketogulonic acid (20 per cent), and dehydroascorbic acid (2 per cent) (Hellman and Burns, 1958).

Requirements

Early estimates of ascorbic acid requirements indicated that scurvy could be prevented by a daily allowance of 25 to 30 ml of lemon juice which should furnish 10 to 15 mg of ascorbic acid. There are three main types of standards that have been used for indicating the daily requirements of ascorbic acid (Abt et al., 1963):

1. Minimum requirements indicating the quantity of ascorbic acid needed daily to prevent the appearance of symptoms of scurvy.

2. Optimum requirements indicating the quantity of ascorbic acid needed daily to allow the individual the best possible state of health, functional efficiency, and resistance, e.g., to infections.
3. The Nutrition Research Council's recommended dietary allowances (US) which allow enough ascorbic acid above the minimum to cover the requirement of all healthy individuals under all circumstances.

Standards and requirements as listed by Abt et al. (1963) are presented in Table 5.

Table 5. Standards and requirement of ascorbic acid for human and guinea pigs

<table>
<thead>
<tr>
<th>Standards</th>
<th>Guinea pigs</th>
<th>Infants</th>
<th>Adults with req. of 2,400 cal/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>League of Nations, 1938</td>
<td>-</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>U. S. Recommended Dietary Allowance, 1963</td>
<td>-</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>Min. req. determined by macroscopic examination for scurvy</td>
<td>0.5</td>
<td>3-6</td>
<td>Below 10</td>
</tr>
<tr>
<td>Determined by healing of wound and bone fractures</td>
<td>5</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

*From Abt et al., 1963, p. 26.*

Minimum requirements

Early workers were in agreement that the minimum requirement for the
prevention of obvious classical scurvy is 10 to 20 mg daily. There was controversy as to the benefits resulting from the ascorbic acid intakes of 75 mg daily for adults as recommended by the Food and Nutrition Board of the National Research Council. An investigation conducted by the British Medical Research Council from 1944 through 1946 led to the conclusions that the minimum requirements for ascorbic acid to prevent scurvy in adults must be below 10 mg a day.

A daily intake of ascorbic acid by human subjects of 25 and 30 mg to prevent scurvy was originally recommended by the Technical Commission of the League of Nations and by the British Medical Research Council (Abt et al., 1963).

In a study of Royal Canadian Air Force personnel, one group was maintained on a diet that furnished 8 mg of ascorbic acid daily for 8 months. During this period no signs of scurvy developed (Johnstone et al., 1946).

Recommended dietary allowances

The National Research Council (Food and Nutrition Board, 1964) has based and maintained the recommended dietary allowance of ascorbic acid at 75 mg for adults with reference to the comprehensive literature on ascorbic acid studies (Table 6). Two factors which influenced their recommendation were:

1. There is evidence that the minimum requirement may not be satisfactory for the preservation of optimum health through long periods of time or when the body is subjected to common forms of stress.

2. The minimum ascorbic acid requirement may not produce satisfactory healing of wounds, enzyme action, and cell proliferation.
Table 6. Food and Nutrition Board, National Research Council
Recommended Daily Dietary Allowances, Revised 1963

<table>
<thead>
<tr>
<th>Age</th>
<th>Ascorbic acid (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>75</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>70</td>
</tr>
<tr>
<td>Lactating (850 ml daily)</td>
<td>100</td>
</tr>
<tr>
<td>INFANTS, up to 1 year</td>
<td>150</td>
</tr>
<tr>
<td>Children, 1-3 years</td>
<td></td>
</tr>
<tr>
<td>4-6 years</td>
<td>35</td>
</tr>
<tr>
<td>7-9 years</td>
<td>50</td>
</tr>
<tr>
<td>Boys, 10-12 years</td>
<td></td>
</tr>
<tr>
<td>13-15 years</td>
<td>75</td>
</tr>
<tr>
<td>16-20 years</td>
<td>90</td>
</tr>
<tr>
<td>Girls, 10-12 years</td>
<td></td>
</tr>
<tr>
<td>13-15 years</td>
<td>75</td>
</tr>
<tr>
<td>16-20 years</td>
<td>80</td>
</tr>
</tbody>
</table>

Food and Nutrition Board, 1964, p. vii, adapted.

In Table 7 is shown a comparison of dietary standards for ascorbic acid between several countries.

