

Comparison of Aortic Atherosclerosis in the United States, Japan, and Guatemala

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THE study of geographic variations in the prevalence of coronary artery disease, as a measure of atherosclerosis, has provided information which suggests a means of controlling the disorder. As summarized by Keys,¹ the incidence of vascular heart disease is apparently related to the fat content of the diet by virtue of the latter's influence upon the level of serum cholesterol. This is the explanation he has given for the infrequency of coronary artery disease in groups whose dietary fat content is low, e.g. the Bantu in South Africa, the Japanese residents of Kyushu, and the natives of Madrid and Naples. By contrast, the high fat content of the diet seems to be related to the prevalence of coronary disease in the United States, Denmark, Sweden, and England. The distinction is neither a national nor racial characteristic, since it is lost in groups who customarily consume more fat, such as bankers in Naples, Italians residing in Bologna (or the United States), or Japanese residents of Hawaii.

The vital statistics which permit these conclusions, impressive as they may be, are still an indirect measure of an anatomically demonstrable process. Accordingly, autopsy verification is required to establish confidence in their validity. The studies of Higginson and Pepler² upon the South African Bantu and those of Kimura³ upon the Japanese in

Kyushu are pertinent but suffer from a shortcoming which has been common to virtually all pathologic descriptions of atherosclerosis. Until recently there has been no satisfactory objective way of recording the degree of atherosclerosis observed at autopsy. Unavoidably, except for occlusive lesions, there has been considerable inaccuracy in comparing the data of different observers, especially when there has not been a common background of experience.

Accordingly, it has been considered appropriate to extend the use of a more objective appraisal technic⁴ to a series of consecutive autopsies performed in Sapporo, Japan, for comparison with similarly evaluated unselected postmortem material from Guatemala, New Orleans, and Los Angeles. The Guatemalan and New Orleans data have been reported previously⁵ and subsequently have been compared with a representative autopsy sample from Costa Rica.⁶

These studies disclosed that there were no discernible differences in atherosclerosis before the age of 30, by which time virtually all individuals display some degree of intimal disease. Thereafter, differences in the rate of progression characterized the disease process in the three countries. As measured both by extent of surface involvement and by the character of the lesions, atherosclerosis advanced more rapidly in New Orleans than it did in Guatemala or Costa Rica. Of the three countries, Guatemala displayed the lowest incidence of severe disease. Corresponding differences had been described⁷ in dietary fat, serum cholesterol, and S_t 0-12 lipoprotein levels. A similar study comparing atherosclerosis in Los Angeles and India (Vellore)⁸ demonstrated less extensive and less severe arterial disease in the latter.

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MATERIAL AND METHODS

The degree of atherosclerosis was appraised in the unstained aortas of 659 consecutive autopsies performed at the Los Angeles County Hospital and in 260 consecutive postmortem examinations at the University Hospital in Sapporo, Japan. Males and females were included in both groups, but have been combined in tabulating the number of individuals in each decade listed in Figure 1.

As previously described,⁴ the appraisal technic considers both the extent of surface involvement and the character of the lesions observed. Intimal lesions are classified as: grade 1, fatty streaks; grade 2, fibrous and atheromatous plaques; grade 3, necrotic, hemorrhagic, or thrombotic plaques; and grade 4, calcified plaques. In terms of surface area involvement the five groups were: group 0, less than 5 per cent surface involvement; group A, 6 to 15 per cent involvement; group B, 16 to 33 per cent surface involvement; group C, 34 to 50 per cent surface involvement; and group D, more than 51 per cent surface involvement. The findings are listed as an "atherosclerotic profile," a five-digit figure that expresses the proportion of the intima that is diseased and the decimal fraction of the diseased portion constituted by each of the four types of lesion. By weighting, arithmetically for surface extent and logarithmically for the grades of lesion, an atherosclerotic index is derived expressing severity on a scale ranging from 0 to 100.

