Methods capable of quantitatively evaluating atherosclerotic manifestations in a safe, valid, and reproducible way would be of great importance for epidemiological and clinical research relating to the pathophysiology of atherosclerosis and also for the evaluation of preventive measures in randomized clinical trials. As one in a series of seminars entitled "Frontiers in Cardiovascular Science" held at the Wallenberg Laboratory for Cardiovascular Research at Gothenburg University, Gothenburg, Sweden, an international workshop was organized in 1990 to discuss potentially useful methods currently available. A similar workshop, focusing mainly on ultrasound, was organized in Winston-Salem, N.C., in 1989.1 The present report will summarize the 1990th workshop with the aim of addressing some of the important controversies in this field: available methods and their possible usefulness and shortcomings; ultrasound end-point definition; and procedures for evaluation of surrogate variables for "hard" end points, such as myocardial infarction and total mortality, in epidemiological studies and clinical trials.

Anatomy and Autopsy Findings

During the early progression of atherosclerotic plaques, adaptive and compensatory mechanisms tend to preserve an adequate luminal cross-sectional area and an optimal lumen configuration.2-4 Contrary to usual representations, atherosclerotic lesions that are not ulcerated or surmounted by thrombi are associated with a regular, circular, or nearly circular lumen configuration on cross section (Figure 1). As plaques enlarge, they tend to bulge outward away from the lumen. This process may distort vessel shape, but along with fibrous cap formation, it effectively sequesters the plaque from the lumen. Adaptive enlargement is a generalized phenomenon, occurring in all atherosclerosis-prone locations studied. An artery with a large plaque may maintain an adequate lumen. Despite these compensatory processes, there is a point beyond which the artery seems no longer able to adapt, and the lesion begins to constrict the lumen. On average, this situation is approached when the plaque occupies 40% of the cross-sectional area encompassed by the internal elastic lamina (i.e., the potential lumen area; Figure 1). This means that there is a long latent period (often many decades) until the atherosclerotic disease manifests itself in a changed lumen configuration. To monitor the early stages of the disease, therefore, methods with the possible capability of measuring wall thickness must be applied. However, intimal thickening is not necessarily atherosclerosis and is not necessarily a precursor of atherosclerosis.2-4 Therefore, an increased wall thickness recorded with ultrasound or any other technique cannot, a priori, be judged as an indication of early atherosclerotic disease.

Furthermore, not all atherosclerotic plaques are the same even if they are similar in size and location. Some plaques may stabilize, like an inactive volcano. For others, plaque formation may continue with complications such as liquefaction necrosis, inflammation, sclerosis, and calcification that can alter the vulnerability of plaques to disruption. It would be highly desirable to develop methods with the possibility of identifying plaques with different qualitative characteristics.

Atherosclerotic lesions do not appear to occur randomly in the arterial tree. An epidemiological National Institutes of Health multicenter cooperative study, "Pathobiological Determinants of Atherosclerosis in Youth" (PDAY), is in progress with the aim of identifying lesion-prone and lesion-resistant areas in the aorta and coronary arteries.5 This study has included samples of vessels from blacks and whites, males and females, 15–34 years of age, who died of trauma. In PDAY, analytical techniques with image...
processing have been applied that can express this topographic distribution in unambiguous statistical terms. The probability-of-occurrence maps from PDAY have resulted in several new findings about the topography of atherosclerosis. There exists a stable, two-dimensional pattern of distribution of sudanophilic, raised, and calcified lesions in the aorta and right coronary artery. These patterns define discrete lesion-prone and lesion-resistant areas, in which the probabilities may vary from twofold to eightfold.

In both the aorta and the right coronary artery, the pattern of sudanophilic, raised, and calcified lesions does not change with any of the tested risk factors (i.e., age, race, sex, low density lipoproteins [LDL], high density lipoproteins [HDL], LDL to HDL ratio, apolipoprotein A, apolipoprotein B, lipoprotein[a], or smoking). However, the level of the probability of occurrence may be altered. That is, in a group of cases with high LDL levels, a sudanophilic, lesion-prone region may have a 60% probability of lesion occurrence and a lesion-resistant region may have a 20% probability, while in a group of cases with low LDL levels, the probabilities at the same lesion-prone and lesion-resistant sites may be 30% and 1%, respectively. It would appear that the risk factors act as two-dimensional multipliers as opposed to factors that act independently at different locations in the arterial wall. Risk factors may act to increase (i.e., multiply) the probability of lesions occurring at specific sites (i.e., lesion-prone regions) by several-fold while having a lesser effect on global (i.e., entire abdominal aorta) percent surface involvement.

Angiography, Gamma Camera, and Magnetic Resonance Tomography

Among the methods available to study atherosclerosis, angiography is the traditional reference method. However, atherosclerotic disease is often "silent" on angiography, as the method mirrors lumen diameter rather than wall thickness. Furthermore, there are large problems involved in the quantitative evaluation of coronary angiography, despite the computerized analyzing systems that have been developed. The angiographic technique has also been applied to the quantitative evaluation of atherosclerosis progression and regression in iliac and lower-limb arteries. This technique, although invasive, seems to offer promising results in regard to both quantifiable data and patient safety.

