STUDY OF CARDIOVASCULAR DISEASE – HIROSHIMA AND NAGASAKI

CLINICOPATHOLOGIC APPRAISAL OF ATHEROSCLEROSIS
IN A DEFINED JAPANESE POPULATION

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STUDY OF CARDIOVASCULAR DISEASE – HIROSHIMA AND NAGASAKI
広島および長崎における心臓血管疾患の研究

CLINICOPATHOLOGIC APPRAISAL OF ATHEROSCLEROSIS
IN A DEFINED JAPANESE POPULATION
日本人の固定集団におけるアテローム性動脈硬化症の臨床・病理学的評価

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Departments of Pathology,† Medicine,‡ and Statistics§ 病理部,†,臨床部,‡および統計部§
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CLINICOPATHOLOGIC APPRAISAL OF ATHEROSCLEROSIS
IN A DEFINED JAPANESE POPULATION

INTRODUCTION

Atherosclerotic vascular disease in the Japanese has several features. While ischemic heart disease and myocardial infarction are uncommon compared with many Western countries, stroke is the leading cause of death in Japan. Age-adjusted death rates for cerebrovascular disease in the Japanese are among the highest in the world.

Geographic variation in the occurrence rates of myocardial infarction is generally ascribed to environmental factors, notably the content of fat in the diet. Recent anatomic studies have confirmed the very slight degree of coronary atherosclerosis in Japan when compared with countries such as the United States.

Further evidence for the important role of environment in atherogenesis comes from observations on Japanese living in Hawaii and continental U.S.A., in whom death rates from ischemic heart disease are much higher than for those in Japan. Recent autopsy data have demonstrated occurrence rates of myocardial infarction among Japanese in the United States approaching those of the Caucasian population.

Aorta and coronary atherosclerosis are similar in severity in the United States. In Japan, however, a marked disparity between aortic and coronary disease has been demonstrated. Aortic atherosclerosis in Japan, where fat intake is low, has been demonstrated to progress nearly as rapidly as it does in the United States where fat intake is high. This is in striking contrast to the difference in coronary atherosclerosis in these populations. Observations such as these cast doubt on a simple relationship between dietary fat and atherosclerosis.

A recent study at ABCC has confirmed the high rate of stroke in Japan. Indeed, the incidence of cerebrovascular disease in this study population exceeds any reported in a defined population, white or non-white, in the United States.

日本にみられるアテローム性動脈硬化性血管疾患には、いくつか特徴がある。日本では、多くの西欧諸国と比較して、虚血性心機能不全および脳動脈硬化がまれであるのに、脳卒中は死因第1位である。日本人における脳血管病の年齢訂正死亡率は、世界で最も高いものの一つである。

心筋梗塞症の発生率の地理的な差異は、一般に環境的因子、とりわけ食糧中の脂肪の含有量に起因すると考えられる。最近行なわれた解剖学的解剖によれば、米国のような諸外国と比較し、日本の冠動脈のアテローム性硬化はごく軽度である。

アテローム性動脈硬化の発生に、環境が重要な役割を果たしていることは、ハワイおよび米本土に居住する日本人の観察によってさらに裏づけられた。在米の日本人の虚血性心機能不全による死亡率は、日本におけるそれよりもはるかに高い。最近の剖検資料によれば、米国における日本人にみられる心筋梗塞症の発生率が白人のそれによく接近している。

米国では、大動脈のアテローム性硬化症および冠状動脈のアテローム性硬化症の重症度は高い。しかし、日本では、大動脈症と冠状動脈症との間に著しい相違が認められている。脂肪摂取量の低い日本では大動脈アテローム性硬化と、脂肪摂取量の高い米国のそれとは同様に進行する。これは、両国における冠状動脈のアテローム性硬化症における差異に対して著しく対照的である。このような観察所見は、食糧中の脂肪とアテローム性動脈硬化症との間に単純な関係があるという考え方に対する疑問をいだかせる。

最近のABCC調査で、日本における脳卒中が高率であることを確認した。この調査集団における脳血管障害の発生率は、米国における白人その他の人種の固定集団に認められた発生率よりも高い。
The ABCC research program offers a unique opportunity to study atherosclerosis in a defined population. The basic study group (NIH-ABCC Life Span Study sample) consists of about 100,000 individuals who were resident in the cities of Hiroshima and Nagasaki on October 1, 1950. The sample is divided according to distance from the hypocenter at the time of the atomic bomb. Detailed study of this population has not revealed an association between exposure to radiation and the development of cerebral or cardiovascular disease. A subgroup of about 20,000 from this sample is examined in detail at the ABCC clinics every 2 years.

Deaths in the Life Span Study sample are investigated by the ABCC Department of Medical Sociology and autopsies are procured in about 40% of the subjects. The autopsy population is unusual in that it is not selected for hospitalized patients and represents, therefore, a sample of deaths from all causes occurring in the community both at home and in hospitals.

MATERIALS AND METHODS

The sample for anatomic study included all male and female Life Span Study subjects, aged 40-69, autopsied at ABCC Hiroshima, from 1 February 1965 to 1 March 1966 and all male subjects from the same group autopsied at ABCC Nagasaki, from 1 May 1965 to 1 March 1966. In Hiroshima, 117 persons (70 males, 47 females) were autopsied during this period from whom 117 aortas, 116 sets of coronary arteries and 111 sets of cerebral arteries were available for study. In Nagasaki, 15 persons (all male) were autopsied, and the aorta, coronary, and cerebral arteries were available from each. Table 1 shows the age and sex distribution of the autopsy group for study. Also shown is the age and sex distribution and autopsy rates for the population from which the autopsies were procured. The age and sex distribution for the autopsied and non-autopsied group show no evidence of selection.

