THE QUANTITATIVE APPRAISAL OF ATHEROSCLEROSIS *

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The customary pathologic grading of atherosclerosis does not portray adequately the prevalence and extent of subclinical vascular disease, although it has permitted satisfactory clinical correlation with occlusive arterial disease. Since it is based upon the experience of the observer, it is poorly adapted to a study by a variety of observers in widely separated localities and under assorted circumstances.[1] Accordingly, it is not surprising that some of our prevalent concepts stem largely from indirect evidence. The low frequency of myocardial infarction among the natives of Japan, or the Bantu of South Africa, is the basis for believing that atherosclerosis is less severe among them. Higginson and Pepler[2] deplored the lack of more precise comparative pathologic data in evaluating the incidence of coronary atherosclerosis among the South African Bantu. Similarly, the reduced frequency of coronary arterial disease under conditions of chronic undernutrition in World War II has been attributed to a reduced prevalence of atherosclerosis.[3,4] Although such conclusions may be correct, direct substantiating pathologic evidence would be more satisfactory and would reduce the possibility of missing unsuspected factors. A more objective procedure of assay in recording necropsy observations of atherosclerosis must be adopted. Practically, the procedure must be easy to apply and must avoid undue demands upon the time and resources of the pathologist. Even the most precise technique would be doomed to failure if its complexity discouraged widespread adoption. The following procedure, devised to compare the prevalence of atherosclerosis in Guatemala, other countries of Central America, and in the United States of America, seems to meet these requirements. Although it will be described as it is applied to the aorta, which is the most readily available vessel and the one most uniformly examined, it is equally applicable to any other vessel. It is limited to gross inspection and requires nothing more than systematic observation, estimation, and recording.

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TECHNIQUE

Appraisal

In an atherosclerotic aorta, the extent or area of intimal involvement and the character of its lesions are to be considered separately. Extent of disease may be expressed by the use of five groups which correspond roughly with the traditional grades of severity; these are outlined in Table I. In practice, the fractional areas listed parenthetically facilitate visual estimation.

TABLE I

Extent of Atherosclerosis

Group	Traditional grading	Proportion of intima diseased
0	Negligible	Less than 5% (less than 1/20)
A	Minimal (+)	6–15% (less than 1/6)
B	Mild (+ +)	16–33% (less than 1/3)
C	Moderate (+ + +)	34–50% (less than 1/2)
D	Severe (+ + + +)	More than 50% (more than 1/2)

The character of the intimal lesions observed is the second factor to be considered since grouping does not include this information. In general, atherosclerotic lesions, as listed in Table II, are of four types graded from 1 to 4 in the order of their pathologic importance and also, presumably, in the order of their development.

TABLE II

Types of Atherosclerotic Lesions

Grade 1: ***Lipid streaks, spots, and patches.*** These are very superficial, thin, yellow, subendothelial accumulations which may just perceptibly elevate the internal surface. Small, punctate, discrete, yellow, pure lipid, nodular elevations (lipid spots) in the ascending aorta are included in this category (Figs. 1 and 2).

Grade 2: ***Elevated, smoothly surfaced, fibrous plaques of variable lipid content.*** The pearly white fibrous plaque is the type lesion of this category but others are yellow and distinguishable from grade 1 only by the associated presence of sclerosis (Fig. 3).

Grade 3: Plaques with ulceration, necrosis, or hemorrhage (Fig. 4).

Grade 4: Calcified plaques.

By grouping and grading according to Tables I and II, both the extent of atherosclerosis and its character may be expressed by a simple formula or "atherosclerotic profile." This consists of the group letter followed by a number, each of whose four digits corresponds respectively and sequentially with one of the grades of lesions. In this fashion, the figure representing the proportion of grade 1 lesions would be the first digit while that representing grade 4 lesions would be the

fourth. By expressing the whole of the disease as unity or one, the part each grade contributes to it, and the number representing it in the profile, may be estimated visually in tenths. Each individual figure may vary from 0 to 10, but it is apparent that their sum must always be 10 (10 tenths), unless atherosclerosis is completely absent. For example, a severely diseased aorta with involvement of more than half of its intimal surface would be classed as group D. If it is ascertained that one tenth of the lesions are grade 1, two tenths grade 2, one half grade 3, and two tenths grade 4, the atherosclerotic profile would be D 1252.

Evaluation

For statistical evaluation of large numbers of cases, it would be advantageous to reduce the profile to an "atherosclerotic index." This may be accomplished by assigning weights to the factors involved in the profile. Simple arithmetic weighting based on the area involved is suggested for the groups as listed in Table III, since it seems reasonable to infer that the extent of atherosclerosis is directly related to its clinical importance.