Magnetic resonance tomography is a method under development. At present, the resolution is not good enough for quantitative studies of atherosclerosis in humans, and further development of the method is thus needed.

A scintigraphic technique, based on injected, technetium-labeled lipoproteins, has also been applied to the study of atherosclerotic manifestations. These lipoproteins, with a high affinity for atherosclerotic plaque, are then deposited in the vessel wall and may be indirectly visualized with a gamma camera. This technique may also permit the study of certain metabolic variables in the tissue.

Ultrasound Technique

A large number of studies have utilized the ultrasound technique, which has been applied mainly to the study of carotid arteries. A two-dimensional image of the carotid artery may be described as one containing seven echo zones (Figure 2). Measurements of intimal-medial thickness and lumen diameter from these images are, at present, not performed in a uniform and standardized way. Some groups perform measurements on both the near wall and far wall and present mean values from those measurements, while others perform measurements only on the far wall. There is agreement that measurements of intimal-medial thickness on the far wall can be measured in a valid way, but different opinions exist as to the validity of measurements on the near wall.
The upper demarcation line of an echo is defined as the “leading edge” and the lower demarcation line as the “far edge” (Figure 2). The location of the leading edge of an echo is on the same level as that of the interface that creates the echo, and the location of this is not gain dependent. The far edge is defined by the gain setting and other properties of the recording system and not by the thickness of the anatomic structure (Figure 2). Therefore, a general principle used in echocardiography for many years has been to perform all measurements on the leading edge of echoes. Measurements on the near wall depend on measurements on the far edge of echoes (Figure 2). Therefore, it has been suggested that even if measurements on the near wall are also performed by some groups, then all groups should also separately present measurements from the far wall, and if the lumen diameter is measured, that this measurement of lumen diameter be performed according to the leading-edge principle as illustrated in Figure 2. This will simplify comparisons between different studies and also aid in a uniform interpretation of results.

A large number of studies and controlled, randomized, clinical trials in progress use two-dimensional ultrasound evaluation of the carotid arteries. It is important in these trials to correlate readings of the intima-media complex on the far wall of the common carotid artery with quantitative evaluations of plaques in the carotid artery bulb and elsewhere in the carotid artery. It is also important to evaluate readings from the femoral artery. The data presented indicate that not only measurement of wall thickness but also quantitative analysis of plaque area can be performed with B-mode images from both the carotid and femoral arteries. The possibility of identifying in vivo plaques with different qualitative tissue characteristics seems to be limited at present.

**Comments on the Role of Surrogate End Points for Coronary Events in Epidemiological Studies and Clinical Trials**

During the past decade, we have seen a tremendous increase in the number of clinical trials performed and also in the number of patients involved in these trials. These enormous trial sizes emerge from the fact that hard end points like mortality or morbidity from cardiovascular disease are rather uncommon in most situations, and therefore, large trial sizes are necessary to achieve an acceptable power of the trial. The cost, however, is considerable, and important questions regarding effects on the disease process may not evolve from the trial. A growing interest in studies of “softer” end points, or so-called surrogate end points, is therefore natural.

Hard end points like myocardial infarction and sudden death are usually due to a combination of an underlying atherosclerotic disease and triggering or precipitating factors such as left ventricular electric instability, plaque instability, or a disturbed thrombogenesis–thrombolysis balance. A surrogate end point often refers to only one of these two aspects of the disease, for example, to an arterial lesion that can be measured by ultrasound (Figure 3) or to a precipitating factor. As a consequence, the primary end point usually measures clinical benefit, whereas surrogate end points often measure only part of the disease process. Death and myocardial infarction are definitely of greater importance for the patient than a moderate progression of an atherosclerotic plaque. It might be advisable, therefore, to combine different surrogate variables (for both the underlying atherosclerotic disease and the triggering or precipitating mechanisms) to obtain a broader perspective of the disease process.

**Advantages and Disadvantages of Surrogate End Points**

The advantages of studies with surrogate end points are considerably smaller sample sizes, shorter follow-up periods, and the fact that some end points may be easier to measure. A special advantage is that the statistical tests with quantitative end points are much more sensitive than those with qualitative end points, which is evidently the reason for the smaller sample sizes needed. A further advantage may also...
be that the end points are more directly associated with the disease process. Thus, the direct influence of the tested agent can be studied.

There are also disadvantages. Drop-outs due to major clinical events constitute a major problem. In the study design, it is necessary to take that problem into account. This is usually done by giving the serious events the most advanced scoring. A decision regarding such scoring must be taken prospectively. It is evident that such events may ruin the results of the entire trial.