At autopsy the complete aorta and the three major coronary arteries were removed, cleaned of excess adventitial tissue, opened longitudinally, sewn to transparent vinyl plates and fixed in 10% neutral buffered formalin. When zones of marked stenosis were encountered in the coronary arteries, they were by-passed and examined on cross section after fixation. The cerebral arteries were fixed in 10% neutral buffered formalin in situ for several days before removal and were sewn, unopened, to vinyl plates (Plate 1).
### Table 1: Age and Sex Distribution of Autopsy Cases, Deaths, and Autopsy Rates

<table>
<thead>
<tr>
<th></th>
<th>Hiroshima</th>
<th>Nagasaki</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy Cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>60-69</td>
<td>49</td>
<td>70.0</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100.0</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>15</td>
<td>8.1</td>
</tr>
<tr>
<td>50-59</td>
<td>35</td>
<td>18.9</td>
</tr>
<tr>
<td>60-69</td>
<td>135</td>
<td>73.0</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>100.0</td>
</tr>
<tr>
<td>Autopsy Rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>50-59</td>
<td>31.4</td>
<td>58.6</td>
</tr>
<tr>
<td>60-69</td>
<td>36.3</td>
<td>63.7</td>
</tr>
<tr>
<td>Total</td>
<td>37.8</td>
<td>62.2</td>
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</table>

Several grading methods were used in evaluating the collected material. All grading for the study was done by a single observer. For the aortas and coronary arteries a slight modification of previously published techniques based on surface involvement by atherosclerosis was employed. The method used in this study is based on the gross estimation of the surface area involved by atherosclerosis and each of three types of lesions: fatty streaks, fibrous plaques, and complicated lesions. Initially the total percentage of the intimal surface area involved with all types of atherosclerotic lesions was estimated followed by separate percent of surface estimates for fatty streaks, fibrous plaques and complicated lesions. Included as complicated lesions were those with ulceration, hemorrhage, thrombosis, or calcification. For the aortas, separate appraisal was made for the entire vessel, the arch, and the descending thoracic and abdominal segments. The three coronary arteries were judged separately in the same manner and an unweighted mean calculated for each case. All grading was done without prior staining for sudanophilia. The results reported for the surface involvement are raw scores. No severity indices were employed for this study.

In addition to surface grading, each of the coronary arteries was evaluated for stenosis. The most stenotic zone in each of the three vessels was graded 0 to 4+ in the following manner: grade 0+, less than 25% stenosis; grade 1+, 25%–49%; grade 2+, 50%–64%; grade 3+, 75%–89% and grade 4+, 90%–100%.
The grades for the three coronary arteries were totaled giving a possible stenosis score of 0 to 12 for each case.

Cerebral atherosclerosis was assessed by the method developed by Baker.\(^{19}\)\(^{20}\) With this technique 22 sites in the cerebral arterial system were evaluated on cross section for atherosclerosis and graded 0 to 4+. The individual grades, although based on cross section examination, take into account both surface involvement and stenosis. The grades are totaled giving a possible score range from 0 to 88.

In addition to evaluation of atherosclerosis, the heart and brain in each case were examined grossly, and appropriate sections made for histologic study. Lesions which grossly had an area of at least 1 cm\(^2\) on any sectioned surface were included as myocardial infarcts. Any gross cerebral lesions later confirmed as infarcts by histologic study were included, the lower limit in size generally being about 2 mm. The lesions in cases of intracerebral and subarachnoid hemorrhage were all sufficiently striking to require no special definitions. All routine histologic sections from each autopsy were also available for study.

Clinical and environmental data about the autopsied subjects were available from several sources. Many of the subjects, male and female, had been evaluated periodically in the ABCC medical clinic providing extensive historical, clinical, and laboratory data. In Hiroshima, through the very kind cooperation of the personal physicians of those not examined at ABCC, blood pressure information was obtained in nearly all cases. In many instances the recordings were available from a time considerably antedating the onset of the terminal illness.

The major source of environmental information was the Mail Survey on Cardiovascular Disease sent from ABCC to all males aged 40-69 of the Life Span Study sample in Hiroshima and Nagasaki. Of the 13,076 subjects who received the questionnaire, 92% in Hiroshima and 93% in Nagasaki responded. The questionnaire provided information such as residential history, socioeconomic status, occupation, diet, educational level, medical history, family history, etc. The results of this survey are to be reported.\(^{21}\)

Because of few cases in Nagasaki, most of the results reported here are based on Hiroshima subjects alone. Where effects of specific factors such as serum cholesterol are evaluated, however, Nagasaki cases are included.

4+とした。3つの冠状動脈についての狭窄の数値を集計したので、各例に0から12の値が得られた。

脳動脈のアテローム性硬化は、Bakerが開発した方法によって計測した。\(^{19}\)\(^{20}\) 脳動脈の22の区域を、この方法によって、その横断面でアテローム性動脈硬化の程度を計測して、その程度を0から4+まで表わした。横断面の検査による計測は、表面の病変の面積と厚さの両者を考慮に入れた。以上の数値を集計して得られる値の範囲は0から88になる。

アテローム性動脈硬化の計測のほかに、各例の心臓および脳を肉眼的に検査したのち、適当な切片を作って組織学的検査を行なった。切片に1 cm\(^2\) 以上の病変が肉眼的に認められたものは、心筋梗塞として扱った。脳病変のうち、その後の組織学的検査で偽善と認められたものは含めたが、その大きさの下限値は約2 mmであった。脳内出血およびクモ膜下出血例の病変は、いずれも顕著で、特に定義を下す必要はなかった。各剖検例から入手した組織の標本も観察した。

剖検例の臨床的および環境的な資料は、いくつかの資料から入手した。対象者の多くはABCCでの定期的検診によって、広範な病歴、臨床および臨床検査資料が得られている。広島では、ABCC以外で受診した患者についても、その主治医の協力によって、ほとんど全例の血圧の資料を入手することができた。多くの場合、死に至る疾患の発生時よりも相当きさかのばって記録が入手できた。

環境に関する資料は、もともと広島・長崎の寿命調査サンプルのうち40-69歳の男性を対象に行なったABCCの心臓血管疾患研究の郵送調査から得られた。質問票を受け取った対象者13,076人中、広島では92%および長崎では93%が回答した。この質問票で、居住歴、社会経済状態、職業、食物、学歴、病歴、家族歴等が得られた。この郵送調査の成績は別に報告する。\(^{21}\)

長崎の例数が少ないので、ここに報告する成績の大部分は、広島の対象者のみに限定した。しかし、ある因子のたとえば血清コレステロール値の観察には長崎の例も含まれた。
RESULTS

Aortic and Coronary Atherosclerosis Figure 1 illustrates graphically the percent of surface area involvement by atherosclerotic lesions for the aorta and coronary arteries. The results are estimates for the entire aorta and the unweighted mean of the three coronary arteries. Surface involvement of both the aorta and coronary arteries rises progressively with age. The extent of disease is similar in both sexes, the gradient of increase being slightly greater in the males. Of particular interest is the remarkable disparity between involvement of the aorta and of the coronary arteries. The difference is quite constant in each age group.

Figure 2 illustrates for the aorta the effect of age on the absolute percent of intimal surface involved by each of the three types of lesions studied. Involvement of fatty streaks in the male is constant for all ages, with the female there is a decline from about 20% at age 40-49, reaching a level similar to the male at age 60-69. Involvement by fibrous plaques in both sexes parallels the total for the combined lesions. The leveling off of fibrous plaques at age 50-60 possibly reflects the increase in complicated lesions which becomes most marked at this age for both sexes.

