

# Vitamins C and P in Cardiovascular and Cerebrovascular Disease

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FOLLOWING the discovery of ascorbic acid, isolated by King and Waugh in 1932,<sup>1</sup> enthusiastic results were reported by Wright and Lilienfeld<sup>2</sup> in the treatment of purpura, pyuria, pyorrhea, agranulocytosis, and thrombocytopenia, but the initial enthusiasm soon abated. In 1940, Goodman and Gilman<sup>3</sup> stated that there was no conclusive evidence that ascorbic acid was of any value except in relief of symptoms casually associated with scurvy.

Investigations during the past ten years have shown that ascorbic acid plays a vital rôle in many functions of the body. A new concept of the importance of vitamin C in maintaining the intercellular substance of connective tissue<sup>4</sup> has developed. Vitamin C has been shown to be essential to cellular metabolism, helpful in wound healing, necessary for proper functioning of the adrenal gland, useful in detoxifying certain drugs such as arsenic and sulfanomides, also useful in the treatment of gingivitis<sup>5</sup> and infections.

Observations made on metabolic function of ascorbic acid in the body indicate that it may be an important key to cellular integrity.<sup>6</sup> Zintel<sup>7</sup> stated that vitamin C was necessary for the maturation of precollagen to collagen of fibrous tissue. With the help of an enzyme, precollagen is transformed into a collagen which helps strengthen the cells of the body and cause them to stick together. Meyer and McCormick<sup>8</sup> concluded, however, that a deficiency of vitamin C produced a degeneration of cytoplasm instead of a lack of intercellular cement. They found evidence that normal cells did not separate, but often degenerated cells may lie in normal positions.

## EFFECT ON CAPILLARY FRAGILITY

AFTER the announcement by Rusznyak and Szent-Györgyi<sup>9</sup> in 1936, a new field of research in vascular disturbances was begun. A newly discovered substance was called vitamin P because of its effect upon the permeability of the vascular system. Hesperidin, a flavanone glucoside, was felt to be the active principle of vitamin P in controlling capillary resistance. Uniformly successful results in controlling capillary resistance were obtained by Scar-

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borough.<sup>10</sup> Other workers confirmed the fact that hesperidin was capable of restoring capillary fragility to normal in a large percentage of cases. In 1944, rutin, a flavanone glucoside related to vitamin P, was found to be effective in the treatment of increased capillary fragility associated with hypertension. Griffith, Couch, and Lindauer<sup>11</sup> studied 14 hypertensive patients with an increased capillary fragility. Capillary fragility became normal in eight patients after two months, but when rutin was discontinued, it showed an increase after six weeks. A monograph by Couch and co-workers,<sup>12</sup> was published in 1946 on studies of 173 patients with an increased capillary fragility. Eighty-eight per cent had a return to normal capillary strength. Eleven per cent had a history of apoplexy but had no further attacks while under treatment.

VARIOUS investigations have suggested a synergistic relationship between the flavanones and vitamin C. Some workers believed vitamin P to be necessary for proper use of ascorbic acid in cells. Others, however, have stated that vitamin C alone has effect upon capillary resistance. Soloff and Bello<sup>13</sup> found that the capillary fragility in all but 2.5 per cent of 50 hypertensive patients responded to vitamin C therapy. They felt, therefore, that hypertensive patients may have a higher incidence of subclinical scurvy. Although the specific need of the body for vitamin P has not been definitely established, the importance of vitamin C to cellular integrity seems well-founded.

The use of vitamin C and vitamin P in treatment and prevention of cardiovascular diseases may be based on five premises: (1) A deficiency of vitamin C in the diet has been found commonly in older people. In 1946, Thewlis and Gale<sup>14</sup> analyzed several hundred diets of older people and found that one of the most frequent deficiencies was vitamin C. (2) Reports have described the effectiveness of rutin in preventing capillary fragility. (3) It was discovered that vitamin C plays an important rôle in formation of intercellular cement of connective tissues and in tissue metabolism. (4) Vitamin P and vitamin C apparently complement each other in maintaining vascular integrity. (5) Alvarez<sup>15</sup> pointed out in 1946 that small cerebrovascular thromboses may occur repeatedly and may result in gradual deterioration of the nervous system.