TABLE III
Weighting for Extent of Disease

Group	Area involved	Approximate mean area	Weighting
	%	%	
0	0— 5	2.5	1
A	6— 15	10.0	4
B	16— 33	25.0	10
C	34— 50	40.0	16
D	51—100	75.0	30

On the other hand, a linear relation would not adequately express the difference in clinical significance between lipid streaks and ulcerated plaques. Since the physiologic processes of growth and degeneration have a semi-logarithmic relation, it is proposed that the grades be weighted logarithmically as in Table IV. However, grades 3 and 4 are assigned equal weight since there is no basis for considering that calcified lesions are more important than the ulcerated, necrotic, or hemorrhagic plaques of grade 3.

TABLE IV
Weighting for Grade of Lesion

Grade	Weight
1	1
2	10
3 and 4	100

Utilizing the example cited above, with the profile D 1252, an atherosclerotic index may be derived by the following calculation: 30 (1/10 × 1 + 2/10 × 10 +

$5/10 \times 100 + 2/10 \times 100) = 30 \times 72.1 = 2163$. Since the theoretic range is from 0 to 3,000, the additional introduction of a constant multiple, 1/30, provides a more convenient index ranging from 0 to 100. In the cited example, the final atherosclerotic index, to the nearest whole number, then becomes $2163 \times 1/30$ or 72.

Narrowing Index for Visceral Arteries

The major clinical problems in atherosclerosis arise from occlusive changes in the arteries to the heart, brain, and/or lower extremities. Since they may dilate, narrowing is not an invariable consequence of even severe disease in these vessels. Accordingly, adequate pathologic correlation requires some index of luminal constriction to augment the evaluation represented by the atherosclerotic profile. Fortunately, multiple transection, a common technique for examining the coronary arteries at necropsy, is ideally suited for estimating luminal patency. The impairment of circulation by narrowing, following Poiseuille's principle, is proportional to the cube of the fractional lumen remaining. For example, a coronary artery reduced to one fourth of its usual size can convey only 1/64th of the normal volume; its capacity is reduced 64 fold. This factor then provides the weighting to be applied to each of the four degrees of narrowing (Table V) to derive a "narrowing index."

TABLE V

Luminal Narrowing

Degree of narrowing	Diameter of residual lumen	Significance of weight
0	More than 9/10 of normal	0
1	More than 3/4 of normal	2
2	More than 1/2 of normal	8
3	*Less* than 1/2 of normal (assuming an average of 1/4)	60

Inasmuch as atherosclerosis is characteristically irregular and patchy, multiple foci of narrowing are the rule. Of these only the five most severe are considered. Their sum, when weighted according to Table V, would range from 0 to 300 and must be multiplied by the constant factor, 1/3, to yield an index of narrowing which ranges from 0 in normal, to 100 in maximally diseased vessels.

DISCUSSION

The foregoing assay procedure provides for stepwise changes in a process which is continuously variable. Its application, therefore, is bound to require arbitrary decisions. Nevertheless, experience with it

in more than 1,000 cases has convinced us that it is practical and yields reasonably consistent results. The entire length of the opened aorta is examined from the valve ring to the bifurcation. Omission of the aortic ring may mean missing some of the lesions that Holman's group[5] have found to be a frequent and early manifestation in young individuals. Although many of the grade 1 lipidic lesions may be seen in the fresh or formalin-fixed aorta, there is no doubt that Sudan staining as done by the workers of Louisiana State University[5] increases the quantity detected in the first 2 decades. The discrepancy is not great in adults. Since our immediate goal is to learn the prevalence of gross disease rather than its earliest manifestations, staining is not done as a routine procedure. In any case, data derived from stained aortas are not comparable with figures derived from unstained ones.

Little difficulty is encountered in grouping by area of involvement. Although visual estimation results in considerable overlapping between consecutive groups, statistically such errors cancel each other. Puckering, scarring, and even focal calcification at the site of the obliterated ductus is not considered part of the atherosclerotic process.

In the characterization of the lesions the portion of the disease which is calcified or ulcerated is estimated in tenths. Of this total value, the proportion which is calcified constitutes grade 4 lesions, the remainder are grade 3. As a radiologically detectable feature, the clinical importance of calcification is such that it has been our practice, though it may magnify the situation, to record even a small single focus. Similarly, any ulceration observed means that at least one tenth of the disease is to be considered grade 3. Although mural thrombi are really a complication rather than a part of atherosclerosis, by and large, they originate upon and cover areas of ulceration. Accordingly, they have been classed with grade 3 lesions, acknowledging the impossibility of distinguishing incorporated areas of intact endothelium once organization has appeared. For purposes of record, we have indicated the proportion of such involvement in the entry on the original data sheet.

