Regression of Atherosclerosis in Humans: Fact or Myth?

M. R. Malinow, M.D.

IN the 1979 Lewis A. Connor Memorial Lecture, Richard S. Ross presented a list of the 10 most important developments in the past 30 years in cardiopulmonary research. The list did not include the regression of atherosclerosis in humans.1 Although this process could be of major significance in cardiology, the omission was justified because the concept that atherosclerosis progresses relentlessly is widely held and few studies have demonstrated regression. In this report I will review some information that suggests regression occurs in humans.

Studies have clearly demonstrated that arterial lesions induced in animals by cholesterol feeding become smaller when cholesterol feeding is discontinued. At the same time, several changes occur in atheromatous plaques, including regeneration of the overlying endothelium, arrest of the increased cell proliferation, decreases in the number of cells and the amount of lipids, changes in the composition of glycosaminoglycans, and decreases in insoluble proteins and the extent of calcification and necrosis.2 Findings in rabbits, dogs, birds, and pigs have been recently confirmed in several species of nonhuman primates.3

Regression has not been limited to experiments in which cholesterol feeding has been discontinued. The addition of cholesteryamine4,5 or alfalfa meal6 to a high-fat, high-cholesterol diet is effective in inducing regression in monkeys, and estrogens induce regression of coronary atherosclerosis in cholesterol-fed birds.7 Regression of spontaneous aortic lesions has been observed in pigeons subjected to ileal bypass,8 and arterial lesions disappear after the addition of canola oil to cholesterol-rich diets given to rats deficient in essential fatty acids.9 At any moment, one cannot decide by anatomic observation whether an atherosclerotic plaque is progressing, arrested, or regressing, so most experiments have involved comparisons between groups of animals killed at different times, although in a few instances sequential studies have been performed in the same animal and evaluations have been carried out by serial angiography, surgical exploration, biopsy and autopsy.10

Reversibility of arterial lesions seems to be present in a wide range of species, so a similar evolution may occur in humans. However, extrapolations from animal experiments are fraught with perils, especially because of pathogenetic differences between animals and humans in the role of dietary cholesterol and saturated fats, the anatomy of the arterial lesions, and the levels of plasma lipoproteins attained during the intervention period.3-11 Thus, to determine if regression of atherosclerosis occurs in humans, one must study humans.

Regression has been assessed in humans by postmortem evaluation and by examination of death certificates. Recently, sequential angiographic visualization has added much information. However, not all of the data are unequivocal. For instance, information from death certificates that indicates a decrease in the coronary heart disease mortality rate in the Scandinavian countries during World War II12,13 and in the last 20 years in the U.S.14 does not distinguish between regression of arterial wall lesions and other changes, e.g., decreases in the incidence of arrhythmias or thrombosis superimposed on atherosclerotic plaques.

Interpretation of postmortem findings also has limitations. Aschoff stated that atheromatous spots in the aorta were observed less frequently at the end of World War I.15 Although no quantitative data were presented and the data were presumably not age-standardized, these findings were corroborated by other German pathologists.16 In Finland, age-stratified data on 1456 postmortem examinations also demonstrated less tissue necrosis and complicated

From the Oregon Regional Primate Research Center, Beaverton, and the University of Oregon Health Sciences Center, Portland, Oregon.

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Address for correspondence: M. R. Malinow, M.D., Oregon Regional Primate Research Center, 505 Northwest 185th Avenue, Beaverton, Oregon 97006.

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plaques from 1940–1946 than 1933–1938, and a negative correlation between the extent of atherosclerosis and the state of nutrition has been observed in carcinoma, pulmonary tuberculosis, and wasting disease. Nevertheless, such postmortem evidence is difficult to interpret. Differences in the extent of lesions may have been due not only to regression, but also to arrest of the progression of atherosclerosis or a lack of thrombotic complications, and to selection of cases, i.e., patients in the control group may have died because of atherosclerotic disease. A decrease in the extent of coronary atherosclerosis has been adequately documented in New Orleans, but the responsible pathogenetic mechanisms can only be speculated upon.