Figure 3 shows the effect of age on the various types of coronary artery lesions. The distribution of lesions by age is similar to that of the aorta, although the increase in complicated lesions occurs about 10 years later. The inordinately high values for fibrous plaques in females aged 50-59 may reflect the small number of cases in this age group.

The percent of surface scores for coronary arteries were compared with the stenosis scores in each case. The correlation coefficient was .85 demonstrating marked agreement in the assessment of the severity of coronary atherosclerosis by either surface involvement or stenosis. Surface estimates are of greater value in this study, since they allow a direct comparison with the results for the aorta.

Cerebral Atherosclerosis Figure 4 shows the effect of age on the score (Baker) for cerebral atherosclerosis. Cerebral atherosclerosis gradually increases throughout the age range studied with little difference between sexes. The Baker brain score represents a total of individual measurements of atherosclerosis based on appraisal of cross sections from 22 separate sites in the cerebral vasculature. It is, therefore, not directly comparable with the results for the aorta and coronary arteries. The increment with age, however, is very similar to that for the aorta and coronary arteries.

結果

大動脈および冠状動脈のアテローム性硬化症 図1に、大動脈および冠状動脈に認められたアテローム性動脈硬化の相関区分子計率をグラフで示した。図に大動脈と3つの冠状動脈の単純平均値を示したが、大動脈および冠状動脈の病変区域は、年齢とともに増加している。病変の大きさに男女差は認めないが、病変部位の増加の程度は男性の方が大きく2-4大である。大動脈の病変の大きさは特に興味深い。病変の差異は、年齢群において一定である。

図2に、大動脈の内層に認められた3つの型の病変部分の全体に対する割合（百分率）と年齢との関係を示した。男性では、内膜面は全年齢を通じて一定であるが、女性では60-69歳で約30％であったが、その後増加して60-69歳で男性と同程度に達した。男女における線維性硬化板は、全病変合計と同様の傾向を示した。50-60歳で線維性硬化板の曲線が水平になったことは、おそらく混合型の増加によるものと思われ、その増加は男女ともこの年齢で著しくなる。

図3に冠状動脈の各病変型に対する年齢の影響を示した。年齢別の分布は、大動脈のそれに類似しているが、混合型の増加は約10歳遅れて起きている。50-59歳の女性にみられる線維性硬化板の異常な高値は、この年齢群の例数が少ないことによるものかもしれない。

冠状動脈に病変のある区域の百分率値を、各例の狭窄の計測値と比較したのが相関係数は0.85であった。これは病変区の百分率と狭窄の程度を表わす冠状動脈アテローム性硬化症の重症度がきわめてよく一致することを示している。冠状動脈の表面区の推定値は、大動脈について得た結果と直接比較できるから、本研究によってはいっそう大きな価値がある。

脳動脈のアテローム性硬化症 図4に脳動脈のアテローム性硬化の評点（Baker法によるスコア）に対する年齢の影響を示した。脳動脈のアテローム性硬化は年齢とともに増加し、男女間の差はほとんどみられない。Baker法による脳動脈の評点（スコア）は、22か所の脳血管の横断面に基づいて与えられたアテローム性動脈硬化の程度を表す数値の合計である。したがって、大動脈および冠状動脈の成績と直接比較することはできない。年齢とともに増加することは、大動脈および冠状動脈の場合ときわめてよく類似している。
Effect of Hypertension  Blood pressure recordings were available in nearly all cases. The few cases without records were considered hypertensive or nonhypertensive after appraisal of heart weight and the degree of renal arteriolar sclerosis. Hypertension is defined for this study as blood pressure above 160/95 mm Hg. Using this definition, 31 of 70 males (44.3%) and 23 of 47 females (48.9%) were hypertensive.

Figure 5 compares the effects of hypertension on the combined and individual lesions for the aortas and coronary arteries of male subjects. The accelerating effect of hypertension is apparent in both the aorta and coronary arteries. There appears to be no effect on the proportion of fatty streaks in either aorta or coronary arteries, while the fibrous plaques increase in both. Involvement by complicated lesions in this sample is accelerated only in the aorta with the increase occurring about 10 years earlier than in the nonhypertensive subjects.

The same comparisons for females are shown in Figure 6. The results are similar to those for the males but the accelerating effect of hypertension is apparently greater in the females for both aorta and coronary arteries. The effect on the specific...
lesions is nearly identical in both sexes. For females, however, an increase in complicated lesions is apparent in the coronary arteries as well as the aorta.

Figure 7 shows for males and females the effect of hypertension on cerebral atherosclerosis as determined by the Baker grading method. Again, the accelerating effect is apparent, especially in females.

Effect of Serum Cholesterol Serum cholesterol determinations were available in 34 subjects. Because of few cases, results are given for sexes and cities combined. All cholesterol determinations were performed at the ABCC Department of Clinical Laboratories. For comparison, subjects with serum cholesterol above and below 200 mg/100 ml were separated. When more than one determination was available, that which was performed at the earliest date was chosen. The results are based on serum cholesterol values determined an average of 4.7 years before death and therefore in most cases before the onset of the terminal illness. Twenty-three subjects had serum cholesterol below 200 mg/100 ml (mean, 145.1 mg/100 ml) and 11 subjects had serum cholesterol equal to or greater than 200 mg/100 ml (mean, 227.6 mg/100 ml).

女では、混合型の増加は、冠状動脈ならびに大動脈にも著明である。

図7にBaker法で計測した男女の脳動脈のアテルーム性硬化に対する高血圧の影響を示した。ここにも促進効果が、特に女において明らかに認められる。

血清コレステロールの影響 34名について、血清コレステロール値が得られた。例数が少ないので、両市の男女を合計して観察した。血清コレステロールの測定は、すべてABCC臨床検査部で実施した。比較のため、200mg/100ml未満の者とそれ以上の者とに分けた。1つ以上
以上の測定値があった場合は、最初に実施したものを選んだ。血清コレステロール値は死亡時より平均4.7年前、したがって、多くの場合最終疾病の発現前に得られたものである。23名は血清コレステロール値が200mg/100ml以下で、平均値は145.1mg/100ml、11名は血清コレステロール値が200mg/100ml以上であった（平均値は227.6mg/100ml）。
FIGURE 3 EFFECT OF AGE ON INVOLVEMENT BY EACH TYPE OF LESION IN THE CORONARY ARTERIES - HIROSHIMA