There has been only an occasional suggestion in the literature that vitamin C might be of benefit in the control of vascular illnesses. King<sup>6</sup> stated that there was an "obvious and serious need for long-time experiments to gain a better appraisal of the cumulative effects of moderate deficiencies."

#### ROLE IN CARDIO- AND CEREBROVASCULAR DISEASE

THERE are many varieties and degrees of heart and cerebrovascular disease, but regardless of the underlying anatomical disease, the basic pathological process is a failure of the blood vessels to maintain a normal equilibrium. The viability of cells of the body depends on a good blood supply for proper

respiration, nutrition, excretion, and water balance. Evidence has accumulated that proper nutrition can favorably influence the state of the capillaries and other blood vessels.

When capillaries are damaged they dilate and blood is slowed. The permeability of cells is increased. Plasma, leucocytes, and red blood cells pass through the capillary walls. When the osmotic pressure of the exudate rises, more plasma is attracted outside the capillaries. The walls of the capillaries are further weakened; a localized diapedesis results. If clotting of blood occurs, adjacent tissues become necrotic and the process may spread to involve other capillaries and arterioles. The phenomenon of hemorrhage and thrombosis is intimately associated. Instances of coronary occlusion have been found which resulted from hemorrhage within the arterial walls. Patterson<sup>16</sup> concludes that "capillary rupture with intimal hemorrhage is concerned with the mechanism of cerebral arterial thrombosis and possibly, in certain cases the causation of cerebral spasm and rupture." He suggested that the rupture of the capillaries may be due to a high intracapillary pressure, atheromatous degeneration of supporting tissues, and a decrease in the cellular content of ascorbic acid. The blood vessels are considerably weakened thereby, and cannot stand stress.

In 1946, we began to observe the effect of supplementary vitamin P and vitamin C in the treatment and prevention of heart disease and cerebrovascular disease.

Thirty-two patients were followed for from one to four years during which all took vitamin P and vitamin C continuously. Ages of patients varied from 43 to 92 years, with 66 as the average. Each patient presented a prominent vascular disturbance. The patients can be grouped according to the most outstanding finding:

1. *Dizziness.* Five patients who had had repeated attacks of severe dizziness were relieved. All five had normal blood pressure readings. All were able to lead active lives.
2. *Epistaxis.* Two patients had had recurrent nose bleeds. Hypertension, moderate to marked, was present. No further attacks have occurred.
3. *Myocardial infarction and cerebral accident.* Ten patients had had one or more severe myocardial infarctions or cerebrovascular accidents. Five had a history of one to several episodes of heart failure. Two patients died—one from cerebral thrombosis, and one from a dissecting aneurysm.
4. *Hypertension.* Of seven patients with moderate to marked hypertension, three died—one from a massive cerebral hemorrhage, one from coronary thrombosis, and one from complications following a fractured hip.
5. *Heart failure.* Two patients had suffered from chronic heart failure with intermittent dyspnea, which was completely relieved.

There were six deaths among the 32 patients, and four were directly due to a heart attack or a cerebral episode. Of these four not one had taken more than 100 mg. of vitamin C daily. In each of five who died, the final attack was severe enough to cause death within a short period. The 26 patients who remained alive were active and had few or no symptoms referable to the vascular system.

It was not possible to compare the results with patients who had similar symptoms and illnesses. Several hundred persons have been started on vitamin P and vitamin C. Some did not continue therapy; others have not been followed for a long enough time. Prolonged and controlled studies should

be made on a large number of people. This could be done by public health departments or geriatric clinics.

#### VITAMIN C REQUIREMENT

NO ACCURATE way of determining whether a deficiency of ascorbic acid exists in the body tissues has been developed. A determination of blood plasma level, whole blood level, or the amount of vitamin C necessary to saturate the blood does not reveal the need of the body for vitamin C.