**Infants.** Infants nourished on diluted cow's milk which contains from 0.1 to 2.5 mg ascorbic acid per 100 ml will get an average daily allowance of 3 to 6 mg of ascorbic acid, and 3 to 6 mg will not be sufficient in all cases against manifestations of scurvy. Consequently the minimum requirement for infants would be greater than the 6 mg of ascorbic acid in milk (Van Ekelan, 1953).

Mother's milk contained between 0.8 to 3.5 mg per 100 ml during the season when least ascorbic acid was eaten, while the content ranged between...
Table 7. Comparison of dietary standards for ascorbic acid for selected age groups

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>US-NRC</th>
<th>USSR</th>
<th>Canada</th>
<th>Japan</th>
<th>Britian</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>-</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>30</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>4-6 years</td>
<td>30</td>
<td>50</td>
<td>50</td>
<td>20</td>
<td>40</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Boys, 13-15 years</td>
<td>30</td>
<td>80</td>
<td>70</td>
<td>30</td>
<td>80</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>70</td>
<td>70</td>
<td>30</td>
<td>65</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>30</td>
<td>70</td>
<td>70</td>
<td>30</td>
<td>69</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Lactating</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>100</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>120</td>
<td>50</td>
<td>150</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

\[a\] Wohl and Goodhart, 1964, p. 436.

4.1 to 6.8 mg per 100 ml during the season when more ascorbic acid was available (Uhl, 1958). In such instances, breast fed infants receive a daily allowance of at least 20 mg of ascorbic acid. These infants never develop scurvy. Plasma ascorbic acid levels in healthy breast fed infants have been found to range between 0.5 to 1.5 mg per 100 ml, whereas levels in healthy infants fed diluted cow's milk show averages of 0.25 mg per 100 ml (Uhl, 1958).

The concentration of ascorbic acid in plasma could be increased from 0.4 to 0.8 mg per 100 ml by administration of 20 mg or more of ascorbic acid daily which was as satisfactory as 75 mg in adult (Goldsmith, 1961).

**Pregnancy and lactation.** Ascorbic acid requirement appears to be increased during pregnancy and lactation. This might be anticipated since ascorbic acid plays an important role in growth processes and is found in abundance in active and growing tissues. The fetal needs must be met from...
the stores of the mother and maternal diet. Placental tissue contains a relatively high concentration of ascorbic acid, and the levels of ascorbic acid in the plasma of infants are two to four times higher than than those in maternal plasma (Goldsmith, 1961).

Decreases in plasma ascorbic acid occur between the first and third trimesters of pregnancy with a further decrease postpartally (Macy et al., 1954). The lower postpartum concentration may reflect a decrease in food intake, an increased need for ascorbic acid for wound healing, an increased requirement for milk production, and for endocrine readjustment. In general, serum concentration decreased during pregnancy but a daily intake of 80 to 100 mg of ascorbic acid supported high levels in the serum. After delivery there is a further decrease in serum ascorbic acid concentration. Serum concentration during lactation did not average more than 0.3 mg per 100 ml even on intakes exceeding 120 mg daily (Goldsmith, 1961).

An intake of 100 mg ascorbic acid per day during the pregnancy and 150 mg during lactation should result in optimal levels in their reproduction. In experimental guinea pigs the average total birth weight of the young was greater and their period of survival tended to be longer when the mother pigs were fed adequate ascorbic acid (Orrea et al., 1961).

Therapeutic uses. The primary use of ascorbic acid in clinical medicine is in the prevention and treatment of scurvy which can be prevented by the administration of 10 mg of ascorbic acid daily. In cases of scurvy in infants, 25 mg four times daily will cure scurvy, while in adults 100 mg five or six times daily will result in rapid restoration to normal.
There appears to be no danger of toxicity from ascorbic acid in large doses because of the rapid excretion of the excess by the kidney. Adequate supplies of ascorbic acid are necessary for the normal wound healing process, maturation of collagen, allergic and toxic states, anemia, and stressful situations such as burns, severe injuries, operations, infections, and rheumatic diseases. Large amounts of ascorbic acid are consumed by the adrenal glands during illness in the synthesis of cortical hormones from cholesterol. A high incidence of ascorbic acid deficiency has been found in patients with pellagra, chronic alcoholism, peptic ulcer, and diarrhea. The therapeutic value of large doses of ascorbic acid in these situations has not been determined with certainty. Synthetic ascorbic acid has been available for clinical use since 1933 (Abt et al., 1960).

