

## Perspectives in Nutrition

It is hoped that Perspectives in Nutrition will review the literature selectively, interpret it moderately and present a spectrum of ideas that will serve as a continual stimulation to nutritional research applied to medical problems.

# Ascorbic Acid and Atherosclerosis

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### ATHEROSCLEROTIC PATHOGENESIS

Coronary atherosclerosis is a distinct pathological condition associated with diseases of the coronary and cerebral arteries and the aorta. The histology is characterized by lesions with a high cholesterol content localized in the subendothelial stratum of the arterial intima. Phagocytic cells, of the macrophage type, collect at this site, and cholesterol crystals accumulate in these cells in both fluid and solid forms. Stimulated by the excess cholesterol in the phagocytic cells, the lesion progresses to a proliferation of connective tissue. Later, deeper strata of the intima are invaded and necrosis occurs here because plasma diffusion is insufficient to nourish connective tissues, and eventually calcification occurs (1).

### ATHEROSCLEROTIC PATHOLOGY

A study has been made of the morphological features of atherosclerosis, the disturbance in the intercellular ground substance of the coronary arterial intima at points of mechanical pressure, and the physical principles that govern the pressure points on coronary arteries were correlated with the sites of atherosclerosis in the experimental animal (guinea pig) (3). It was concluded from this study that the main factor of importance was the extent of spreading of the artery and that this was related to the factors outlined by Laplace's law: 1) blood pressure, 2) surround-

ing tissue pressure, 3) radius of the artery, and 4) curvature of the artery.

Cholesterol ingestion both in the experimental animal (and man) does not simulate physiological principles. Inducing ascorbic acid deficiencies in the experimental animal is considered as the ideal method of reproducing the pathological conditions, because the primary alterations in atherosclerosis are morphologically of the intimal ground substance<sup>2</sup> (2). Ascorbic acid deficiency comprises a disease of the ground substance; pressure points localize these lesions either by compression or spreading the artery itself by hydrostatic pressure from within, which is also conducive to localizing of lesions. The particular experimental animal (guinea pig) is the one nonprimate animal that cannot synthesize ascorbic acid and is, therefore, acceptable for the study of atherosclerosis. When adequate deficiency is produced the lipids (mainly cholesterol) deposit in the ground substance.

### THEORETICAL CONSIDERATIONS

The study of resorption of atherosclerosis in experimental animals should have, as its basis, a method of inducing atherosclerosis with forced cholesterol ingestion. The question of reversibility of lesions has been investigated several times and failure of results has

<sup>2</sup> Ascorbic acid is metabolized at a considerably more gradual rate in man than in the guinea pig. This difference can explain the greater length of time for lesions to develop (4).

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been attributed to the persistence of hyperlipemia after discontinuing cholesterol ingestion. This appears to be a valid explanation, as it has been recognized that cholesterol ingestion-induced atherosclerosis is accompanied by extreme lipid deposits throughout the body, particularly in the reticuloendothelial system.

#### ANIMAL EXPERIMENTS

Except in hereditary dyslipoidoses in humans, this state of cholesterol saturation has no counterpart in human atherosclerosis; it has not been proven to be etiological and does not offer an impediment to resorption of plaques as in the manner of forced cholesterol ingestion in the experimental animal. The use of the guinea pig as an experimental animal, through the medium of induced ascorbic acid deficiency, has provided an ideal means of studying the reversibility of atherosclerosis. The method used revealed that after as short a period of time as 3 days, the early atherosclerotic plaques in the animals sacrificed from 1 to 4 weeks began to lose, and shortly thereafter completely lost, their diffuse lipid deposits. Later, plaques were considerably more extensive and although animals sacrificed after 4 weeks therapy with ascorbic acid did not reveal plaques, the number studied was considered too small to warrant the conclusion that there was universal reversibility. There was, however, a consistent decline in the incidence of these deposits in direct proportion to the duration of the therapy (5). Similarly, another study has indicated that total ascorbic acid depletion is common in human arteries and that ascorbic acid therapy is able to replace this deficit (6). This particular study supports the contention that cholesterol plaques should be thought of as resorbable "foreign material," as, e.g., one expects resorption of hematomas and traumatic fat necrosis (7).