Competing events are of a similar nature, especially if the intervention can affect the competing event, which may cause bias. An intervention may or may not be effective in treating the condition of interest but could be harmful in other respects. This may be exemplified with results from randomized, clinical trials: in the International Nifedipine Trial on Atherosclerotic Therapy (INTACT), active pharmacological treatment (nifedipine) reduced the risk for new coronary lesions (the surrogate variable), but at the same time, an unexpected and significantly higher total mortality was seen in the actively treated group compared with the placebo group (12 deaths with nifedipine, two deaths with placebo; \( p=0.014 \)). Another example is the Cardiac Arrhythmia Suppression Trial (CAST). In this study, antiarrhythmic drugs (encainide or flecainide) showed a decrease in complex arrhythmias (the surrogate variable) compared with placebo, but an increased relative risk of death due to arrhythmia and of nonfatal cardiac arrests was concomitantly seen in the actively treated group (relative risk, 3.6; 95% confidence interval, 1.7–8.5). The results also showed higher total mortality in the actively treated group compared with the placebo group (relative risk, 2.5; 95% confidence interval, 1.6–4.5). It is unlikely that studies with only surrogate end points would have given sufficient information to detect this negative effect on total mortality. Therefore, total mortality should be considered as well as cause-specific fatal events, in addition to the primary surrogate variables whenever possible.

### Regulatory Aspects

Regulatory agencies are most interested in how well-designed clinical trials can help refine our assessment of benefit versus risk of particular treatment interventions. Potential benefits and selected risks of drug treatments designed to slow, arrest, or reverse the progression of atherosclerosis are listed in Table 1.

While choosing a surrogate vascular clinical trial end point may provide an earlier, less costly assessment of the atherosclerotic process, for regulatory purposes, attempts to correlate various surrogate outcome variables with cardiovascular morbidity and mortality end points should be performed. The problem with arbitrarily choosing one particular surrogate end point measurement method is that it cannot, at this time, be directly translated into an amount of change in vascular event risk. Toxicities may arise through a variety of mechanisms and may involve different organ systems in different patients. Particularly for treatments aimed at primary prevention of atherosclerosis, it is important to be able to identify instances in which the combined incidence of several unexpected toxicities would exceed the hoped-for reduction in morbid vascular events.

In choosing a surrogate vascular end point, measurements lacking appropriate anatomic validation should be avoided. Furthermore, because of the crucial importance of relating surrogate end points to clinical benefit in terms of risk reduction for subsequent vascular events, premature termination of clinical trials based on interim analysis of a surrogate end point should be avoided.

### Conclusions

Methods capable of quantitatively evaluating atherosclerotic manifestations in a safe, valid, and reproducible way in prospective studies of humans would be of great importance for epidemiological and clinical research relating to the pathophysiology
TABLE 1. Benefit Versus Risk Assessment in Clinical Trials of Medical Strategies to Reverse or Slow Progression of Atherosclerosis

<table>
<thead>
<tr>
<th>Possible benefits of drug therapy</th>
<th>Possible risks of drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved overall mortality</td>
<td>Carcinogenicity</td>
</tr>
<tr>
<td>Fewer fatal vascular events</td>
<td>Hemorrhage (cerebral, GI, etc.)</td>
</tr>
<tr>
<td>Fewer nonfatal vascular events</td>
<td>Myopathy (seen with fibrates and HMG CoA reductase inhibitors)</td>
</tr>
<tr>
<td>Improvement in angina, TIA, claudication</td>
<td>Arrhythmogenicity/cardiac toxicity (as seen with d-thyroxine, encaïnine, and flecaïnine)</td>
</tr>
<tr>
<td>Less restricted activity level</td>
<td>Promotion of thrombogenesis (as seen with the estrogens)</td>
</tr>
<tr>
<td>Improved quality of life</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Gastric toxicity</td>
</tr>
<tr>
<td></td>
<td>Renal toxicity</td>
</tr>
<tr>
<td></td>
<td>Neurotoxicity</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack; GI, gastrointestinal; HMG CoA, hydroxymethylglutaryl coenzyme A.

of atherosclerosis and also for the evaluation of preventive measures in randomized clinical trials. The ultrasound method is a promising technique, with a great potential for refined, computerized analyzing techniques. However, atherosclerotic manifestations are complex structures and, therefore, difficult to measure. Thus, there is a need for improved interaction between pathologists and researchers, who use different methods to measure atherosclerosis in vivo, to increase our understanding of what the recordings show. In addition, agreement about standardized measurement routines should be reached. This will simplify comparisons between different studies and will also aid uniform interpretation of results. Furthermore, more studies are needed to clarify the relation between the surrogate variables from large arteries (e.g., carotid wall thickness and plaque) and coronary heart disease. In doing so, we must be aware of the contrasting goals for the clinician and the epidemiologist and the fact that clinical patient groups are not representative of the population at large.

Hard end points like myocardial infarction and sudden death are usually due to a combination of an underlying atherosclerotic disease and triggering or precipitating factors such as left ventricular electric instability, plaque instability, or a disturbed thrombogenesis–thrombolysis balance. It might be advisable, therefore, to combine different surrogate variables (for both the underlying atherosclerotic disease and triggering or precipitating mechanisms) to obtain a broader perspective of the disease process.

An intervention may or may not be effective in treating the condition of interest but could be harmful in other respects. Therefore, total mortality should be considered, as well as cause-specific fatal events, in addition to the primary surrogate variables whenever possible.

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