图3 冠状動脈における各病変型に対する年齢の影響 - 広島

CORONARY ARTERIES 冠状動脈

% Surface Involved 表面の汚染

Age 年齢

Combined Sexes 男女合計
Male 男
Female 女

- All lesions 全病変
- Fibrous streaks 硬化性線
- Fibrous plaques 硬化性斑块
- Complicated 混合型

FIGURE 4

EFFECT OF AGE ON CEREBRAL ATHEROSCLEROSIS (BAKER SCORE) - HIROSHIMA

脳動脈のアテローム性硬化症 (Baker 法による評点) に対する年齢の影響 - 広島

CEREBRAL ARTERIES 脳動脈

Score 評点

Age 年齢
FIGURE 5 EFFECT OF HYPERTENSION ON PERCENT TOTAL SURFACE OF AORTA AND CORONARY ARTERIES INVOLVED BY EACH TYPE OF LESION - MALE, HIROSHIMA

図5 大動脈および冠状動脈における各型の病変区域の割合（%）に対する高血圧の影響—男、広島
FIGURE 6 EFFECT OF HYPERTENSION ON PERCENT TOTAL SURFACE OF AORTA AND CORONARY ARTERIES INVOLVED BY EACH TYPE OF LESION - FEMALE, HIROSHIMA

図6 大動脈および冠状動脈における各型の病变区域の割合（％）に対する高血圧の影響 - 女，広島
Figure 8, 9 show the effect of serum cholesterol on the absolute percent of surface involvement by the combined and individual lesions of atherosclerosis for the aorta and coronary arteries. Cases are few and the differences, while not statistically significant, are very consistent. Involvement with atherosclerosis in subjects with serum cholesterol levels greater than 200 mg/100 ml is consistently more severe in both the aorta and coronary arteries. The difference is not reflected in the involvement by fatty streaks but is quite constant for fibrous plaques and complicated lesions. Of interest is the appearance of complicated lesions about 10 years earlier in patients with serum cholesterol above 200 mg/100 ml. This is most striking for the aorta but is present to a lesser degree for the coronary arteries also.

The effect of serum cholesterol on cerebral atherosclerosis is shown in Figure 10. Here again those with levels above 200 mg/100 ml have more severe disease; the difference, however, is not as striking or uniform as in the aorta and coronary arteries.

Effects of Other Factors Data derived from the mail questionnaires and from clinical examinations provided information on other factors associated with atherosclerosis. Included were socioeconomic

その他の因子の影響　郵送調査および臨床検診から得られた資料を用いて、他の因子とアテローム性硬化との関連を観察した。得られた項目に、社会経済状態、職業、
FIGURE 8 EFFECT OF SERUM CHOLESTEROL ON PERCENT TOTAL SURFACE OF AORTA INVOLVED BY EACH TYPE OF LESION - SEXES AND CITIES COMBINED

図8 大動脈における各型の病変区域の割合(%)に対する血清コレステロールの影響 - 男女・両市合計
FIGURE 9 EFFECT OF SERUM CHOLESTEROL ON PERCENT TOTAL SURFACE OF CORONARY ARTERIES INVOLVED BY EACH TYPE OF LESION - SEXES AND CITIES COMBINED

図9 冠状動脈における各型の病変区域の割合（％）に対する血清コレステロールの影響 - 男女・両市合計

CORONARY ARTERIES

All Lesions

全疾病

Cholesterol ≥ 200 mg/100 ml

コレステロール

< 200 mg/100 ml

Fibrous Plaques

線維性硬化斑

Complicated

複合型

% Surface Involved

% 表面が病変

Age

年齢

40 50 60 70

CEREBRAL ARTERIES

脳動脈

Cholesterol ≥ 200 mg/100 ml

コレステロール

< 200 mg/100 ml

Score

評点

Age

年齢

40 50 60 70

FIGURE 10

EFFECT OF SERUM CHOLESTEROL ON CEREBRAL ARTERIOSCLEROSIS (BAKER SCORE) - SEXES AND CITIES COMBINED

脳動脈のアテローム性硬化に対する血清コレステロールの影響 (Baker 法による評点) - 男女・両市合計

14
status, occupation, education, diet, physical activity, body weight, smoking habits, diabetes, and electrocardiogram abnormalities. The effects of these factors on clinically observed cardio- and cerebrovascular disease studied at ABCC will be reported elsewhere. Analyses of these data for the present anatomic survey revealed no significant or consistent differences except when smoking data were examined.

Cigarette smoking histories were available for 78 of the 85 male subjects in the two cities. Results for aortic, coronary, and cerebral atherosclerosis are presented in Table 2. Recorded by age groups are the absolute percent surface involvement by all lesions for aorta and coronary arteries and the Baker atherosclerosis score for the cerebral arteries. Because of the small number of cases, only two smoking groups are defined, one including all nonsmokers (never smoked and ex-smokers) and one including all smokers (about equally divided between subjects smoking more and less than 20 cigarettes per day).

巻きたばこの喫煙歴を、広島・長崎県市の男子85名中78名について入手した。大動脈、冠状動脈および脳動脈のアテローム性硬化についての結果を表2に示した。年齢階級別に、大動脈および冠状動脈における全病変の区域百分率、および脳動脈における Baker 法によるアテローム性硬化スコアを観察した。例数が少ないので、たとえ2つの喫煙群に別けた。すなわち、非喫煙群（喫煙したことのない者と以前喫煙していたものが現在止めていない者）と喫煙群（1日に巻きたばこ20本以上の者と20本以下の者がほとんど同数）。

| 表2 非喫煙者および喫煙者のアテローム性動脈硬化症 男、両市合計 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| 年齢 | 非喫煙者 | 喫煙者 | 非喫煙者 | 喫煙者 | 非喫煙者 | 喫煙者 | 非喫煙者 | 喫煙者 |
| 40-49 | 6.0 | 42.9 | 8.0 | 8.6 | 17 | 13.7 | 1 | 7 |
| Cases 例数 | 1 | 7 | 1 | 7 | 1 | 7 |
| 50-59 | 53.3 | 53.3 | 11.8 | 22.3 | 29.0 | 22.7 | 4 | 9 |
| Cases 例数 | 4 | 9 | 4 | 9 | 4 | 9 |
| 60-69 | 49.8 | 68.8 | 22.6 | 39.6 | 32.8 | 38.0 | 24 | 33 |
| Cases 例数 | 24 | 33 | 24 | 33 | 24 | 33 |

In the youngest age group the few cases make interpretation unreliable. In the older ages and especially from 60-69 a rather striking increase in coronary atherosclerosis is noted in the smokers. Aortic atherosclerosis is greater also in smokers between 60-69 years. The differences in aortic and coronary atherosclerosis between smokers and nonsmokers is statistically significant (P<0.01) for those aged 60-69.

