THE ROLE OF ASCORBIC ACID IN
ATHEROSCLEROSIS

Previous studies of the bloodvessels in scurvy—In human and experimental scurvy, fat deposits occur in capillaries and small veins. Koch observed bivalve degeneration and fat deposits in arteries in human scurvy. Widespread atherosclerosis and arterial thrombosis in young people was reported amongst fatal cases of malnutrition in prison camps. Mallen and King produced "diffuse hypertrophic atherosclerosis" in scurvy guinea pigs which had received sublethal doses of diphtheria toxin. The lesion described was medial proliferation. Bailey produced a similar lesion with diphtheria toxin in normal guinea pigs.

The influence of ascorbic acid on the ground substance—Scurvy is a disease of ascorbic acid deficiency with a resulting disturbance in the ground substance. I have shown that it is effective in producing lesions in guinea pig arteries which are morphologically identical with human atherosclerosis. Intraperitoneal injection of ascorbic acid usually prevents and always greatly decreases the lesions of experimental cholesterol atherosclerosis. Thus ascorbic acid metabolism seems vital in the pathogenesis of atherosclerosis.

Morphologically, the ground substance in scurvy, assumes a watery appearance. Chemically it has been shown that the glycoprotein which characterizes the normal ground substance undergoes depolymerization in scurvy. There is a release of glycoprotein into the bloodstream. When ascorbic acid is administered, the normal state of the ground substance is quickly restored. An increase in serum glycoprotein occurs under a variety of conditions including myocardial infarction, tumours, induction and trauma. It is noteworthy that ascorbic acid metabolism is disturbed under these and other circumstances including acute and chronic infection, rheumatoid arthritis, the toxemia of diphtheria, traumatic and hemorrhagic shock, burns and cold. In one autopsy series of cases showed a condition of latent scurvy by chemical analysis of the tissues. One might speculate that in all these conditions in which ground substance is affected there would be a tendency towards atherosclerosis.

Atherosclerosis and infection.—The aorta was studied histologically for fat staining of the intima in 17 guinea pigs which had died of acute lobar pneumonia. These animals were drawn from the laboratory stock and had received a full diet including greens. They were noticeably sick for 24 to 36 hours and no bacteriological studies were made. Using the system of plus signs previously described for grading the fat staining, it was found that 6 of the 17 animals had some degree of lipid deposit in the intima. One of the lesions was 2+, and the remaining 5 were 1+. No plasma cholesterol determinations were made in this group. The depletion of ascorbic acid which occurs in infections is considered to be important in the deposition of lipid in the aortic intima of these animals.

Atherosclerosis and the thyroid.—Desiccated thyroid has been given to cholesterol-fed rabbits with resulting inhibition of atherosclerosis. I have given 0.1 gm. of desiccated thyroid 3 times a week to 6 guinea pigs receiving the acute scurvy diet previously described. These animals were fed 0.5 gm. of cholesterol in corn oil each day and a liberal supply of powdered ascorbic acid. Three of the 6 animals died on the 6th day, 2 of them exhibiting fat staining of the intima. The remaining 3 animals were killed on the 15th, 25th and 41st day respectively and all were found to have atherosclerosis. The average degree of lipid deposit was 2+.

In 5 animals fed the acute scurvy diet alone, desiccated thyroid was given in the same dose as in the previous experiment, starting on the 13th day. In this way the effect of thyroid was studied in the animal just prior to the time of expected ascorbic acid depletion (about 12 days). Fat deposits were noted in the intima of 2 of the 5 scorbutive animals and the average lesions were 3.5+. Thus desiccated thyroid fails to inhibit atherosclerosis of cholesterol feeding or of scurvy in this small series. This might be expected as thyrotoxicosis increases the utilization of ascorbic acid.

Atherosclerosis and cholesterol.—Much emphasis has been placed on cholesterol metabolism in atherosclerosis. Hypercholesterolemia produces atherosclerosis in animals, but there is some information which suggests that it does so only after a preliminary injury of the intimal ground substance. I have shown in two rabbits that cholesterol feeding produces a relative depletion of ascorbic acid (this animal can synthesize ascorbic acid) as measured by the intradermal dye injection method of Rotter using the modification of Slobody. This effect was also seen in cholesterol-fed guinea pigs receiving