Reports on the therapeutic requirements of vitamin C have varied considerably. Jolliffe<sup>17</sup> suggested that the therapeutic requirement of vitamin C may be ten or more times the minimum daily requirement. This would indicate that some people need a thousand milligrams per day in order to correct a severe deficiency. Kyhos, Sevringhaus, and Hagendorn<sup>18</sup> found that under certain conditions 1,500 to 2,800 mg. per day were necessary to saturate the body. Not only is it necessary to give large doses of vitamin C to correct severe deficiencies, but it is necessary to treat the patient over a long period. Linghorne<sup>5</sup> and co-workers believed that in the case of some deficiencies of long duration, 500 mg. of vitamin C should be given daily for a year.

The Food and Nutrition Board of the National Research Council in 1945 recommended a daily requirement of 75 mg. of vitamin C for men and 70 mg. for women. Kline and Eheart<sup>19</sup> found, however, a wide variation in the need of vitamin C among normal individuals.

#### ASCORBIC ACID AND DIET

THERE is tendency to omit foods which have a high ascorbic acid content. Even when fruits and vegetables are eaten freely, it is still possible to get little vitamin C in the diet, as these products vary considerably in vitamin C content.<sup>20</sup> Raw cabbage is an excellent source, but allowed to stand for as long as two hours, one-fourth of the vitamin C content is lost. Fruits, when properly canned, will retain up to 90 per cent of their original potency. Long cooking<sup>21</sup> destroys most of the ascorbic acid. Vegetables should be cooked in as short a time as possible and in a small amount of water, which should be boiling before foods are added. Baking soda, stirring, too much heat, light, copper, pickling, salting, curing, and fermenting cause a great reduction in ascorbic acid content.

#### FACTORS AFFECTING UTILIZATION OF VITAMIN C

EVEN when the intake of ascorbic acid is optimum, many factors may contribute to poor utilization. According to Musser,<sup>22</sup> poor storage, chronic passive congestion, poor absorption, anorexia, and vomiting can lead to vitamin C deficiency. Wright and Lilienfeld<sup>2</sup> found that ascorbutic states may develop even though the patient is taking large doses of vitamin C by mouth. They believed that anacidity, diarrhea, inflammatory changes of the

gastro-intestinal tract, and destruction of vitamin C by bacteria might prevent absorption.

Many conditions may be present in the body to cause an increase in the need of vitamin C. Doll Dorf<sup>23</sup> listed fever, physical stresses, infection, diabetes, muscle regeneration after injury, endocrine dyscrasia, gastrointestinal disorders, diarrhea, anorexia, vomiting, stomach ulcers, adentia, restricted diet, and liver disease—all of which are commonly found in older patients. If special attention is not paid to the need for vitamin C during such illnesses, severe deficiencies bordering on scurvy can occur.

Upper respiratory tract infections may severely tax the vitamin C reserve of elderly patients. It is usually during or following a cold that patients have epistaxis or cough up blood-streaked sputum. Local inflammation and depletion of vitamin C may be responsible for this hemorrhagic tendency. Large doses of ascorbic acid can minimize or prevent post-infectious bleeding. On numerous occasions, we have observed a dramatic alleviation of symptoms of an upper respiratory tract infection after an injection of 500 mg. of ascorbic acid. One cannot ignore the fact that a high rate of heart disease tends to occur in areas where influenza death rates are high.<sup>24</sup> Heart attacks and cerebral accidents tend to occur within a few weeks after upper respiratory tract infections.

#### SCURVY AND LATENT SCURVY

**O**F ALL animals, only guinea pigs, primates, and man must obtain vitamin C from an outside source. Various symptoms and pathological findings of scurvy have been described in man, monkey, and guinea pig: loss of weight, insomnia, gingival and dental complaints, tendency to bleed from the skin and mucous membranes, easy bruising; also difficult healing, anemia, susceptibility to infection, petechiae, skin eruptions; besides joint pains, backache, bloody diarrhea, hematuria, menorrhagia, edema, epistaxis, and tachycardia. When any of these symptoms or signs are outstanding, a lack of ascorbic acid in the tissues may be the cause, and latent scurvy should be suspected. Only in a total lack of vitamin C for a long period of time would one expect to encounter the classical findings of scurvy.

In a random survey of 50 patients in general practice, 36, or 72 per cent, stated that they bruised easily. Gingivitis, epistaxis, loss of weight, anorexia, fatigue, and muscle and joint pain are common symptoms in the aged, and may be due to lack of vitamin C.