Conservation of Ascorbic Acid in the Preparation and Preservation of Foods

Factors of destruction

Ascorbic acid is an unstable compound, water soluble, and easily destroyed by heat. Ascorbic acid, with the formula $C_6H_8O_6$, is known as a reduced compound and is very susceptible to oxidation. The first product of the oxidation is dehydroascorbic acid, $C_6H_6O_6$, which can be used equally as well by the body as the reduced form. Further oxidation of dehydroascorbic acid produces diketogulonic acid which contains no antiscorbutic properties.
Reduced Ascorbic acid $\xrightarrow{\text{Oxidation}}$ Dehydroascorbic acid $\xrightarrow{\text{Reduction}}$ +H$_2$O

Diketogulonic acid

Many vegetables and fruits which contain high concentrations of ascorbic acid may lose a considerable proportion of their ascorbic acid values in the ordinary cooking process. It is not so much destroyed by heat itself as by a process of oxidation which is accelerated by increase of temperature.

The rate of destruction is lower when air is excluded as by steam or by vacuum and is higher when acidity has been reduced or alkalinity increased by the addition of soda to the food. Some metals, such as copper, catalyze the destruction of ascorbic acid. In the case of tomato juice of natural acidity, the boiling for one hour destroyed about 50 per cent and for four hours destroyed practically 68 per cent of the antiscorbutic factor of ascorbic acid (Sherman and Langford, 1957).

Both time and temperature of heating must be held to the lowest minimum for ascorbic acid to be conserved to the best advantage. As ascorbic acid is readily soluble in water, the rejection of cooking water, or of the fluid contents of the can, may involve a loss no less than that of the actual destruction which occurs in the cooking and canning processes (Table 8). An important further consideration in conserving the ascorbic acid value during cooking is to place the food in boiling water and bring it as quickly as possible to the boiling temperature because the ascorbic acid destroying enzymes present in many foods may be inactivated by heat.
Proper blanching of vegetables before freezing serve to inactivate the enzymes and reduce the deterioration of the ascorbic acid value in storage. Many plants contain an ascorbic acid destroying enzyme, oxidase, that facilitates the oxidation of the ascorbic acid in the presence of air. This enzyme begins to destroy the ascorbic acid when vegetables or fruits are damaged by drying, bruising, pounding, or cutting but is inactivated at temperature of $60^\circ$C. However, heat may facilitate the oxidation of ascorbic acid even in the absence of this enzyme, especially in an alkaline medium, soda, and in the presence of copper.

Table 8. Ascorbic acid content in raw, canned, and cooked food$^a$

<table>
<thead>
<tr>
<th>Food</th>
<th>Raw</th>
<th>Cooked</th>
<th>Canned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/100 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Asparagus</td>
<td>33</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Turnip greens</td>
<td>136</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Banana</td>
<td>10</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Broccoli</td>
<td>118</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Brussels sprout</td>
<td>94</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>Cabbage</td>
<td>50</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Cantaloupe</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>64</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Chard</td>
<td>38</td>
<td>17</td>
<td>-</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>40</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>Kale</td>
<td>115</td>
<td>51</td>
<td>-</td>
</tr>
<tr>
<td>Mustard greens</td>
<td>102</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>Orange or juice</td>
<td>49</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Green peas</td>
<td>26</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>23</td>
<td>-</td>
<td>16</td>
</tr>
</tbody>
</table>

$^a$From Watt and Merrill, Agriculture Handbook No. 8, 1963, p. 6-62, adapted.
Ascorbic acid retention

Ascorbic acid retention in vegetables remains an important criteria in choosing cooking methods for vegetables. A warm environment, exposure to air, solubility in water, heat, alkali, and dehydration are detrimental to the retention of ascorbic acid in foods. The ascorbic acid content of cooked cabbage reported in Table 8 could be greatly increased by the method of cooking. When cabbage is cut in wedges or coarsly shredded and cooked in a small amount of water until just done, from 90 to 95 per cent of the original ascorbic acid is retained; shredded and cooked in excess water until just done, retentions of 75 per cent are obtained; and shredded cabbage cooked in excess water until overdone or 30 minutes or longer retains 50 per cent or less (Wilcox, 1967).