Frequently, lesions are both calcified and ulcerated. In this event, it has been our policy to tabulate them with grade 3 lesions and indicate the mineralized portion parenthetically under grade 4. The latter figure, of course, does not enter into the calculation of the atherosclerotic index, but does provide a record of the extent to which the aorta is calcified. In the example cited above, if somewhat more than half of the ulcerated lesions were also calcified, the previous profile would be written as D 125(3)2. According to this representation, half of the atherosclerotic lesions are calcified, a parenthetic three tenths, already

counted under grade 3, and an additional two tenths of pure grade 4. The proportion of grade 3 and grade 4 lesions which results from the presence of an aneurysm may be similarly recorded in the appropriate space on the original data sheet.

That portion of the disease which remains unclassified constitutes grades 1 and 2. Estimation of the part due to subendothelial accumulation of lipid (grade 1) allows grade 2 to be determined by difference. It is in distinguishing lesions of grades 1 and 2 that difficulty is encountered and the choice is sometimes arbitrary. The choice depends upon recognizing whether or not there is a fibrous tissue component diluting the yellow (intensely sudanophilic) color of the plaque and causing a localized elevation. The purely lipidic spots found in the ascending aorta are distinctly elevated, so that feature alone is not a reliable criterion; nor is the superficial localization of lipid a reliable criterion, since deposits may be superimposed upon dense sclerotic plaques and indeed very frequently encircle and outline them.

For those situations where clear distinction between lesions of grade 1 and 2 is not possible, we have adopted the practical expedient of categorizing them as half-grade 1 and half-grade 2. The difficulty is not a major one, however, either from the number of instances where it arises or the maximum error it could create in the atherosclerotic index (an increment not more than nine). Accordingly, the shortcoming should not interfere with the accumulation and comparison of data by different groups. This same conclusion pertains to one other difficulty we have encountered infrequently in the older age groups. This is a more or less diffuse fibrous intimal thickening[6] which is interpreted as atherosclerosis (grade 2) only when there is irregularity and slight nodularity of the surface.

It is also pertinent to mention an intimal structural alteration characterized by slight fibrous thickening in the form of multiple, closely spaced, transverse "striae." These striae are found most commonly in the thoracic aorta below the level of the ligamentum arteriosum, and in the abdominal aorta above the bifurcation and proximal to the ostia of the celiac axis and mesenteric arteries. Deposition of lipid upon these lesions is haphazard and coincidental. Infrequently, they may be greatly hypertrophied and thickened so that they resemble keloids. Having been observed only in infants and children, they presumably become effaced as the intima thickens with maturation and aging; they are not considered part of the atherosclerotic process.

Examination of the coronary arteries begins at and includes the

ostia and extends distally along the epicardial portions of the three major channels as far as it is possible to trace them. Narrowing beyond the ostia can be detected and measured by sequential transection at intervals of 0.5 cm. To establish the atherosclerotic profile, however, it is essential to open the previously transected vessels longitudinally; for this purpose we have used an iridectomy scissors with blunt points.

The degree and extent to which atherosclerosis remains undetected by multiple transection is often surprisingly great. At times narrowing in successive cross sections is due to the same plaque; nonetheless, this situation is recorded as two (or more) points of narrowing. In a schematic inflexible system, a second site of narrowing would not enhance the impairment of circulation more than a single one of equal degree; but *in vivo,* this circumstance would distinctly handicap the possibility of compensatory collateral flow. Calcification may interfere to a variable extent with examination, but it has rarely been necessary to resort to preliminary decalcification. There is obviously no conflict between this type of evaluation and the necessity for removing short segments of vessel for histologic examination.

Cerebral or other visceral arteries may be examined in like fashion. In the brain the vessels examined, all superficial, include the circle of Willis, the stumps of the internal carotid arteries, the vertebral and basilar arteries, and the proximal portions of the anterior, middle, and posterior cerebral arteries. These vessels are most conveniently examined, *in situ,* at the base of the brain after formalin fixation. If the brain is to be examined in the unfixed state, removing, spreading, and orienting the circle of Willis and its tributary branches on stiff blotting paper are essential to maintain relations during preliminary fixation.

Summary

A description has been given of a method for quantitating the atherosclerosis observed at necropsy. Its widespread application and use will allow better comparisons of the extent and severity of the disease in various ethnic, geographic, and economic groups.