The presence of diabetes was documented for only four males and three females thus precluding 最若年群では、例数がきわめて少ないので、信頼できる解析ができなかった。高齢群、特に60-69歳群では、喫煙者の冠状動脈のアテローム性硬化症にやや著しい増加が認められる。60-69歳群においては、大動脈のアテローム性硬化症も喫煙者も多い、大動脈および冠状動脈のアテローム性硬化症については、60-69歳群の喫煙者と非喫煙者との間に、有意な統計的差異が認められた（P<0.01）。

嗜尿病は、男4名と女3名のみが認められなかったのすうがないので、この因子に対して信頼できる観察はできなかった。
reliable evaluation of this factor. Clinical information was generally insufficient to establish or negate the diagnosis.

Cardiac and Cerebrovascular Lesions. Examination of the heart and brain of the autopsied subjects permitted a thorough appraisal of the frequency and type of cardiovascular and cerebrovascular lesions occurring in the study group.

In the following sections the subjects with various types of tissue lesions are characterized both for atherosclerosis and for factors such as hypertension, diabetes, serum cholesterol, and smoking habits. Comparison is also made between subjects with and without the specific lesions and with a group of 'normal' controls from this population, who were defined as those without hypertension, diabetes mellitus, and cardiovascular lesions. The purpose of this category is to provide a sample free of any lesions or diseases usually associated with atherosclerosis.

Myocardial Infarction. Hearts were available for examination in all 117 and coronary arteries in 116 of the Hiroshima cases. Myocardial infarcts were found in 12 cases (10.3%), 8 males and 4 females. Except for one 53-year-old man, all were between age 60 and 69 with an average age of 63.5 years. Myocardial infarction was the cause of death in 4 (3.4%) of the subjects, 2 males and 2 females. A total of 14 lesions were present in the 12 patients, accounted for by old scars in one subject with a recent infarct and one with an organizing infarct. Of the total of 14 lesions there were 3 recent, 1 organizing and 10 old myocardial infarcts. There were no myocardial infarcts in the 15 Nagasaki subjects.

Of the 12 subjects with myocardial infarcts 9 were hypertensive, including 5 of 8 males and all 4 females; 1 male with a myocardial infarct was diabetic, 5 were not and no information was available for 2; of the 4 women with infarcts 2 had diabetes.

Serum cholesterol values were available in only two cases with myocardial infarcts, each with diabetes mellitus. One, a 67-year-old man, had a serum cholesterol level of 262 mg/100 ml 5 years before death, and the other, a 66-year-old woman, had a serum cholesterol of 208.5 mg/100 ml 6 years before death.

Since all but one of the subjects with myocardial infarcts were aged 60-69, data for coronary atherosclerosis are compared with other subjects in this age group only.
Table 3 compares coronary atherosclerosis in the subjects with myocardial infarcts, without myocardial infarcts and the 'normal' controls. Tabulated are the total percent of surface involvement by the combined and individual lesions and the stenosis score for Hiroshima subjects aged 60-69.

There is a striking difference apparent in both surface area and stenosis measurements between the infarct group and both noninfarct groups, the results for the latter two being very similar. The increased severity of surface involvement by atherosclerosis in the infarct group is reflected almost completely in the proportions of fibrous plaques and complicated lesions. The proportion of complicated lesions, as suspected, is also highest in the subjects with myocardial infarcts. The severity of stenosis for all groups closely parallels the extent of surface involved. The differences in coronary atherosclerosis, except for fatty streaks, between subjects with and without myocardial infarcts are highly significant (P<0.01).

Of the 11 subjects with infarcts in the 60-69 year age group 9 (81.9%) were hypertensive and 34 of the 69 subjects (49.3%) without infarcts were hypertensive (Table 4). As demonstrated earlier, hypertension has an accelerating effect on coronary atherosclerosis. However, it does not alone explain the difference in coronary atherosclerosis between the subjects with and without infarcts since the 'normal' group which includes no hypertensives does not differ from the group selected only for the absence of myocardial infarcts in which the rate of hypertension approaches 50%.

<table>
<thead>
<tr>
<th>% Surface Involved</th>
<th>With Myocardial Infarcts</th>
<th>Without Myocardial Infarcts</th>
<th>'Normal'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 Subjects</td>
<td>69 Subjects</td>
<td>25 Subjects</td>
</tr>
<tr>
<td>All lesions</td>
<td>64.0%</td>
<td>24.2%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Fatty streaks</td>
<td>2.2%</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Fibrous plaques</td>
<td>36.8%</td>
<td>15.3%</td>
<td>12.4%</td>
</tr>
<tr>
<td>Complicated lesions</td>
<td>25.0%</td>
<td>6.2%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Stenosis score</td>
<td>9.2%</td>
<td>2.3%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

*Subjects without hypertension, diabetes mellitus, and cardio-cerebrovascular lesions.

高血压、糖尿病等および心臓・脳血管病のない者。

60-69歳の年齢群において、心筋梗塞を有する11名のうち9名 (81.9%) には高血圧があった。心筋梗塞のない69名のうち34名 (49.3%) には高血圧が認められた (表4)。先に述べたように、高血圧は冠状動脈アテローム性硬化症を促進する効果がある。しかし、心筋梗塞を有する者と心筋梗塞を有しない者との間に認められた冠状動脈アテローム性硬化症の差を、高血圧のみで説明することはできない。というのは、高血圧者がいていない「正常な」群は、心筋梗塞がない群(高血圧の頻度が約50%)と比較して差が少ないからである。

Table 3: Coronary Atherosclerosis in Subjects with and without Myocardial Infarcts and 'Normal' Controls; Hiroshima, Age 60-69, Sexes Combined

表3 心筋梗塞のある者、ない者、および「正常な」対照における冠状動脈硬化症－広島、60-69歳、男女合計
TABLE 4  HYPERTENSION IN SUBJECTS WITH AND WITHOUT MYOCARDIAL INFARCTS - HIROSHIMA, AGE 60-69, SEXES COMBINED

表4 心筋梗塞のある者および少ない者の高血圧症 - 広島, 60-69歳, 男女合計

<table>
<thead>
<tr>
<th>Category</th>
<th>Subjects</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>With myocardial infarcts</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>'Normal'</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

Data for serum cholesterol and diabetes mellitus were insufficient to characterize the groups with regard to these factors.