In vegetables cooked with the boiling water method, 45 per cent of the original content was retained which was significantly less than in the steaming methods, 69 per cent (Gordon and Noble, 1964). Of the several steaming methods, that in the pressure saucepan, which uses a short cooking time but high temperature, was not significantly different from the average retention in the other cooking methods which use longer cooking time but lower temperature (Table 9).

Higher retention of ascorbic acid was obtained in vegetables cooked in an electronic range when compared to using conventional boiling methods. However, there was no statistical difference in the amount of ascorbic acid retained when fresh and frozen vegetables were cooked by conventional and microwave methods.
Table 9. Ascorbic acid in raw vegetables and percentage retention after cooking

<table>
<thead>
<tr>
<th>Vegetables</th>
<th>Mean</th>
<th>Retention in cooked vegetables</th>
<th>Retention in cooking water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pressure saucepan</td>
<td>Waterless saucepan</td>
</tr>
<tr>
<td>Broccoli</td>
<td>131.7 ± 13.27</td>
<td>85</td>
<td>51</td>
</tr>
<tr>
<td>Brussels sprouts</td>
<td>97.6 ± 2.84</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Cabbage</td>
<td>59.5 ± 2.65</td>
<td>74</td>
<td>56</td>
</tr>
<tr>
<td>Rutabagas</td>
<td>60.0 ± 3.03</td>
<td>88</td>
<td>69</td>
</tr>
<tr>
<td>Turnips</td>
<td>30.6 ± 0.84</td>
<td>85</td>
<td>75</td>
</tr>
</tbody>
</table>

\[\text{Mean \pm SE}\]

\[\text{Retention in cooked vegetables}\]

\[\text{Retention in cooking water}\]

\[\text{From Gordon and Noble, 1959, p. 579, adapted.}\]

Citrus fruits retained from 95 to 96 per cent of their ascorbic acid content at temperatures of 4 to 8°F and after two days of storage 91 per cent. The frozen concentrated citrus juices stored at 8°F for 12 months retained 95 per cent (Huggart et al., 1954).

Effect of radiation

Losses of ascorbic acid in the processing of foods may be large. Dried fruits and vegetables show little or no ascorbic acid activity. Canned or frozen fruits generally contain most of the ascorbic acid present in the original fresh fruits, especially acid fruits like grapefruit and tomatoes.

Ascorbic acid is affected immediately and quite noticeably by radiation.
because of its redox function. It is one of the more radio sensitive vitamins. While most of the ascorbate oxidation occurred during the exposure period, there was a continuing decrease in ascorbic acid levels after irradiation. Gamma irradiation of strawberries at doses of 0.3 and 0.4 megarad resulted in respective losses of ascorbic acid of 62 and 81 per cent (Chichester and Mrak, 1966). Maxie et al. (1964) studied the effect of cold storage on the irradiated fruits. Severe injury in the form of cavities along the segment walls was observed following cold storage. These workers found that gamma irradiation could not be used with lemons destined for long term storage.

It is interesting that niacin and riboflavin have a protective action for ascorbic acid against radiation but most fruits contain sources of vitamin A and ascorbic acid and are relatively low in thiamine, riboflavin, and niacin.

Sources

Citrus fruits, tomatoes, strawberries, cantaloupe, pineapple, and guavas are excellent or good fruits sources while broccoli, brussels sprout, spinach, kale, turnips, green pepper, cabbage, and leaves from the more actively growing parts of the plant are excellent plant sources. The use of potatoes and sweet potatoes as staple food items enhances ascorbic acid intake provided that preparation methods have been good.

Other nonacid fresh fruits such as peaches, pears, apples, banana, and blueberries contribute small amount of ascorbic acid.

Frozen and canned citrus fruits such as orange, grapefruit, and lemons
are also excellent sources. Animal sources are as a whole, poor; liver is superior to muscle tissue, and raw fresh milk from a cow fed green grass may contain considerable ascorbic acid. However, when milk is pasteurized, a large proportion of the original amount has been destroyed.

The ascorbic acid content of plant foods is known to vary with such factors as variety, climate, amount of sunshine, soil, degree of maturity, and storage. Ascorbic acid accumulates throughout the ripening process following the setting of the fruit. The longer the fruit remains on the vine or tree before harvesting, until the fruit becomes overripe, the higher the ascorbic acid content.