Appendix

Charts 1 and 2 are copies of the data and work sheets we have been using. Undoubtedly, other associations and correlations will suggest themselves to others who may then modify them to suit their own purposes. For those pathologists whose obligations and circumstances preclude such elaboration, but who are still interested in the investigation of this problem, we suggest that application of this technique and incorporation of the essential information in their necropsy protocols will provide a more informative record of their observations.

Chart 1

DATA SHEET FOR ATHEROSCLEROSIS STUDY

Acc. no.:

Name: Age: Sex: M.... F.... Abode: Rural.... Urban....

Occupation:

Hospital and location:

Race: White..... Negro..... Indian..... Yellow..... Others.....

Acute accidental death (less than 24 hours):

Physical activity: Hard..... Moderate..... Sedentary.....

MAJOR PATHOLOGIC DIAGNOSIS:

Wasting disease present more than 2 months....., more than 4 mos....., more than 8 mos.....

Nutritional status: Severely obese....., Mild to moderately obese....., Average....., Thin....., Malnourished.....

Syphilitic aortitis....., Aneurysm (Arteriosclerotic.....) (Syphilitic.....) (Dissecting.....) Rheum. H. D..... Rheum. Arth.....

Aortic mural thrombosis....., Cerebral thrombosis....., Mesenteric, renal, or iliac arterial thrombosis.....

Angina pectoris....., Myocardial infarct....., Coronary thrombosis.....

Disabling peripheral arteriosclerosis.....

Hypertension (Established.....) (Presumptive.....) Asthma.....

Diabetes mellitus...., 0 to 5 years...., 6 to 10 years...., more than 11 years....

Alcoholism....., 0 to 5 years....., 6 to 10 years....., more than 11 years.....

Laennec cirrhosis....., Posthepatitic cirrhosis....., Biliary cirrhosis.....

Nephrotic syndrome.....

Hyperthyroidism....., Hypothyroid state....., Hyperlipemia.....,

Hypercholesterolemia.....

Indicate presence of condition or state by a plus mark (+) or its absence by zero (0)

If unknown, insert a minus sign (–)

Chart 2

Acc. no.:

ATHEROSCLEROTIC PROFILE AND INDEX

Name:

Hospital:

	Grade°° 1	Grade°° 2	Grade°° 3	Grade°° 4	
Aorta O, A, B, C, or D°	....× 1/10 +	.... +	....× 10 +	....× 10	× 1/30 =
Coronary Arteries O, A, B, C, or D°	....× 1/10 +	.... +	....× 10 +	....× 10	× 1/30 =
Cerebral Arteries O, A, B, C, or D°	....× 1/10 +	.... +	....× 10 +	....× 10	× 1/30 =

° Circle appropriate one. To calculate index, substitute numerical values 1, 4, 9, 16, or 30 for O, A, B, C, or D, respectively.

Area or disease: Group O — 1/20 or less
Group A — 1/6 or less
Group B — ⅓ or less
Group C — ½ or less
Group D — More than ½

°° The sum of the grades, representing the total disease, always has a value of 10.

Indicate by numbers which add to ten, the proportion of each grade of lesion as follows:

Grade 1 — lipid streaks
Grade 2 — fibrous and lipid plaques
Grade 3 — necrosis, ulceration, and hemorrhage
Grade 4 — calcified plaques

NARROWING INDICES

Select five narrowest foci in cerebral or coronary arteries, gauge degree, check the appropriate column, and calculate as indicated.

DEGREE OF NARROWING°°°

Coronary Arteries	....× 0 +	....× 2 +	....× 8 +	....× 60	× 1/3 =
Cerebral Arteries	....× 0 +	....× 2 +	....× 8 +	....× 60	× 1/3 =

°°° 0 — Residual lumen more than 9/10 of normal
1 — Residual lumen more than ¾ of normal
2 — Residual lumen more than ½ of normal
3 — Less than ½ of the normal lumen remains