Table 5 compares cigarette smoking histories for Hiroshima males, aged 60-69, with and without myocardial infarcts. All seven males in this age group with myocardial infarcts were smokers. By Western standards, the use of cigarettes by these patients would at most be described as moderate. Because of few cases and the prudent smoking habits of those involved, no conclusions are warranted about the relationship of cigarette smoking to subsequent myocardial infarction in these study subjects. The findings, however, are consistent with the demonstrated accentuation of coronary atherosclerosis among cigarette smokers in this population (Table 2).

Table 5 SMOKING HABITS - HIROSHIMA, MALE, AGE 60-69

表5 喫煙習慣 - 広島, 60-69歳, 男

<table>
<thead>
<tr>
<th>Category</th>
<th>With Myocardial Infarcts</th>
<th>Without Myocardial Infarcts</th>
<th>'Normal'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 Subjects</td>
<td>39 Subjects</td>
<td>13 Subjects</td>
</tr>
<tr>
<td>Never smoked</td>
<td>0</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Smoker</td>
<td>5 cigs/day</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>10本/1日</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>(吸喫きたばこ)</td>
<td>20</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
In view of the demonstrated disparity between aortic and coronary atherosclerosis in this population (Figure 1), it seems appropriate to ascertain whether those with marked coronary atherosclerosis and myocardial infarction demonstrate an equivalent increase in aortic disease. Table 6 compares aortic atherosclerosis in the myocardial infarct and the two non-infarct groups. Aortic atherosclerosis, like coronary disease, is more severe in the subjects with myocardial infarcts, but the magnitude of increase is much less. The increase in aortic involvement is manifested almost entirely by an increment in complicated lesions. It is apparent that in the subjects with myocardial infarction the disparity between aortic and coronary artery atherosclerosis is much less than in those without infarcts. This suggests that the factor or factors responsible for the marked increase in coronary disease in these patients has had a somewhat selective effect on the coronary arteries. Interestingly, the potentiating effects of hypertension and elevated serum cholesterol demonstrated in Figures 5, 6, 8, and 9 tended to be greater in the aorta than the coronary arteries.

<table>
<thead>
<tr>
<th>% Surface Involved</th>
<th>With Myocardial Infarcts</th>
<th>Without Myocardial Infarcts</th>
<th>'Normal'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 Subjects</td>
<td>69 Subjects</td>
<td>25 Subjects</td>
</tr>
<tr>
<td>All lesions</td>
<td>75.7</td>
<td>55.7</td>
<td>54.5</td>
</tr>
<tr>
<td>Fatty streaks</td>
<td>5.5</td>
<td>7.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Fibrous plaques</td>
<td>36.7</td>
<td>35.5</td>
<td>35.7</td>
</tr>
<tr>
<td>Complicated lesions</td>
<td>33.5</td>
<td>12.3</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Cerebrovascular Disease: The study of vascular lesions of the brain is complicated by the inconsistent relationship to atherosclerosis of some of the entities included under the general term, cerebrovascular disease. For the purposes of this study, four general categories were considered: cerebral infarcts (related to atherosclerosis), cerebral infarcts (embolic), primary intracerebral hemorrhage, and ruptured saccular aneurysm. A diagnosis of infarct due to embolism was made when lesions characteristic of 'embolic' infarcts were found in subjects with an adequate source of emboli.

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Lesions in the above categories were found in 47 of the 111 Hiroshima cases (41.4%) in which brains were available for study. The large number of lesions reflects in part the numerous small old cerebral infarcts found, many of which were of little clinical significance. The distribution of the various lesions is tabulated in Table 7. There is considerable overlap between diagnostic groups, small infarcts being present in many subjects with other lesions. In four of the five cases with ruptured aneurysm, bleeding was mainly into the brain substance.

Death was attributed to cerebrovascular disease in 22 of the 111 subjects (19.9%). This includes all cases of intracerebral hemorrhage and ruptured aneurysm and seven cases with cerebral infarcts. In the latter group, the lesions were more often only contributory with the immediate cause of death being pneumonia.

Table 8 compares cerebral atherosclerosis for subjects with and without cerebrovascular lesions and the 'normal' controls. Because of few cases

Table 8 cerebrovascular lesions in subjects with and without cerebrovascular lesions, and 'normal' controls - Hiroshima

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Death was attributed to cerebrovascular disease in 22 of the 111 subjects (19.9%). This includes all cases of intracerebral hemorrhage and ruptured aneurysm and seven cases with cerebral infarcts. In the latter group, the lesions were more often only contributory with the immediate cause of death being pneumonia.

Table 8 compares cerebral atherosclerosis for subjects with and without cerebrovascular lesions and the 'normal' controls. Because of few cases

上記区分による病変が、検査できた広島例111のうち47例（41.4%）に発見された。病変の数が多いことは、小さく古い脳の変性が多かったためにもよろしいのである。このような古い脳の変性は臨床上ほとんど意義はなかった。病変の分布は、7表に示した。小さな脳血管、その他の血管を有する多くの者に存在して、診断区分間に相当な重複がある。破裂した動脈瘤を有する5例のうち4例において、主として脳内の出血があった。

111名中22名（19.9%）の死因は脳血管疾患であった。これには脳内出血および破裂した動脈瘤の全例および脳梗塞症7例が含まれる。後者においては、その病変は主として脳死因で、直接死因は脳炎であった。

表8に、脳血管変性がある者、ない者、および「正常な」対照者の脳動脈のアテローム性硬化症を比較した。
and the irregular age distribution, the results are expressed both as crude scores (mean of scores for each age group) and as age-adjusted scores based on the distribution of the non-lesion cases. The only difference between crude and age-adjusted scores appears in the aneurysm group where slightly younger patients predominated.

As expected, cerebral atherosclerosis in subjects with embolic infarcts is similar to that for the groups without lesions. Cerebral atherosclerosis, however, is considerably higher in all the other diagnostic categories compared with non-lesion groups. Atherosclerosis in subjects with primary cerebral hemorrhage was less severe than in those with infarcts and ruptured aneurysms. Except for embolic infarcts, the differences in cerebral atherosclerosis between subjects with and without lesions are significant (infarcts and ruptured aneurysms, \( P < 0.01 \); intracerebral hemorrhage, \( P < 0.05 \)).