The only method that provides a time-related view of the regression (or progression) of atherosclerosis is contrast angiography, but there are methodologic difficulties in comparing films recorded years apart. Techniques must assure that the films are identical in several respects, including magnification, position, ratio of film density of background tissue to that of the contrast material in the vessel, timing in relation to the cardiac cycle or to the pulse wave, arterial blood pressure, vascular tone, and heart rate. In practice, interpretations of images of stenosis must exclude changes associated with spasm, thrombosis, vascular ectasia, and arterial rotation. Investigators well aware of such limitations have reported regression of atheromatous plaques. Table 1 shows documented cases of regression in 32 of 143 variously treated patients. These numbers do not reflect the actual incidence of such evolution because table 1 does not include data from numerous studies in which regression was not observed, and it is likely that positive, but not negative, observations were reported. In addition, there are few clinical indications for repeated angiography in well patients after modification of various risk factors, and most serial studies are performed in persons with advanced lesions, which are less likely to regress than lesions of "latent atherosclerosis."

Spasm and other possible confounding features have been adequately ruled out on the basis of clinical judgment, so organic arterial stenosis may widen in humans (table 1). However, histologic studies could not be carried out and the favorable angiographic evolution might indicate changes in the arterial wall — as demonstrated in regression in animals — or reabsorption of thrombi superimposed on atherosclerotic plaques. Although the cases listed in table 1 cannot be construed as an indication of the actual incidence of regression, they do indicate that atherosclerotic obstruction is reversible in humans and suggest that regression may be more common than is usually admitted.

Therefore, the following questions about regression should be answered: What is its incidence? At what stage is it more likely to occur? Are certain lesions unlikely to regress? What are the parameters that define regression in different circumstances? Do regression, retardation, and arrest of progression constitute a continuum in arterial disease, and can these processes be documented with risk-free methods? What clinical interventions are most likely to accelerate regression? Would arteries after regression be less likely to show progression and other complications, such as ulcerations and superimposed thrombosis? Does regression (and retardation or arrest of progression) influence the clinical course in patients with cardiovascular, cerebrovascular, or peripheral arterial disease?

Answers to these questions may have important therapeutic implications and may well modify the

<table>
<thead>
<tr>
<th>References</th>
<th>No. of pts</th>
<th>Arterial bed</th>
<th>X-ray interval (years)</th>
<th>Therapy</th>
<th>Patients with regression</th>
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<tr>
<td>Ost and Stenson, 1967</td>
<td>31</td>
<td>Femoral</td>
<td>3.5</td>
<td>Nicotinic acid</td>
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<td>DePalma et al., 1970</td>
<td>1</td>
<td>Femoral</td>
<td>0.8</td>
<td>Diet, antilipidemic drugs, cessation of smoking, exercise</td>
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<td>Buchwald et al., 1974</td>
<td>22</td>
<td>Coronary</td>
<td>2</td>
<td>Ileal bypass</td>
<td>3</td>
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<td>Thompson et al., 1975</td>
<td>8</td>
<td>Aorta, coronary</td>
<td>Not stated</td>
<td>Long-term plasma exchange</td>
<td>3</td>
</tr>
<tr>
<td>Basta et al., 1976</td>
<td>1</td>
<td>Renal</td>
<td>3</td>
<td>Diet, antilipidemic drugs, pressure reduction</td>
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<td>Barndt et al., 1977</td>
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<td>1.1</td>
<td>Diet, antilipidemic drugs, pressure reduction when needed</td>
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<tr>
<td>Crawford et al., 1979</td>
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<td>Femoral</td>
<td>1.2</td>
<td>Exercise, weight reduction</td>
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<td>Rafflenbeul et al., 1979</td>
<td>25</td>
<td>Coronary</td>
<td>0.3–2.5</td>
<td>Propranolol, nitrates, pressure reduction when needed, cessation of smoking, low-saturated-fat diet</td>
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<tr>
<td>Nash, 1980[33]</td>
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<td>Coronary</td>
<td>2</td>
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<td>Thompson and Myant, 1980[34]</td>
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<td>Coronary</td>
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<td>Roth and Kostuk, 1980[35]</td>
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<td>Coronary</td>
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<td><strong>Total</strong></td>
<td><strong>143</strong></td>
<td></td>
<td></td>
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most important cause of death in the adult population of the Western world. These questions are unanswerable with the present technology, including the use of ultrasound images. Animal models are needed for the induction of arterial thrombosis superimposed on atherosclerotic plaques. With them, we may be able not only to understand better the pathogenesis of arterial occlusion, but also to test new noninvasive or risk-free invasive methods of documenting in humans the evolution of atherosclerosis and thus to answer some of these questions.

References