A 92-year-old man had a severe attack of epistaxis. He bruised easily and had a chronic dermatitis of his legs suggesting scurvy. His diet contained very little vitamin C. Rutin and vitamin C were prescribed. There was no further bleeding from the nose and the dermatitis of the legs improved.

The pathological changes in scurvy, as shown in guinea pigs, involve primarily the structure of the cells and the vascular system. There are nervous disorders with permanent locomotor disabilities, necrotic areas in the liver and adrenal glands, and degenerative changes in the costal car-

tilages. Submucosal hemorrhages are commonly found in the brain, posterior root ganglia, and lumbar motor roots. Usually there is little phagocytosis at the site of hemorrhages in scurvy. The epidermis, endothelium, fibroblasts, and osteoblasts seem to lose the power to proliferate.

Scurvy appears slowly in man. Crandon<sup>25</sup> found that it was 132 days before the first signs appeared and the plasma ascorbic acid level was zero for 90 days before there was clinical evidence. It took two weeks of 1,000 mg. of ascorbic acid daily to clear up petechiae on the buttocks. Shaw and co-workers,<sup>26</sup> in a study of vitamin C deficiency in monkeys, found that an acute deficiency appeared 30 to 50 days after vitamin C was withheld.

Recently, we have analyzed the diets of 50 patients and considered the various foods from which the chief amount of ascorbic acid was derived. Only nine, or 18 per cent, were found to be taking over 500 mg. of vitamin C per week. The diets of five, or 10 per cent, contained no vitamin C; 17, or 34 per cent, were taking less than 200 mg. per week. Many people undoubtedly can carry on normally even with a diet low in vitamin C. With additional stress, the need for vitamin C is greatly increased. Increased demands cannot be supplied from within, since vitamin C is not appreciably stored in the body.

#### THERAPEUTIC USE OF VITAMIN C

**M**ANY PERSONS who have myocardial infarctions or cerebral accidents, experience prodromal symptoms for days or even weeks before the attack occurs. Transient dizziness, vertigo, slight or severe headache, loss of appetite, indigestion, weakness, numbness in one or more of the extremities, or disturbances of vision may precede a cerebral accident. Cough, shortness of breath, indigestion, listlessness, dizziness, palpitation, substernal oppression, and cardiac pain may be present before a myocardial infarction. The impending significance of these symptoms often goes unrecognized. Ascorbic acid, if given in large amounts, may avert a vascular crisis.

A man, aged 59, with normal blood pressure was first seen in January, 1949. He stated that he had had four episodes of "dizziness" over a period of 15 years. For three weeks he had experienced "dizziness" several times each day and had on three occasions "blacked-out" and fallen. He was taking no vitamin C and an analysis of his diet revealed very little. Testing revealed an increased capillary fragility. An injection of five hundred milligrams of ascorbic acid was given on three consecutive days and two tablets of 20 mg. of rutin and 100 mg. of vitamin C were given orally each day. For two and one-half years he has worked actively as a door-to-door insurance collector. He has had no further symptoms referable to his vascular system.

**S**INCE it has been shown that rutin apparently complements vitamin C in improving the integrity of blood vessels, rutin and vitamin C are best given together. Both drugs are relatively nontoxic and can be used with impunity. Elderly patients should be encouraged to take liberal quantities of foods with high vitamin C content. Many elderly people, however, cannot tolerate the quantity of food necessary to obtain enough vitamin C. When symptoms or signs reflect the possibility of a cerebral accident or myocardial

infarction, the diet should always be supplemented with rutin and vitamin C tablets. Supplementary rutin and vitamin C should be given when any of the following conditions exists: (1) low vitamin C intake over a long period; (2) intolerance of foods containing vitamin C; (3) any chronic disease or illness which might deplete the body tissues of vitamin C and cause vascular accidents; (4) acute illnesses or unusual periods of stress when the patient's requirement for vitamin C is great; and (5) whenever cardiovascular disease is present, particularly hypertension.