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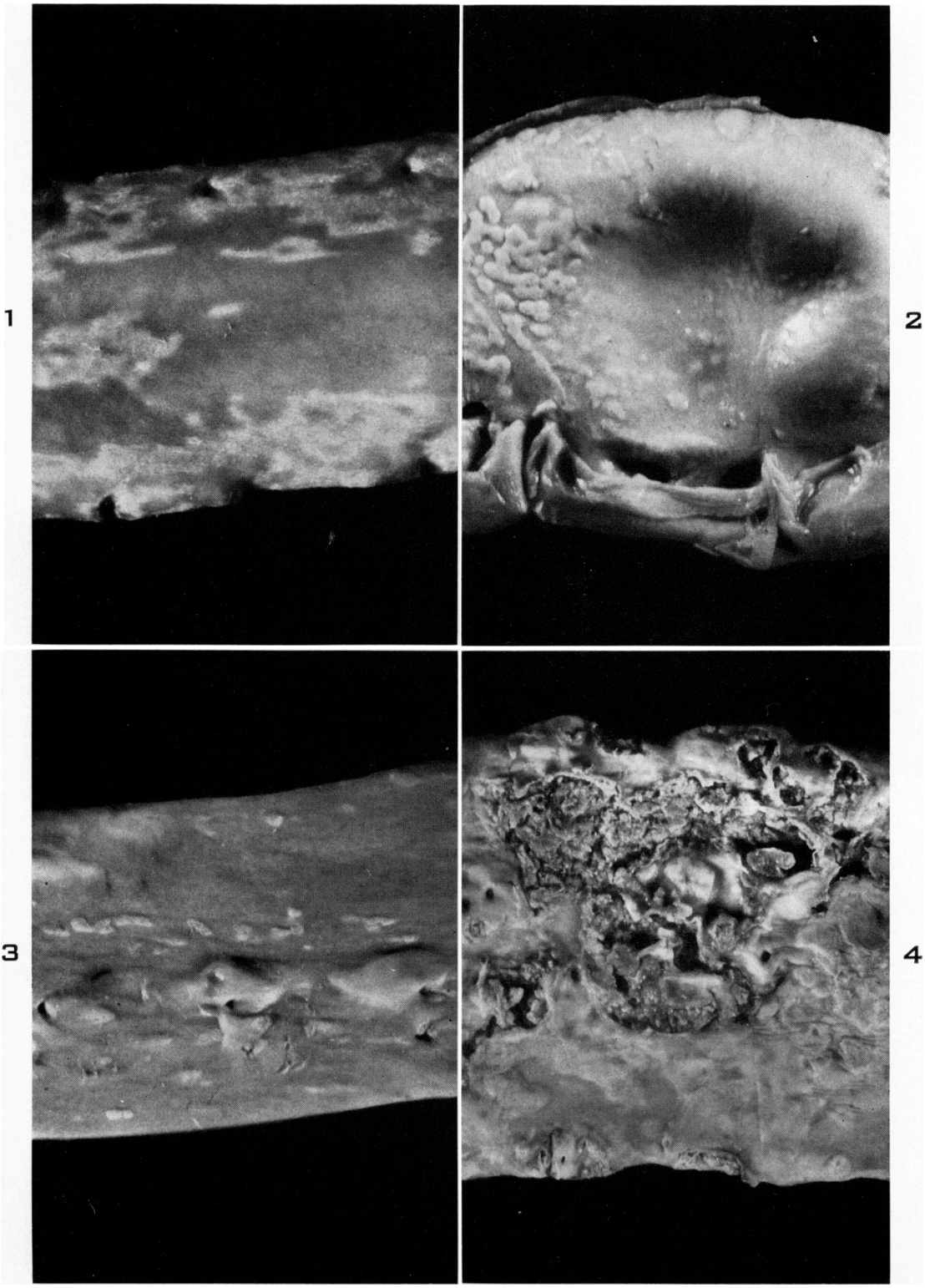
LEGENDS FOR FIGURES

FIG. 1. Internal surface of aorta presenting extensive superficial deposits of lipid in the form of streaks and patches, grade 1 lesions. × 1.

FIG. 2. Intimal surface of supravalvular portion of aorta, showing the sharply delineated, slightly elevated, focal and superficial deposits of pale-staining lipid, grade 1 lesions. Two grade 2 lesions may be observed also, one bordering the coronary ostium showing above the middle valve cusp and the second, centrally, at the distal margin of the aortic segment. × 1.5.

FIG. 3. Intimal surface of aorta presenting several smoothly surfaced, elevated plaques. These grade 2 lesions, most conspicuous about the segmental ostia, are pearly white and contrast with the smaller, more superficial, sharply marginated yellow deposits, grade 1 lesions, in the same field. × 1.

FIG. 4. Intimal surface of aorta with severe atherosclerosis. Only small segments of uninvolved intima are present; the major portion is roughened and thickened by confluent fibrous plaques. The extensive ulceration which characterizes grade 3 lesions may be observed, and the pale superficial lipidic deposits superimposed upon the fibrous plaques. Calcified plaques, grade 4, also present, are not demonstrable photographically. × 1.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