Immature seeds such as peas and beans contain some ascorbic acid, but lose it all at maturity. Ascorbic acid is not present in dry mature seeds, but develops in the sprout as soon as they begin to grow.

Prevention of Signs of Deficiency

Ascorbic acid nutritional status in U.S.A.

Many studies in the U.S.A. are reported on the intake of ascorbic acid by boys, girls, men, and women, living in different sections of the country. The diets of the boys and men in these studies met or exceeded the allowances recommended in 1963, while ascorbic acid in the diets of girls between the ages of 12 and 16 years and women from about 30 to 45 years and after 70 years tended to be marginal or below the recommended allowances (Chaney and Ross, 1966).

In infants the incidence of scurvy is probably higher than is usually
stated. Among 1303 children aged 1 to 2 years, on whom microscopic examination were made, 69 were found to have scurvy. Of this number 60 had been recognized clinically. In another comparison relating types of feeding to incidence of scurvy, 51 of 155 infants fed on cow's milk had scorbutic symptoms but none of the 58 breast fed babies showed symptoms of scurvy (Chaney and Ross, 1966). South Carolina has the highest infant death rate. Most cases of infant death show a low level of serum protein, such as albumin and globulin associated with marginal protein nutrition, and a low concentration of serum ascorbic acid. Today, the diet can easily contain much more ascorbic acid than it did in 1900, but many diets still tend to be low in this vitamin. Adults with scurvy are still reported in large city and county hospitals. Recognition of cases of scurvy is based on the classic signs and symptoms.

Approximately 10 per cent of the Navajo Indian children who attend the Intermountain School, Brigham City, Utah, show severe hemorrhagic gingivitis when they arrive from the reservation. It is related to ascorbic acid deficiency. Wilcox and Grimes (1961) found that ascorbic acid levels in the white cell-platelet fraction of blood were low in most cases. When the children who had low ascorbic acid values below 0.3 mg were given an ascorbic acid supplement of 300 mg for three weeks, serum values returned to normal and the gingivitis responded satisfactorily. Six months after initiation of the study during which time the school cafeteria diet was eaten, all groups of subjects had normal white cell values and the gum condition was normal. McDonald (1963) found the school cafeteria diet to be adequate in ascorbic acid content.
Other countries

Britian and Australia lead the world in the incidence of infantile scurvy. A more vigilant educational campaign is advocated to offset the ignorance and neglect. Infantile scurvy occurs more frequently in developed countries rather than in undeveloped countries. Even breast fed infants may show clinically ascorbic acid deficiency if the mother's diet is restricted in ascorbic acid intake. Three major forms of disturbed nutrition that may be found in underdeveloped countries are hunger and starvation due to lack of food; protein malnutrition; and the classical vitamin deficiency disease such as pellagra, beriberi, rickets, and scurvy. Infants in Czechoslovakia, Lybia, Mexico, Africa, Far east, India, and Spain show very low level of serum ascorbic acid concentration, and these countries have a high rate of infant death and infantile mortality.

In Korea, nutritional deficiency states of men in the army include angular cheilosis, underweight, edema, hypoproteinemia, neuropathy of thiamine deficiency, and low plasma ascorbic acid values with gingival changes.

Solving the problem

An important factor responsible for deficiency diseases is the lack of knowledge of causes and methods of prevention. Ignorance of nutritional needs and of the nutritive value of foods plays an important role in the etiology of deficiency diseases. In many technically undeveloped areas nutrition education can be incorporated into campaigns against ignorance which greatly retards progress and economic development. The prevention of deficiency diseases requires that the basic principles of nutrition be included in the curriculum of future teachers,
nurses, social workers, agricultural workers, extension workers, home economists, and all other professional persons who use their knowledge in community activities.

Nutrition workers in the United States have found that the easiest way that the average housewife can be assured of giving her family a good diet is to use the Basic Four Groups (Table 10 from Page and Phipard, 1957). The use of the minimum number of servings listed for each of the food groups forms a foundation for a good diet. Workers in other countries have adapted this plan using foods common to their localities and the dietary customs of their people.

In Korea, the nutrition workers adapted the basic 4 plan into 5 basic food groups which fit the needs of the Korean people (Table 11).