$\frac{1}{2} \text{ 表9 脳血管病変のある対象者の高血圧 - 広島 }
\begin{align*}
\text{Lesion} & & \text{Hypertensive} & & \text{Normotensive} & & \text{Total} \\
& & \text{50 Subjects} & & \text{61 Subjects} & & \\
& & \text{Number} & \text{Rate} (%) & \text{Number} & \text{Rate} (%) & \\
\text{Cerebral infarcts, old and recent} & 20 & 40.0 & 12 & 19.6 & 32 \\
\text{脳の古い梗塞および最近の梗塞} & & & & & \\
\text{Intracerebral hemorrhage} & 10 & 20.0 & 0 & 0 & 10 \\
\text{脳内出血} & & & & & \\
\text{Ruptured aneurysm 破裂した動脈瘤} & 4 & 8.0 & 1 & 1.6 & 5 \\
\end{align*}$

The relationship between hypertension and cerebrovascular disease is well known. Results from this study have substantiated the potentiating effect of hypertension on cerebral atherosclerosis (Figure 7). Table 9 shows the relationship between hypertension and the individual cerebral lesions. Since embolic infarcts in this study were not related to the severity of atherosclerosis, they are not considered here. Of the 32 patients with atherosclerotic cerebral infarcts 20 were hypertensive. The rate of infarction among all hypertensives was 40% while among normotensive subjects it was only 19.6%, a difference which is statistically significant (\( P < 0.05 \)). As could be expected, intracerebral hemorrhage occurred only in hypertensive subjects, a statistically significant difference (\( P < 0.01 \)).

刷字が少なくその年齢分布が不規則なので、各年齢別の計測値の単純平均値、および「病変がない」群の年齢分布を基準とした年齢修正数値を示した。若年者が多かった動脈瘤群で年齢を訂正しない数値と年齢訂正数値の間 に差が認められた。

予想されたとおり、高血圧を有する者が起こる脳動脈のアテローム性硬化症は、病変のない群のそれに等しい。しかし、他の診断区分のいずれも病変がない群と比較して、脳動脈のアテローム性硬化症は、かなり高利率である。脳の原発性出血のある者のアテローム性動脈硬化症は、梗塞および破壊した動脈瘤を有する者よりも軽い。高血圧を除き、病変のある者とない者の間の脳動脈アテローム性硬化症の差は有意である（梗塞および破壊した動脈瘤 - \( P < 0.01 \); 脳内出血 - \( P < 0.05 \))。

高血圧と脳血管疾患との関係は周知の事実である。本調査でも、脳動脈のアテローム性硬化症に対する高血圧の影響が認められた（図7）。高血圧と脳病変との関係を表9に示した。本調査では、高血圧を有する者32名中20名は、高血圧症であった。高血圧者のうちの梗塞症の頻度は40%であったが、正常血圧者では、その頻度は19.6%にすぎず、統計的に有意差が認められる（\( P < 0.05 \)）。予想されたとおり、脳内出血は高血圧者にのみ起こり、統計的に有意差（\( P < 0.01 \)）がある。
Among all hypertensives in the study, the rate of intracerebral hemorrhage at autopsy was 20%, consistent with the reported high incidence of this disease in the Japanese. Four of the five subjects with ruptured aneurysm had hypertension. The rate of 8% among all hypertensives seems unusually high. However, it must be recalled that in four of the five cases bleeding had occurred directly into the brain. Had the vessels not been removed during dissection, these cases would probably have been considered primary intracerebral hemorrhage.

Analyses of serum cholesterol and smoking data revealed no consistent or significant differences between the various groups. In the case of cholesterol results were available for only a few of the subjects with cerebrovascular lesions.

<table>
<thead>
<tr>
<th>Category</th>
<th>Intact Aneurysm</th>
<th>Ruptured Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td>63.1</td>
<td>53.8</td>
</tr>
<tr>
<td>平均年齢</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral atherosclerosis (Crude Score-Baker)</td>
<td>40.4</td>
<td>45.8</td>
</tr>
<tr>
<td>脳動脈のアテローム性硬化症（粗評点- Baker 法）</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Subjects with hypertension</td>
<td>42.8 (3)</td>
<td>80.0 (4)</td>
</tr>
<tr>
<td>高血圧のある対象者%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cerebral Aneurysms Twenty-four saccular aneurysms were found in 12 of the 111 Hiroshima subjects (10.8%). Particularly interesting was the finding of multiple aneurysms in 9 of these 12 cases (75%). Ruptured aneurysms were present in 5 of these 12 cases. The mean age of the seven subjects with intact aneurysms was 63.1 years and for the five with ruptured lesions was 53.8 years. The high frequency of hypertension and rather severe degree of atherosclerosis in patients with ruptured aneurysm (Tables 8, 9) suggest a possible role of these factors in the rupture of the lesions. Table 10 compares these factors in the subjects with ruptured and intact saccular aneurysms. Because of the small number of cases in each group and the differences in age distribution, age-adjusted scores could not be calculated. The subjects with ruptured aneurysm had slightly more severe cerebral atherosclerosis than did their counterparts with intact lesions. Since atherosclerosis increases with age,
this difference would have been much greater had age-adjusted scores been compared. Hypertension was far more frequent in the patients with ruptured aneurysm. Although the small number of cases prevents any definite conclusions, it appears that both hypertension and an increased severity of cerebral atherosclerosis may predispose to the rupture of intracranial aneurysms.

**DISCUSSION**

The study group being limited to subjects aged 40-69 years precludes adequate analysis of the natural history of atherosclerosis in this population. The observations on atherosclerosis reported here, however, are similar to other studies on Japanese populations using comparable techniques. The expected increment with age of aortic, coronary, and cerebral atherosclerosis is documented. A consistent or significant sex difference is not apparent. Since the grading method used for cerebral arteries does not consider the individual lesions, only the aorta and coronary arteries can be directly compared.

Fatty streaks, except in the aorta of the female, comprise a small and rather uniform proportion of the total lesions (Figures 2, 3). Other studies have demonstrated a decrease in the proportion of fatty streaks after the first several decades and the subsequent appearance and increase in the more advanced lesions. By initiating the study at age 40, the transition from the earliest to the more advanced lesions has not been observed except for the aorta of the female. Fibrous plaques are the principal lesions at all ages studied (Figures 2, 3). The extent of the lesions reaches a plateau at age 50-60 concomitant with an increase in complicated lesions. This pattern of change in the proportion of different lesions supports the concept of the sequential development of atherosclerosis suggested by Holman et al.

The augmenting effects on atherosclerosis of hypertension and elevated serum cholesterol are confirmed in this study (Figures 5-10). The patterns of increase in vascular disease are similar for both factors.