RESULTS

The findings in Japan and Los Angeles are presented graphically in the accompanying figures. For purpose of comparison the New Orleans and Guatemala data³ have been plotted as well. There is a progressive rise of the atherosclerotic index (Fig. 1) with age in all localities. Prior to 30 years, the intimal process is identical in the four areas. Subsequently, severity progresses most rapidly in the two United States groups and least rapidly in Guatemala. The statistical significance of this difference has been previously established.⁵ The Japanese figures indicate a relative lag in the accretion of intimal disease

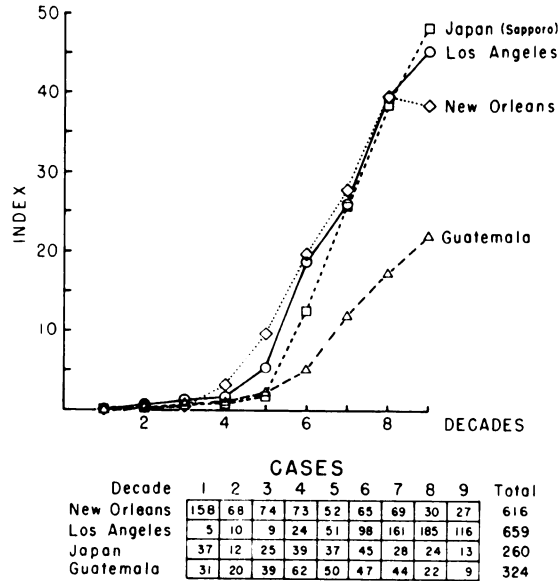


Fig. 1. Atherosclerotic index, aorta.

during the fifth and sixth decades, but thereafter the severity of aortic atherosclerosis in Sapporo coincided with that found in New Orleans and Los Angeles. Statistically the differences between Sapporo and New Orleans in the fifth and sixth decades are significant. However, the intermediate position of the Los Angeles figures in the fifth decade cannot permit us to consider this finding as more than suggestive.

The surface extent of aortic involvement is depicted in Figure 2 for the first, third, fifth, and seventh decades. With aging, there is a progressive increase of the proportion of cases displaying maximal surface involvement (group D). This occurs at a slower rate in Sapporo than in the two United States cities and is most evident in the fifth decade; but, as the graph of the seventh decade discloses, the process is slower still in Guatemala.

Figure 3 and Table I demonstrate the relative proportions of the four grades of atherosclerotic lesions. It is to be noted that, following the widely accepted concept of atherogenesis, grade 1 lesions (lipid streaks) predominate in the early decades and are succeeded by a growing proportion of fibrous plaques (grade 2). The complicated, ulcerated, or calcified lesions (grades 3 and 4) appear in the fourth decade in both New Orleans and

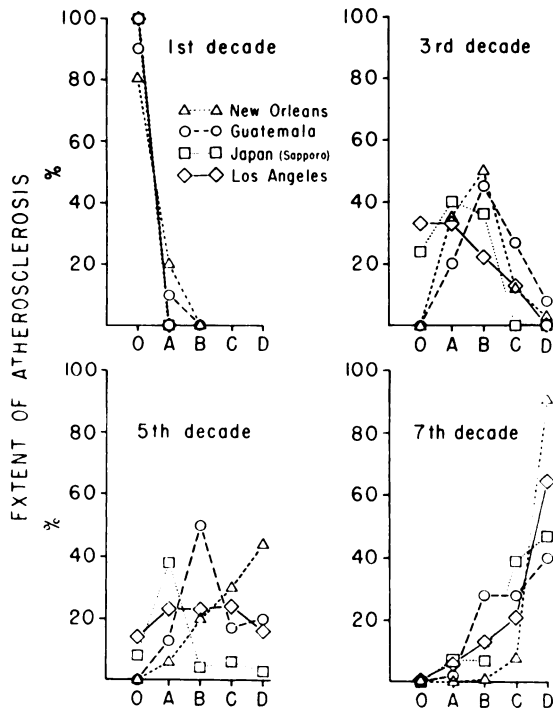


Fig. 2. Aortic atherosclerosis, by area involved.

