

ascorbic acid by mouth. This may possibly be the way in which cholesterol produces ground substance injury under conditions of hypercholesterolaemia. The accumulation of the lipid is probably also related to its overwhelming quantity under these circumstances.

*Atherosclerosis and cortisone.*—The administration of cortisone to cholesterol-fed rabbits inhibits atherosclerosis.<sup>49</sup> However cortisone fails to prevent or cure scurvy<sup>50</sup> or to decrease the hypersensitivity of the tuberculin test in BCG infected scorbutic guinea pigs.<sup>51</sup> In 5 guinea pigs fed the acute scorbutic diet for 12 days followed by intra-peritoneal injection of 2 mgm. of cortisone twice a day, atherosclerosis developed in 2, the average lesions being 3.5—. The plasma cholesterol levels in a group of 5 animals fed the same diet with 0.5 gm. of cholesterol in corn oil and liberal oral ascorbic acid were higher than in any other group studied. Despite cortisone, all 5 of these animals developed extensive atherosclerosis, the average lesion being 3.5+.

*Phospholipid cholesterol ratio.*—The ratio of cholesterol to phospholipid has been considered important in the pathogenesis of atherosclerosis. In alloxan diabetes in rabbits fed cholesterol the preservation of a normal phospholipid cholesterol ratio was considered responsible for the inhibition of atherosclerosis.<sup>52</sup> In a personal communication Maddoch<sup>53</sup> reported normal phospholipid cholesterol ratios in scorbutic guinea pigs. It is assumed that the atherosclerotic lesions in scorbutic guinea pigs occur without disturbance of this ratio.

#### DISCUSSION

I conclude that ascorbic acid is essential for the maintenance of the ground substance of the arterial intima. Any factor disturbing ascorbic acid metabolism either systemically or locally results in ground substance injury with subsequent lipid deposit.

Local ascorbic acid depletion is additive to systemic depletion. Thus although scurvy produced by dietary deficiency of ascorbic acid is a systemic process, its manifestations are first apparent at sites where local stress produces additional depletion. Lesions are localized only at points where the sum of the systemic and local depletion exceeds the critical point necessary for the preservation of the ground substance. Infection of the gums thus produces manifestations of scurvy in the gums. Similarly mechanical stress

localizes scorbutic lesions in bones, muscles, attachments of ligaments and in the blood vessels.

*Local stress.*—The local stress in atherosclerosis is the mechanical stretching of the arterial wall.<sup>4</sup> Just how it causes ascorbic acid depletion is obscure, but it is a factor constantly present to a greater or lesser degree.

There is some evidence that ascorbic acid is important in cell oxidation<sup>54</sup> but this is still not well established.<sup>55</sup> One theory might be that at points of greatest stretching the arterial wall does most work and here cell oxidation is greatest. If ascorbic acid is necessary for cell oxidation, local increased oxidation would be expected to result in local ascorbic acid depletion, and its resulting ground substance disturbance. The arterial wall is capable of respiration<sup>57</sup> and can synthesize<sup>58</sup> and oxidize<sup>59</sup> fatty acids, phospholipids and cholesterol. One objection to this theory is that the lesions are not located in the media where one would expect the most active oxidation to be taking place.

Another idea is that local stress acts in the same way as the stress depicted in the general adaptation syndrome of Selye. Certainly the general adaptation syndrome is accompanied by profound changes in ascorbic acid metabolism,<sup>60</sup> and these may be of a localized nature.

*Systemic stress.*—Atherosclerosis must not be considered as a disease of dietary ascorbic acid deficiency although it certainly seems to be true that such a dietary deficiency results in lesions identical with atherosclerosis. As previously mentioned, systemic depletion of ascorbic acid may follow the systemic stress of toxæmia, infections, tumours, rheumatic states, trauma, shock and cold. I have shown that cholesterol feeding has a systemic effect on ascorbic acid metabolism and that infection produces atherosclerosis in guinea pigs on a full diet and apparently only sick for a day or two.

Under certain circumstances it may be necessary to provide parenteral ascorbic acid to protect the ground substance.<sup>54</sup> The failure of cortisone to preserve the ground substance in ascorbic acid depletion suggests that ascorbic acid is the intermediary between the adrenal cortex and the ground substance. This idea is supported by the dramatic effect of parenteral ascorbic acid in the inhibition of experimental atherosclerosis of both scurvy and cholesterol feeding.