Nutrition research has demonstrated the relationships of nutritional status to health, vigor, and achievement; the far-sighted leaders of many nations are seeking information and assistance in solving their urgent problems. Three international organizations, actively interested in nutritional aspects of health, stand ready to help. The Nutrition Committee of the Food and Agriculture Organization of the United Nations (FAO) is especially concerned with nutritional problems related to production, distribution, and consumption of food. The Nutrition Section of the World Health Organization (WHO), also of the United Nations, has as a primary obligation, the investigation of conditions related to clinical aspects of nutrition. The United Nations Children's Fund was established to better the health standards of children in needy areas.
Table 10. A daily basic four food guide used in the United States\textsuperscript{a}

<table>
<thead>
<tr>
<th>1. Milk Group</th>
<th>Children under 9---2 to 3 cups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children 9 to 12---3 or more cups</td>
</tr>
<tr>
<td></td>
<td>Teenagers---------4 or more cups</td>
</tr>
<tr>
<td></td>
<td>Adults-----------2 or more cups</td>
</tr>
</tbody>
</table>

2. Meat Group
2 or more servings

- Beef, veal, pork, lamb, poultry, fish, eggs.
- As alternates--dry beans, dry peas, nuts.

3. Vegetables and Fruits Group
4 or more servings

- Include--A citrus fruit or other fruit or vegetable important for vitamin C
- A dark green or deep-yellow vegetable for vitamin A--at least every other day.
- Other vegetables and fruits, including potatoes.

4. Bread and Cereal Group
4 or more servings

- Whole grain, enriched, or restored

\textsuperscript{a} Plus other foods as needed to complete meals and to provide additional food energy and other food values. Taken from Page and Phipard, 1957, p. 1.
Table 11. A daily basic five food guide used in Korea

<table>
<thead>
<tr>
<th>The basic five food groups</th>
<th>Food groups used for family food plan</th>
<th>Main nutrient contributed by each food groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Milk, all kinds of anchovy, and seaweed group</td>
<td>1. Milk and milk product group</td>
<td>Complete protein Calcium, casein, riboflavin</td>
</tr>
<tr>
<td></td>
<td>2. anchovy, which can be eaten bones, group</td>
<td>Calcium, phosphorus, iron</td>
</tr>
<tr>
<td></td>
<td>3. Seaweed group</td>
<td>Iodine, calcium, iron, vitamin A</td>
</tr>
<tr>
<td>2. Meat Group 2 or more servings</td>
<td>4. Meat, fish, and poultry group</td>
<td>Complete protein, thiamine, riboflavin, niacin, calcium, iron</td>
</tr>
<tr>
<td></td>
<td>5. Beans and bean product</td>
<td>Protein, iron</td>
</tr>
<tr>
<td></td>
<td>6. Eggs</td>
<td>Protein, thiamine</td>
</tr>
<tr>
<td>3. Vegetable-fruit Group 4 or more servings</td>
<td>7. Dark-green veg.</td>
<td>Ascorbic acid, iron, calcium, Vit-A, carotene, ascorbic acid</td>
</tr>
<tr>
<td></td>
<td>8. Yellow-green veg.</td>
<td>Calcium, ascorbic acid, Vit-A</td>
</tr>
<tr>
<td></td>
<td>9. Fruits and other veg.</td>
<td>Calorie source, some protein</td>
</tr>
<tr>
<td></td>
<td>10. Rice group</td>
<td>Thiamine, niacin, riboflavin</td>
</tr>
<tr>
<td></td>
<td>11. Other grain incl. potatoes</td>
<td>Vitamin A, saturated and unsaturated fatty acid</td>
</tr>
<tr>
<td>5. Butter-oil and All seasoning Group 2 or more servings</td>
<td>12. Butter, fat, and oil group</td>
<td></td>
</tr>
</tbody>
</table>

Meeting daily ascorbic acid allowances

The vegetable and fruit group of the basic diet fulfills the recommended allowances of adults and children for ascorbic acid (Figure 12 and Table 12).

