

## DISCUSSION

*Significance of ascorbic acid depletion.*—The atherosclerosis which develops in the guinea-pig as a result of ascorbic acid depletion has all the characteristics of human atherosclerosis. The lesions are morphologically identical with those of human atherosclerosis. The plasma cholesterol levels of these animals are normal and there is no lipid deposit in the reticulo-endothelial system. Ascorbic acid deficiency is not usually considered to exist in subjects with atherosclerosis where nutrition seems good. The results in Table III indicate, however, that a gross deficiency does in fact exist in the arteries of many well-nourished autopsy subjects, except in cases 15, 27, 36 where the patient was cachectic.

Recent biochemical studies show that radioactive acetate is incorporated into cholesterol considerably more rapidly in tissues depleted of ascorbic acid.<sup>10</sup> The significance of this fact is that the aorta can synthesize cholesterol<sup>11</sup> and Table III shows that severe degrees of arterial ascorbic acid deficiency are commonly found. These observations are all integrated in the finding that atherosclerosis rapidly develops in guinea-pigs rendered scurvy.<sup>4</sup>

*Plasma glucoproteins.*—Another manifestation of the disturbance of ground substance in atherosclerosis is the appearance of glucoprotein in the blood.<sup>12</sup> This release of glucoprotein is believed to result from the depolymerization of ground substance and is a phenomenon seen in scurvy.<sup>13</sup>

## MECHANISM OF ASCORBIC ACID DEPLETION

The fact that it takes about 150 days of a scurvy diet to induce scurvy in man<sup>14</sup> makes it seem that the ascorbic acid deficiency noted in human arteries is not due to malnutrition. It is known that systemic stress, such as infection,<sup>15</sup> toxemia<sup>16</sup> or burns,<sup>16</sup> is accompanied by a great increase in the ascorbic acid requirement. We presume that the stress of the various fatal diseases listed in Table III accounts for much of the ascorbic acid deficiency found in the arteries concerned.

*Localized ascorbic acid deficiency.*—Superimposed upon the systemic stress, our studies indicate the presence of a local form of stress peculiar to the artery.<sup>4</sup> In a previous paper<sup>17</sup> we reviewed the mechanical factors in the pathogenesis of atherosclerosis which comprise this

local stress. Very appreciable differences in mechanical stress can be demonstrated along the major arteries, and the sites where stress is greatest coincide with the localization of atherosclerotic plaques. A good example of the localization of atherosclerosis by mechanical stress occurs in the carotid artery. Because of the dilatation associated with the carotid sinus and bifurcation of the common carotid artery, this site is highly susceptible to atherosclerosis. The immediately adjacent internal carotid artery is only rarely involved by atherosclerosis. Our results suggest that the local point of excess mechanical stress in the carotid sinus is associated with a relative depletion of ascorbic acid in most instances as compared with the adjacent internal carotid artery.

*Ascorbic acid therapy.*—Our preliminary work on the efficacy of ascorbic acid therapy in terminal cases suggests that it is possible to restore the ascorbic acid content to normal in the arterial wall.

## CONCLUSIONS

1. A gross and often complete deficiency of ascorbic acid frequently exists in the arteries of apparently well-nourished hospital autopsy subjects. Old age seems to accentuate the deficiency.
2. The ascorbic acid depletion is probably not nutritional, but rather related to the stress of the fatal illness.
3. A localized depletion often exists in segments of arteries susceptible to atherosclerosis for reasons of mechanical stress. Adjacent segments, where mechanical stress is less, tend to have a higher ascorbic acid content and atherosclerosis here is rare.
4. The significance of this ascorbic acid depletion lies in the fact that scurvy in guinea-pigs results in the rapid onset of atherosclerosis. Furthermore it has been reported that the aorta can synthesize cholesterol and the incorporation of radioactive acetate into cholesterol in tissues is said to be several times more rapid in tissues depleted of ascorbic acid.
5. Ascorbic acid deficiency in arteries with resulting ground substance depolymerization may account for the release of glucoprotein noted in the blood of subjects with severe atherosclerosis.
6. Preliminary studies suggest that it is possible to replenish the ascorbic acid in arteries by ascorbic acid therapy.