#### VITAMIN CONCEPTS

Ascorbic acid is one of the most perplexing of all vitamins with regard to its mechanism

of action. The most definitely established functional role of ascorbic acid is that concerned with maintenance of connective tissue of various types—the intercellular or ground substance. This manifests itself in scorbutic animals by the inability of fibroblasts to produce collagen; the deficiency of ascorbic acid debilitates the integrity of the capillaries by reason of an inadequacy of the ground substance. Of all the animal species studied, only the primates and the guinea pig depend on external sources of ascorbic acid. All other species are capable of endogenous synthesis in amounts adequate to prevent a tissue deficiency, provided metabolism is normal (the animals that synthesize ascorbic acid maintain their tissues at saturation levels). These facts correlate the animal experiments producing atherosclerosis to the human pathogenesis of this disease. However, the intima receives its nourishment by diffusion from the arterial lumen and the vasa vasorum, which penetrate into the outer two-thirds of the media. The pathology of atherosclerosis reveals dilated capillaries to invade the intima from the vasa vasorum and occasionally directly from the arterial lumen. These capillaries frequently rupture and produce intimal hemorrhage; this may occlude the artery by its expansion or by precipitating thrombosis. The nature of this capillary disturbance produces an increased tension in the artery and the intercellular cement substance is altered, similarly to that of the ground substance of the atherosclerotic plaque that they invade. Their rupture is similar to that in ascorbic acid deficiencies with injury to the vascular endothelium resulting in development of a mucilaginous state of the intercellular cement. Platelets then adhere at the time of injury and promote thrombus development. This situation is common in the malnutrition of ascorbic acid deficiency in man.

#### EXPERIMENTAL CONSIDERATIONS

There is general agreement that, experimentally, ascorbic acid has a major role in

the integrity of the ground substance of the arterial intima; a deficiency results in the disturbance of the substance and is effective in producing lesions in animal arteries (guinea pig), which are morphologically identical to human atherosclerosis. Correction of this deficiency usually prevents and generally decreases the lesions of experimental atherosclerosis, suggesting that ascorbic acid metabolism is related to the pathogenesis of atherosclerosis (5).

Any factor disturbing ascorbic acid metabolism, either systemically or locally, results in ground substance injury with subsequent lipid deposit. Local ascorbic acid depletion combines with systemic depletion, and lesions are localized only at points where the sum of local and systemic depletion exceeds the critical point required for the preservation of the ground substance. The concepts of local factors in coronary atherosclerosis are that mechanical distention of the artery and the local distention acts in the same manner as that depicted in the general adaptation syndrome (Selye); apparently this is because the latter is accompanied by alterations in ascorbic acid metabolism that may be of a localized nature. Coronary atherosclerosis, therefore, appears to be, in part, a possible result of deficient ingestion of ascorbic acid.

#### CASE REPORTS

Scorbutic cases have been reported revealing electrocardiographic abnormalities that could be interpreted as evidence of significant myocardial disorder although no clinical features of cardiac disease were evident (10). After a week of corrective ascorbic acid therapy the electrocardiograms returned to normal. The possibility was considered that such abnormalities may develop in those persons with subclinical deficiency, especially in relation to the prevalence of malnutrition among the elderly. From this it was recommended that abnormal recordings, in the appropriate circumstances, be reviewed after vitamin supplementation in order that

diagnostic and prognostic implications can be avoided.

#### FACTUAL COMMENT

Atherosclerosis in ascorbic acid deficiency occurs at normal cholesterol levels and without deposits of lipids in the reticuloendothelial system, and this morphology closely simulates that of human atherosclerosis. The disturbance of the ground substance associated with atherosclerosis becomes important in the pathogenesis of intimal hemorrhage, thrombosis, and later calcification.

#### FACTUAL AND HYPOTHETICAL SUMMARY

There are certain facts and hypotheses to permit a basis for the *presumption* of deficiency in ascorbic acid in persons to be a contributing factor in the development of myocardial, aortic, and cerebral atherosclerosis.

1) A main function of ascorbic acid is to facilitate the production of intercellular substances, fibroblasts, associated with the formation of collagen.

2) A major anomaly in the pathogenesis of myocardial infarction that has not been explained is the relation of intermediate processes occurring from the deposition of whole blood to the formation of collagen within the atherosclerotic plaque.

3) Atherosclerosis has been produced in the experimental animal by creating ascorbic acid deficiency in the presence of normal levels of serum cholesterol and without deposits of lipid in the reticuloendothelial system.

4) Ascorbic acid deficiency, as proved by nutritional studies, is more common in the older age groups where the majority of atherosclerosis occurs.

5) Ascorbic acid, in respect to the information presented herein, is theoretically considered to have only a vitamin deficiency influence in the complexity of atherosclerosis.

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