When a patient is seen with an acute cerebral or myocardial infarction the body is in a state of alarm, and extra vitamin C is needed to prevent weakened capillaries from deteriorating and to promote healing of damaged tissue. Lamén and Ingalls<sup>27</sup> pointed out that tissues which have been injured have a high concentration of vitamin C which is transferred from other parts of the body. When ascorbic acid is given parenterally to patients who have had cerebrovascular accidents an alleviation of symptoms and signs occurs quicker than when not given. A more complete return to normal of motor and sensory paralysis is brought about. Rutin and vitamin C may be given readily by mouth. Best absorption is obtained when taken on an empty stomach. However, if given only by the oral route, the desired effect on the vascular system may be delayed two to four weeks. When a more rapid and adequate saturation of the body is desired, vitamin C should be given parenterally in doses of 500 to 1,000 mg. daily. It may be given intramuscularly or intravenously.

Patients who are thought to have a minimum degree of poor vascular nutrition may be protected with 20 mg. of rutin and 100 mg. of vitamin C. When symptoms do not subside or if stress occurs—such as in infection—parenteral injections may be administered. Daily oral doses may need to be increased to 180 mg. of rutin and 900 mg. of vitamin C in patients whose vascular system is seriously embarrassed. It is not difficult to get patients to take tablets of rutin and vitamin C. It can be explained that the tablet is a food supplement which strengthens the blood vessels.

A patient, aged 55, had a moderately severe coronary occlusion in May, 1947. Few or no foods containing vitamin C were taken in his diet. His blood pressure was 190 mm. Hg. systolic and 100 mm. diastolic. A daily dose of 150 mg. of vitamin C was prescribed. The patient remained well until July, 1950, when he suffered complete hemiplegia. Blood pressure at that time was 245 mm. systolic and 135 mm. diastolic. Parenteral injections of vitamin C were given and within two weeks the patient made a complete recovery. Rutin was increased to 120 mg. daily and vitamin C to 600 mg. daily. He remained well for three months when he suffered an attack of acute heart failure with pulmonary edema. Again, parenteral vitamin C was administered. Rutin was increased to 180 mg. and vitamin C to 900 mg. daily. He recovered from the attack of heart failure within a few days and has since remained well. He has been able to travel and carry on a moderate amount of activity.

**A**N ADEQUATE vitamin C intake may prevent many illnesses in the aged. Incidence of disabilities from heart and cerebrovascular disease may be appreciably reduced. When treating elderly patients, however, one must not concentrate on one fact in nutrition as a well-balanced diet is always required.

## SUMMARY

Proper nutrition can favorably influence the state of capillaries and other blood vessels. Research has shown that vitamin C plays a vital rôle in cellular metabolism and in maintaining the integrity of cells. Vitamin P apparently aids vitamin C in reducing capillary fragility. It may be that blood vessels are weakened by a decrease in the cellular content of ascorbic acid. Many instances of hemorrhage and thrombosis in the heart and brain may be avoided if adequate amounts of vitamin P and C are provided.

Thirty-two elderly people who had marked vascular symptoms were studied from one to four years. Vitamins C and P, in varying amounts, were taken continuously. Of the four patients who died from vascular diseases, not one had taken more than 100 mg. of vitamin C daily.

Many symptoms of vascular disturbances in the aged suggest that latent scurvy may be a frequent occurrence. Deficient diets, inadequate absorption, and poor utilization cause deficiencies of ascorbic acid in elderly people. Large amounts of supplementary vitamin C may be necessary.

Extended studies should be made by public health departments and geriatric clinics to determine the effectiveness of vitamins C and P in controlling cardiac and cerebrovascular illnesses.