Figure 12. Daily ascorbic acid allowances: food plus serving size.
Table 12. Fruits and vegetables with serving size needed to meet ascorbic acid recommendation

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount</th>
<th>Ascorbic acid (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For men and women (75 mg daily)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>1 med.</td>
<td>66</td>
</tr>
<tr>
<td>Beans, green</td>
<td>1/2 cup</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1/2 med.</td>
<td>50</td>
</tr>
<tr>
<td>Sweet potatoe</td>
<td>1 med.</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Pineapple juice</td>
<td>1/2 cup</td>
<td>11</td>
</tr>
<tr>
<td>Banana</td>
<td>1 med.</td>
<td>10</td>
</tr>
<tr>
<td>Stewed apricot</td>
<td>1/2 cup</td>
<td>3</td>
</tr>
<tr>
<td>Apple</td>
<td>1 med.</td>
<td>3</td>
</tr>
<tr>
<td>Spinach</td>
<td>1/2 cup</td>
<td>27</td>
</tr>
<tr>
<td>Green peas</td>
<td>1/2 cup</td>
<td>12</td>
</tr>
<tr>
<td>Corn</td>
<td>1/2 cup</td>
<td>7</td>
</tr>
<tr>
<td>Carrots</td>
<td>1/2 cup</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Foods</th>
<th>Amount</th>
<th>Ascorbic acid (mg)</th>
<th>Total mg needed</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td>1/2 cup</td>
<td>46</td>
<td>46</td>
<td>4-6</td>
</tr>
<tr>
<td>Potatoes</td>
<td>1 med.</td>
<td>20</td>
<td></td>
<td>10-12</td>
</tr>
<tr>
<td>Banana</td>
<td>1 med.</td>
<td>10</td>
<td>76</td>
<td>16-19</td>
</tr>
<tr>
<td>Cabbage</td>
<td>1/2 cup</td>
<td>25</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

**For children**

- **Ages in years**: 4-6, 10-12, 16-19
- **Daily allowance**: 50 mg, 75 mg, 100 mg

<table>
<thead>
<tr>
<th>Foods</th>
<th>Amount</th>
<th>Ascorbic acid (mg)</th>
<th>Total mg needed</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td>1/2 cup</td>
<td>46</td>
<td>46</td>
<td>4-6</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1/2 med</td>
<td>52</td>
<td></td>
<td>10-12</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>98</td>
<td></td>
<td>16-19</td>
</tr>
</tbody>
</table>
Table 12. Continued

<table>
<thead>
<tr>
<th>Foods</th>
<th>Amount</th>
<th>Ascorbic acid (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange</td>
<td>1 med.</td>
<td>66</td>
</tr>
<tr>
<td>Asparagus</td>
<td>1/2 cup</td>
<td>23</td>
</tr>
<tr>
<td>Banana</td>
<td>1 med.</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>Brussel sprouts</td>
<td>1/2 cup</td>
<td>67</td>
</tr>
<tr>
<td>Apple</td>
<td>1 med.</td>
<td>3</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>1/2 cup</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>103</td>
</tr>
</tbody>
</table>

For lactation one-half cup of orange juice is added daily for a supplement of 150 mg per day.
CONCLUSION AND SUMMARY

Scurvy was probably the first disease to be definitely associated with a food deficiency. It was common in Europe in the fifteenth century and must have been known long before that. Ascorbic acid has multiple functions in the animal body. There has been much progress in research on the origins, end products, and functions of ascorbic acid in recent years.

Ascorbic acid is present in nearly all tissues in plants and animals. All of the higher plants and most animals, with the exception of the primates and the guinea pigs can synthesize it. In plants, it is most abundant in the actively growing zones, regions of high metabolic activity.

The pathological change leading to all of symptoms is a weakening in the endothelial wall of the capillaries, because of a reduction in the amount of intercellular substance. This deficiency in supporting material may extend to the cartilage, bone, muscles, and other tissues and is responsible for the symptoms mentioned that are necessary for the healing of wounds and fracture of bones.

Scurvy is no longer a major problem, but instead is confined almost entirely to local individual accidents or carelessness. Even in the history of ascorbic acid, there have been many erroneous and confusing reports claiming the existence of other nutrients as part of the causative background of scurvy and the classic symptoms associated with ascorbic acid deficiency.
It may safely be concluded therefore that the subclinical effects of ascorbic acid deficiency are very prompt to appear, certainly in the young. Whether ascorbic acid has a definite causal relationship to any other pathologic process is as yet uncertain.
LITERATURE CITED


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