Editorial:
Angiography for Study of Lipid-Lowering Therapy

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THE PRECEDING ARTICLE by Kuo and co-workers is an evaluation of lipid-lowering therapy by coronary and peripheral angiography. This is a new approach to an old, much debated question: Does lipid-lowering therapy benefit hyperlipoproteinemic patients? More studies using angiography will probably appear because Dr. Kuo's paper and others like it offer an attractive alternative to more conventional clinical studies evaluating therapy on blood lipid levels or on coronary heart disease morbidity and mortality rates.

Many fundamental disciplines and techniques focus on problems of atherosclerosis treatment and prevention: epidemiology, immunology, pathology, cell membrane physiology, lipoprotein structure analysis, coagulation studies, smooth muscle metabolite analysis, hemodynamic measurement and hemodynamic computer modeling. Nonetheless, an impasse exists in human atherosclerosis research, and a steady stream of attractive hypotheses have not been adequately tested in man. Most hypotheses progress only as far as testing in an animal model or on human risk factor levels. After this, they join a long, virtually motionless, series of ideas waiting to be tested by human coronary heart disease morbidity and mortality studies. The backup is caused by the length and cost of coronary morbidity and mortality studies. The Coronary Drug Project required 11 years and 41 million dollars to test five treatment regimens. A study with similar endpoints is now in progress, the Lipid Research Clinic trial, will require 7 years and an estimated 100 million dollars to test one lipid lowering agent.

Studies of atherosclerosis treatment in animals are shorter and much less expensive. They deal directly with the effects of treatment on arterial lesions and are showing definite promise. In the last 3 years, 10 laboratories, working independently with various animal species, have reported drugs or procedures which reverse the course of atherosclerotic lesions. Additional therapies are presently under test in many laboratories; some reduce coronary risk factors, others appear to lessen the effects of a risk factor on the arterial wall and can only be evaluated by direct observation of lesions. An agent which only retards lesion growth in man could cause a major decline in age-specific coronary mortality rates.

Dr. Kuo has attempted to evaluate directly the effects of therapy on the atherosclerotic lesions of man. This approach promises to reduce the waiting time for results of basic research to be applied to human treatment. A possible bonus is that drug effects can be tested on early atherosclerotic lesions as well as late stages of the process. Studies such as the Coronary Drug Project and the Lipid Research Clinic trial principally test the effect of therapy on late lesions because late lesions are responsible for coronary deaths.

Angiography is a widely available procedure which causes little discomfort and risk to patients. Unfortunately, although thousands of angiograms are performed each year, the information obtained from all except a few is applied exclusively to planning or evaluating surgical therapy. Since surgical evaluation involves estimating adequacy of blood supply to specific organs, consideration of the state of the arterial wall itself is not a primary goal. Actually, arterial wall lesions receive attention only when they show "significant" degrees of stenosis. Using angiography to study atherosclerosis rather than to plan surgery introduces new problems to many angiographers. In this editorial we discuss problems which may occur during selection of patients for study, obtaining the radiographic images, and interpreting the images.

Patient Selection Process

An easy way to begin using angiograms for study of atherosclerosis is to find patients who have had two examinations. Coronary risk factor levels in these patients can be correlated with change observed in the films. This approach can bias the outcome in advance, since repeat angiography is usually performed only when a patient has new symptoms, which frequently are the result of progression in atherosclerosis. The retrospective studies of Bemis, Kimbris, Marchandise, and Nash appear to have this bias.

A second patient selection problem is the length designated for the interval between angiograms. In Dr. Kuo's study, evidence for benefit from therapy was no change in lesions. When the goal of therapy is to stabilize lesions, the longer the interval between angiograms the more convincing the evidence for benefit can be. However, a long interval between angiograms increases the possibility that patients may drop out of a study. In Dr. Kuo's study, eight of 12 patients showed no change after 3-4 years. These 12 patients were from an original group of 30. The remaining 18 dropped out of the study or were not angiogrammed, so it is difficult to estimate the probability that colestipol therapy will stabilize lesions in any given patient.

Another problem when the observation interval is long is the possibility of change in the x-ray equip-
ment. In Dr. Kuo's study the x-ray equipment was apparently upgraded between angiograms, as image quality appears consistently better in second films. Although angiographers are proud of continued improvement of their product, the quality of information obtained from film pairs can be no better than the worst member of a pair.

Short studies alleviate the problems of changing x-ray equipment and patient dropout. However, since atherosclerosis appears to be a relatively slow process (particularly when it shows improvement), the x-ray must be precise enough to recognize small changes. Changes detected with today's coronary angiographic equipment usually require an interval of approximately 13 months. Femoral angiography can be more precise than coronary and might be useful at shorter intervals. We have unpublished data in men with premature myocardial infarction which suggest that femoral lesions progress more slowly and regress more rapidly than coronary lesions. However, the femoral lesions we observed were at an earlier stage of development than the coronary lesions, and this is a better explanation than any intrinsic difference in atherosclerosis in the two areas.

