



Fig. 3.—A low power photomicrograph of an advanced lesion of atherosclerosis in a formerly scorbutic guinea-pig. This animal received ascorbic acid therapy for 16 days. The lipid is now collected in pools with areas of lipid-free intima intervening.

showed no lesions, the number of such animals was too small to warrant the conclusion that all lesions are reversed in this time. It was true, however, that there was a steady decline in the incidence of lesions in direct proportion to the duration of therapy.

#### DISCUSSION

The obstacle of hyperlipæmia, which has thwarted the studies of resorption of lipid from atherosclerotic plaques of the cholesterol-fed rabbit, was avoided in this study and some insight was gained into the reversibility of atherosclerosis comparable to the human type.

The results of this investigation indicate that early lesions of atherosclerosis are quickly resorbed. The stages in this process are first a fading of lipid staining in the region of the internal elastic membrane with later a disappearance of all extracellular fat. Active phagocytosis of lipid by macrophages occurs, and when these macrophages finally disappear no evidence of the lesion remains.

More advanced lesions are considerably more resistant to reversal. Extensive lipid deposits clear in some parts of a plaque but islands of intensely staining lipid persist in other parts. The macrophage response to such areas is only slight.

Assembling all these various phases of reversal of the atherosclerotic plaque, a certain impression is gained as to the mechanism involved. It would appear that lipid diffusely deposited in the intimal ground substance is easily resorbed. Such resorption is rapid, and as it is associated with a macrophage response of only moderate degree, it may well be that a portion

of the lipid is dealt with in some other way. The independent islands of lipid observed in the healing of advanced plaques appear to be no longer in a stratum of ground substance nor are they intracellular. Rather they seem to be inert pools of fat similar to the "cholesterol abscesses" described in human atherosclerosis. Only the surface area of such pools is in contact with resorptive processes and this may account for their resistance to healing.

The reversibility of human atherosclerosis is, of course, a vital question. Following the observation that total ascorbic acid depletion is common in human arteries<sup>5</sup> and that ascorbic acid therapy is able to replace this deficit,<sup>6</sup> it was possible to make some correlation of human atherosclerosis with that observed in the scorbutic guinea-pig. On this basis, human atherosclerosis was studied by serial arteriography in 16 cases.<sup>4</sup> Ten of these cases received ascorbic acid therapy and six were untreated. Of the 10 treated cases, the plaques visualized radiologically became larger in three, remained unchanged in one and became smaller in six. There was no diminution in the size of the plaques in any of the six untreated cases while in three of them they became bigger.

It seems likely that the histological changes associated with resorption of atherosclerosis in the human would be along the lines observed in this present study with guinea-pigs.

#### SUMMARY

Former studies into the reversibility of experimentally induced atherosclerosis had been seriously hampered by the persistence of the hypercholesterolemia essential for the production of the lesions. This hypercholesterolemia actually causes atherogenesis to proceed even when cholesterol feeding is stopped.

In the present study this difficulty is avoided by employing scorbutic guinea-pigs in which it had previously been shown that atherosclerosis develops rapidly without cholesterol feeding. When ascorbic acid is given to scorbutic guinea-pigs, the early atherosclerotic lesions resorb quickly. The advanced lesions are considerably more resistant to reversal, apparently because of the islands of lipid whose only contact with the resorbing process is at the surface.

A correlation is made between the atherosclerosis of the scorbutic guinea-pig and that