Los Angeles and in the fifth decade in Japan and Guatemala. In Guatemala the progressive increase of grade 3 and 4 lesions is very slow, whereas in Japan they rapidly attain the magnitude observed in the United States material. It is to be noted that the proportion of grade 1 lesions, in the early decades at least, is higher in New Orleans and Guatemala than in Los Angeles and Sapporo. This, however, is only a technical rather than

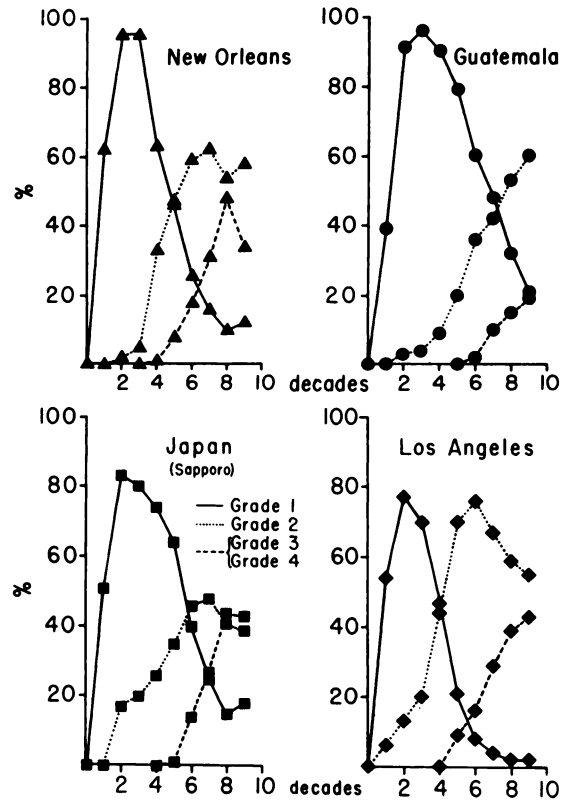


Fig. 3. Aortic atherosclerosis. Type of lesion by decade.

a true distinction and reflects only the accentuation of lipid lesions produced by staining.

DISCUSSION

In view of the comparatively low incidence of fatal coronary artery disease in Japan⁹⁻¹¹ and the relatively low levels of serum chole-

TABLE I
Relative Proportion of Atherosclerotic Lesions (Average Profile)

Decade	New Orleans Grade*				Los Angeles Grade*				Japan Grade*				Guatemala Grade*			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	62	0	0	0	54	6	0	0	51	0	0	0	39	0	0	0
2	95	2	0	0	77	13	0	0	83	17	0	0	91	3	0	0
3	95	5	0	0	70	20	0	0	80	20	0	0	96	4	0	0
4	63	33	0	1	47	44	0	0	74	26	0	0	90	9	0	0
5	46	47	3	5	21	70	2	7	64	35	1	0	79	20	0	0
6	26	59	8	10	8	76	4	12	40	46	8	6	60	36	0	2
7	16	62	13	18	4	67	9	20	25	48	14	13	48	42	4	6
8	10	54	21	27	2	59	9	30	15	41	18	26	32	53	6	9
9 and over	12	58	13	21	2	55	8	35	18	39	21	22	21	60	7	12

* See text for description of grading.

terol¹² among the Japanese, it is surprising not to find more striking differences in the aorta between the United States and Japan. Several possibilities may be suggested:

(1) Major differences may be hidden by individual variation in the application of the appraisal technic. It would indeed be more accurate to have one person assay all the aortas from each locale. Since this is not usually possible it is pertinent to note the compliance of the Los Angeles with the New Orleans data and to suggest that it is practical to compare atherosclerotic data obtained by different observers.

(2) It must be established that this relatively small Japanese sample is representative of the general populace and not biased by the inclusion of numbers of more prosperous individuals with an entirely different, non-average, dietary.

(3) It has been demonstrated that coronary atherosclerosis is generally less severe than aortic atherosclerosis, but parallels the process in the aorta.^{8,13} If this usual disparity were even greater among the Japanese, it would explain a low incidence of vascular heart disease despite severe aortic sclerosis. It is pertinent to note that there were only 10 cases of myocardial infarction or coronary occlusion among 147 Japanese older than 40 years, whereas these were found in 150 of 611 similarly aged Los Angeles residents.

(4) Serious coronary artery disease may not be due to atherosclerosis, per se, but to a complication of it. This, happening less frequently in Japan, would explain the apparent discrepancy.

