It is probably safe to state that atherosclerosis is the sum of several different processes. Each one of the past and current theories of atherosclerosis emphasizes one of these processes. Thus, if we open a contemporary textbook of pathology (1), we find at least four theories: (1) lipid insudation, (b) structural or metabolic alteration of the arterial wall, (c) intimal stress or injury, (d) thrombogenesis or encrustation. To these we should add the two newer theories that emphasize a further aspect of the process, cell proliferation: the theory of Ross et al. (2, 3) which gives platelets the stimulating role, and the theory of Benditt (4, 5) in which the proliferation is considered akin to neoplasia.

Whichever pathogenetic theory one may choose, it is always implied that the arterial wall is injured, to the point of suffering cell death and necrosis. Now, in most organs, tissue injury implies an inflammatory reaction. Does any reaction of this kind occur in the arterial wall? This question, to our knowledge, is not being asked; currently there is no "inflammatory theory" of atherosclerosis, presumably because it is assumed that the vascular wall, being devoid of a microcirculation, cannot develop an inflammatory response.

The purpose of this short paper is certainly not to propose a new theory of atherosclerosis, but to analyze the relationship between atherosclerosis and inflammation -- and thereby to offer a perspective that may have conceptual and practical implications.

We should hasten to add that the idea is over 100 years old. Virchow is credited with having proposed an inflammatory theory of
atherosclerosis (6). However, his concept of inflammation was so far removed from today's that his statement cannot be taken literally, in the context of the inflammatory process as we now understand it.

The first step should be to define what is meant by inflammation. We will adopt a current definition, whereby inflammation represents a response of living tissue to local injury, leading to the local accumulation of fluid and blood cells (7). We must therefore analyze four points: (1) Is there local injury? (the term injury is used here in the passive sense of damage). (b) Can the arterial wall "respond" in a manner comparable to that of other tissues? (c) Is there a local accumulation of fluid? (d) Is there a local accumulation of blood cells?

ATHEROSCLEROSIS AND ARTERIAL INJURY

Whether primary injury is required as a triggering event of atherosclerosis depends on the pathogenetic theory: the neoplastic theory does not imply any pre-existing endothelial damage; the "platelet" theory of Ross et al. does presuppose some form of endothelial damage, so that the platelets may accumulate locally and initiate the presumed chain reaction, beginning with smooth muscle cell proliferation. Secondary injury obviously occurs, leading to cellular death (8-11) of which atheroma is the ultimate expression. Thus tissue injury is a definite component of atherosclerosis; certainly as a secondary event; probably also as a primary event. Would it be severe enough to initiate an inflammatory response? We have no means of measuring it, nor do we know precisely the extent of cell death required for the purpose; however, we can empirically evaluate (on histologic sections) the extent of cell death in atherosclerosis: it is prominent, and experience suggests that - in other tissues - it should be adequate for triggering the inflammatory response.

As a matter of fact, the adventitia of atherosclerotic vessels often shows chronic inflammatory infiltrates. Schwartz and Mitchell (12) have summarized the pertinent literature, and concluded that two mechanisms could account for these infiltrates: an autoimmune reaction is a possibility; but the likeliest hypothesis is that these foci represent a reaction to abnormal material arising from atheromatous lesions.

ON THE CAPACITY OF THE ARTERIAL WALL TO RESPOND

In the typical inflammatory process, the response to injury includes changes (i) in the microcirculatory blood vessels and (ii) in the surrounding stroma.