## REFERENCES

1. KING, C. G. and W. A. WAUGH: Chemical nature of vitamin C. *Science* 75: 357, 1932.
2. WRIGHT, I. S. and A. LILIENFELD: Pharmacologic and therapeutic properties of crystalline vitamin (cevitamic acid) with especial reference to its effects on capillary fragility. *Arch. Int. Med.* 57: 241, 1936.
3. GOODMAN, LOUIS and A. GILMAN: *The Pharmacological Basis of Therapeutics*, New York, Macmillan Co., 1942.
4. KLEMPERER, P.: Recent advances in cellular pathology. *J. Mt. Sinai Hosp.* 12: 416, 1945.
5. LINGHORNE, W. J., W. G. MCINTOSH and J. W. TICE: The relation of ascorbic acid to gingivitis. *Canad. M. A. J.* 54: 106, 1946.
6. KING, CH. G.: Vitamin C. *J. A. M. A.* 142: 563, 1950.
7. ZINTEL, H. A.: The role of nutrition in preoperative and postoperative care. *Am. J. Med. Sc.* 207: 253, 1944.
8. MEYER, A. W. and L. M. McCORMICK: Studies on Scurvy. Stanford Univ., 1928. *Medical Sciences Vol. 2, Forms No. 2, v. 11, of Stanford Univ. Publ. Univ. ser., Med. sc.* 1928.
9. RUSZNYAK, ST. and A. SZENT-GYORGYI: Vitamin P. Flavonols as vitamins. *Nature*, London 138: 27, 1936.
10. SCARBOROUGH, H.: Vitamin P. *Biochem. J.* 33: 1400, 1939.
11. GRIFFITH, J. Q., JR., J. F. COUCH and M. A. LINDAUER: Effect of rutin on increased capillary fragility in man. *Proc. Soc. Exper. Biol. and Med.* 55: 228, 1944.
12. COUCH, J. F., C. F. KREWSON, J. NAGHSKI and M. J. COPLEY: The Chemistry and Therapeutic Use of Rutin. Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Dept. of Agriculture, Eastern Regional Research Laboratory, Philadelphia 18, Pennsylvania. AIC-115, April 1946.
13. SOLOFF, L. A. and C. T. BELLO: "Capillary fragility" in hypertension; the effect of anti-scurbutic therapy on results of tests for "capillary fragility." *Am. J. Med. Sc.* 215: 655, 1948.
14. THEWLIS, M. W. and E. T. GALE: Nutrition in the aged. *J. Am. Inst. Homeop.* 40: 266, 1947.
15. ALVAREZ, W. C.: Cerebral arteriosclerosis with small, commonly unrecognized apoplexies. *Geriatrics* 1: 189, 1946.
16. PATERSON, J. C.: Capillary rupture with intimal hemorrhage in causation of cerebral vascular lesions. *Arch. Path.* 29: 245, 1940.
17. JOLLIFFE, N.: Preventive and therapeutic use of vitamins. *J. A. M. A.* 129: 613, 1945.
18. KYIOS, E. D., E. L. SEVRINGHAUS and D. R. HAGENDORN: Large doses of ascorbic acid in treatment of vitamin C deficiencies. *Arch. Int. Med.* 75: 407, 1945.
19. KLINE, A. B. and M. S. EHEART: Variation in the ascorbic acid requirements for saturation of nine normal young women. *J. Nutrition* 28: 413, 1944.
20. SCHAUSS, B.: Ascorbic acid content of fruits and vegetables used in an institution. *J. Am. Dietet. A.* 21: 364, 1945.
21. GRAY, CORA E.: Ascorbic acid in human nutrition. *The Health Bull. North Carolina State Board of Health* 62: 7, 1947.
22. MUSSER, J. H.: From Wohl, M. G.: *Dietotherapy*. Chapter 24: Nutrition in the Aged. Philadelphia, W. B. Saunders Co., 1945, pp. 505-515.
23. DALLDORF, G.: From Wohl, M. G.: *Dietotherapy: Vitamin C in health and disease*. Philadelphia, W. B. Saunders Co., 1945, pp. 291-305.
24. Federal Security Agency, U. S. Public Health Service, National Office of Vital Statistics. *Summary of Mortality Statistics, U. S., 1947*. Vol. 31, Feb. 8, 1949.
25. CRANDON, J. H., C. C. LUND and D. B. DILL: Experimental human scurvy. *New England J. Med.* 223: 353, 1940.
26. SHAW, J. H., P. H. PHILLIPS, and C. A. ELVEHJEM: Acute and chronic ascorbic deficiencies in rhesus monkey. *J. Nutrition* 29: 365, 1945.
27. LANMAN, T. H. and T. H. INGALLS: Vitamin C deficiency and wound healing; an experimental and clinical study. *Ann. Surg.* 105: 616, 1937.