(5) Sapporo may not be representative of Japan as a whole in regard to atherosclerosis and the factors which contribute to it.

Obviously further investigation is needed to assay these possibilities for the truth.

SUMMARY

Some degree of atherosclerosis is present in virtually all individuals by the thirtieth year in New Orleans, Los Angeles, Japan (Sapporo), and Guatemala.

Subsequent aging is associated with a progressive increase of aortic atherosclerosis.

The rate of increase is least in Guatemala and greatest in the United States. Within the limits of the assay procedure atherosclerosis is identical in Los Angeles and New Orleans.

There is suggestive, but not conclusive, evidence that in Japan the rapid increase in the severity of atherosclerosis that characterizes the middle decades in the United States is delayed. In the latter decades, however, the intimal disease, in this sample at least, is fully as severe in Japan as it is in New Orleans and Los Angeles.

REFERENCES

1. KEYS, A.: Diet and coronary heart disease; in *World Trends in Cardiology, Vol. I. Cardiovascular Epidemiology* (ed. A. Keys and P. D. White). Hoeber, New York, 1956, pp. 135-149.
2. HIGGINSON, J. and PEPLER, W. J.: Fat intake, serum cholesterol concentration, and atherosclerosis in the South African Bantu. Part II. Atherosclerosis and coronary artery disease. *J. Clin. Invest.* 33: 1366, 1954.
3. KIMURA, N.: Analysis of 10,000 post mortem examinations in Japan; in *World Trends in Cardiology* (ed. A. Keys and P. D. White). Hoeber New York, 1956, pp. 22-33.
4. GORE, I. and TEJADA, C.: The quantitative appraisal of atherosclerosis. *Am. J. Path.* 33: 875, 1957.
5. TEJADA, C. and GORE, I.: Comparison of atherosclerosis in Guatemala City and New Orleans. *Am. J. Path.* 33: 887, 1957.
6. TEJADA, C., GORE, I., STRONG, J. P., and MCGILL, H. C., JR.: Comparative severity of atherosclerosis in Costa Rica, Guatemala and New Orleans. *Circulation* 18: 92, 1958.
7. SCRIMSHAW, N. S., TRULSON, M., TEJADA, C., HEGSTED, D. M., and STARE, F. J.: Serum lipoprotein and cholesterol concentrations. Comparison of rural Costa Rican, Guatemalan, and United States populations. *Circulation* 15: 805, 1957.
8. HIRST, A. E., JR., GORE, I., HADLEY, G., and GAULT, E. W.: The gross estimation of atherosclerosis in the aorta, coronary and cerebral arteries. Annual Scientific Session of the A.M.A. San Francisco, June, 1958.
9. KUSAKAWA, A.: Statistical findings on the incidence of coronary heart disease in Japan; in *World Trends in Cardiology, Vol. I. Cardiovascular Epidemiology* (ed. A. Keys and P. D. White) Hoeber, New York, 1956, pp. 159-163.
10. KEYS, A.: Selected vital statistics; in *World Trends in Cardiology, Vol. I. Cardiovascular Epidemiology* (ed. A. Keys and P. D. White). Hoeber, New York, 1956, pp. 167-174.

11. Deaths from arteriosclerotic heart and coronary disease. *United Nations Epidemiological and Vital Statistics Report* 9: 538, 1956.
12. NAKAGAMI, Y.: On the serum cholesterol level of Japanese. *J. Physiol. Soc. Jap.* 19: 453, 1957.
13. GORE, I. and HIRST, A. E., JR.: Comparative severity of atherosclerosis in the aorta, coronary arteries, and cerebral arteries. *Am. J. Path.* 33: 595, 1957.

Errata

In the article "The Metabolism of Plasma Unesterified Fatty Acid," in the November-December issue (Vol. 6, No. 6, pp. 669-680) there are two errors:

Page 670, first column, third line. *1 mg of glucagon* should read: "1 unit glucagon."

Page 677. Equation 1 should read: $\bar{v}_A = \sum v_{Ai} = \sum_i \frac{n_i k'_{Ai} c_A}{1 + k_{Ai} c_A}$ Equation 1.