Technical Factors in Obtaining the Angiograms

In addition to the use of unchanged radiographic equipment, radiographic settings, film and film processing should be identical at the two examinations. Coronary angiographic exposure conditions cannot be controlled at present with the precision of femoral angiographic conditions. Figure 1 of Dr. Kuo's paper shows an example of different exposure conditions with apparently higher kV on the first examination.

The angle must be matched as closely as possible on the two examinations. It is not possible to position patients so that all views are identical, but the matching must be close. Dr. Kuo's figure 4 shows sufficient difference in position that determination of lesion change is risky from these two illustrations alone. Detection of change in cine films must involve comparison of all available views rather than a single frame in one view. It is not practical to publish all views and we use this example to illustrate what we would find unacceptable if all views showed this amount of discrepancy.

In addition to matching the angle of views, it is highly desirable that the sequence of views be matched in the pair of examinations. This facilitates comparison when films are projected simultaneously, as they should be, to look for change in lesions. When views in a pair are not in the same sequence, searching for matched views is an irritating and unnecessary cause of reader fatigue. Reader fatigue can be a major cause of inconsistent interpretation.

The physiologic state of the patient during coronary angiography is also important. Vasovagal reactions with slowing of coronary flow may occur and the film pair may not be comparable. Another cause of non-comparable films is catheter-induced vasospasm; the right coronary artery is particularly susceptible.

Nitroglycerin will relieve vasospasm and, if given at a first examination, it must be administered during the second. When nitroglycerin is necessary during a second examination, but was not given on the first, the films are not strictly comparable. Cases of spontaneous vasospasm in patients with angina have been demonstrated by Maseri. Possibly, these cases illustrate a phenomenon which is more common than is currently realized, but present to a lesser degree. Den-sitometric reconstruction of vessel lumen contours from the angiogram can be used to guard against the artifact of vasospasm. A prototype procedure for lumen reconstruction has been developed for straighter, unbranched arteries, but has not been used in coronary angiograms.

Interpretation of Angiograms

Interpretation should be judged by two interrelated criteria: accuracy and consistency. How accurately does the film reading reflect actual coronary morphology or size? Accuracy is influenced by all factors in production of films and is the most inclusive and valid single standard. Accuracy of coronary angiography must be evaluated by comparing films with postmortem findings. Little is known about the accuracy of film interpretation, since the number of patients examined postmortem in the immediate post-angiogram period has not been large. However, it is possible to analyze change in lesions without knowing their absolute size.

The most important requirement for evaluating lesion change is consistency. How reproducible is the interpretation of an angiogram? The consistency of estimation of stenosis in major vessels has been determined for both individuals and panels of readers. The consistency of detecting other features which can change, such as diffuse vessel irregularity, has not been evaluated. Considering stenosis, sufficient information has been published to present the relative order of merit of several procedures. Least consistent results are obtained by a single reader who evaluates a film pair one at a time. Most consistent results are obtained by either a consensus panel or a group opinion panel viewing both films in a pair simultaneously. For group opinion, panel members read films independently and record separate estimates which are averaged after they have been recorded. A consensus panel shares opinion while viewing the film and renders one estimate in common. Consensus panels may be slightly more consistent than group opinion panels, but are more difficult to convene.

Films must be read systematically and all lesions evaluated rather than directing attention to "significant" lesions. Angiographers tend to disregard lesions which do not appear to affect blood flow, and changes in these lesions may be overlooked. Figure 5 of Kuo's paper shows what may be increasing plaque size in the main marginal branch of the circumflex coronary artery; or it could be vessel rotation so that a plaque originally in front has moved to a more lateral
position on the second examination. It is not possible to decide between these alternatives without considering all available views in the cineangiogram.

The complexity of film interpretation to estimate lesion change accurately makes desirable the development of instrumental evaluation procedures to augment human film readers.27,28 Human readers excel at rendering complex value judgments, such as: Is this vessel segment graftable? Human readers encounter problems with consistent and precise evaluation of plaque size, a process central to evaluation of atherosclerosis treatment.

The films presented by Kuo and co-workers are encouraging examples of apparently stable vessels over 3–4 years. We are impressed by these findings. We do not wish to have our comments on technical details of angiography detract from the importance of this pioneering effort.

References

Addendum

Since submission of this editorial, two presentations at the 51st Scientific Sessions of the American Heart Association have furnished additional relevant information. E. A. Nikkila, P. Viikinkoski, and M. Valle of the University of Helsinki, Finland, reported that among 30 hyperlipoproteinemic patients treated with diet and drug therapy, 15 showed stable coronary lesions when angiography was repeated after 15–20 months. G. Thompson, D. Kilpatrick, C. Oakley, R. Steiner, and N. Myant from the MRC Lipid Metabolism Unit, Hammersmith Hospital, London, reported eight familial xanthomatosus type II patients treated with repeated plasma exchange who achieved major reductions in serum cholesterol. Two homozygous patients and one heterozygote patient showed considerable reduction in xanthoma size and apparent improvement in aortic and coronary lesions.
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