Ample clinical and epidemiological data are available to substantiate the increased risk of ischemic heart disease in subjects with hypertension and elevated serum cholesterol. The results for both hypertension and serum cholesterol strongly suggest that the increased risk is related to an actual increase in the severity of coronary atherosclerosis (Figures 5, 6, 8, 9). An equivalent

考察

調査群の年齢を40-69歳に制限したので、この群におけるアテローム性動脈硬化症の自然史（本論）について十分な解析を行うことができなかった。しかし、ここに報告したアテローム性動脈硬化症の観察結果は、同じような方法を用いて行われた日本人集団を対象にした他の調査に類似している。本調査で、予想どおり動脈硬化、冠状動脈および動脈硬化のアテローム性動脈硬化症の年齢ともに増加することを認めた。男女間に一貫した有意な差異はなかった。動脈硬化の重症度を定める計測法は、個々の変異を対象としないので、動脈硬化と冠状動脈のみを直接比較することができた。

女の動脈硬化を除き、全病変のうち脂質変化、最小ないし一定の割合を占める（図2, 3）。他の群では、40-50歳を越える脂質変化の割合が一時減少し、その後はさらに進行した変化が増加している。4, 10, 13, 22 年齢40歳で本調査を開始したので、女の大動脈を除き、最も初期の変異から、進行した変異に移行する過程を観察することはできなかった。継維性変化は、調査した全年齢における主な変異である（図2, 3）。変異の程度は、混合型の増加に伴って年齢50-60歳で顕著に達する。各種病変の割合の変化は、Holmanら22が示唆したアテローム性動脈硬化症の連続的発症の概念を支持する。

本調査において、アテローム性動脈硬化の悪化に対する高血圧および血清コレステロール値の上昇の影響が認められた（図5-10）。両因子による血管のアテローム性硬化の進行状態は同じである。

高血圧症および血清コレステロール値の高い者で、虚血性心臓疾患に罹患する危険性が高いということが臨床的および疫学的に知られている。21 高血圧症と血清コレステロール値に関する調査結果は、その危険性の増加が冠状動脈のアテローム性硬化症の重症度の増加と関係していることを強く示唆している（図5, 6, 8, 9）。同じ
increase is apparent also for the aorta. The relationships between the risk factors and atherosclerosis, however, are not simple. When, for example, subjects with myocardial infarcts are eliminated from the comparison groups (Tables 3, 4), no difference is observed in coronary atherosclerosis in the remaining groups even though they differ markedly in the rate of hypertension (49.3% vs 0%). These observations suggest that multiple risk factors may be operating in combination and that other factors, possibly genetic, may be important in subjects who develop severe coronary atherosclerosis and myocardial infarction.

Recent data have suggested an association between cigarette smoking and coronary heart disease. The recent report on Smoking and Health by the Surgeon General’s Advisory Committee has summarized mortality data from several of the major prospective studies. Data from the present study for males aged 60-69 show a statistically significant difference in coronary and aortic atherosclerosis between smokers and nonsmokers (Table 2).

Insufficient cases preclude an analysis of the combined risks of hypertension, elevated serum cholesterol, and cigarette smoking in this population.

The recognized relationship between hypertension and cerebrovascular disease is also supported in this study. The association is reflected both as an actual increase in cerebral atherosclerosis among hypertensives (Figure 7) and in the statistically significant greater frequency of cerebrovascular lesions in hypertensives than in normotensives (Table 9).

The disparity between aortic and coronary atherosclerosis in the Japanese was initially observed by Gore et al.10 The present study confirms the disproportionately severe degree of aortic atherosclerosis in a population with mild coronary disease (Figure 1). The pattern of atherosclerosis reported among Jamaicans resembles closely that of the Japanese.10 The disparity, however, does not depend merely on a low level of coronary atherosclerosis. Studies in India, for example, where coronary disease is very slight, have demonstrated a correspondingly low degree of aortic atherosclerosis.10,25,26

The aortic-coronary difference still persists even when the augmenting effects of factors such as hypertension, elevated serum cholesterol, and cigarette smoking are present. In each instance, the relative disparity is maintained despite an increment in severity of atherosclerosis.

よう的な増加が大動脈についてもみられた。しかし、これらの因子とアテローム性動脈硬化症との関係は単純なものではない。たとえば、比較的高血圧を有する群を除いた他の2群間では高血圧の頻度に著しい差があるが（49.3% vs 0%）。冠状動脈のアテローム性硬化症の差はない（表3, 4）。これらの観察から多種の危険因子が組み合わさって作用しているかもしれない。また、他の因子、たとえば遺伝学的因子が冠状動脈のアテローム性硬化症および心筋梗塞が発症した者に重要な意義をもつかもしれない。

最近の研究は、ときにこの喫煙と冠状動脈疾患との関連性があることを示唆している。米国公衆衛生局医務長官の諮問委員会が作成した最新の報告、喫煙と健康は、主要なプロスペクティブ調査から得られた死亡率の資料を要約している。24 本調査の60-69歳の男の喫煙者と非喫煙者との間に、冠状動脈のアテローム性硬化症と大動脈のアテローム性硬化症について統計的に有意差が認められた（表2）。

この群においては例数が少ないので、高血圧、血清コレステロール値の上昇および喫煙はこの喫煙者をもとに考慮した解析をすることができなかった。

高血圧と脳血管疾患との関係はすでに認められているが、本調査においても、高血圧者における脳動脈のアテローム性硬化症の増加（図7）、および、正常血圧者に比べて高血圧者に脳血管病変の頻度が統計的に有意に高かった（表9）。

日本人における大動脈のアテローム性硬化症と冠状動脈のアテローム性硬化症との相違は、ゴレらによって初めて観察された。28 本調査では、程度の冠状動脈疾患を有する者に意外に重症の大動脈のアテローム性硬化症を認めた（図1）。ジャマイカ人のアテローム性動脈硬化症は、日本人のそれに類似している。29 しかし、この相違は単純に冠状動脈のアテローム性硬化症が低いことのみによるものではない。冠状動脈疾患がきわめて軽度であるインドでは、大動脈のアテローム性硬化症も同様に軽度である。20,25,26

高血圧症、血清コレステロール値の上昇および喫煙はこの喫煙者のような関連因子の影響がある場合でさえも、大動脈のアテローム性硬化症と冠状動脈のアテローム性硬化症との差は依然存在する。また、その場合において、アテローム性動脈硬化症の重症度の増加にもかかわらず相対的な相違が存在する。
In subjects with myocardial infarcts the severity of coronary and aortic atherosclerosis is very similar (Tables 3, 6). In these cases the pattern more closely resembles that observed in the United States. Again, it is attractive to invoke the possibility of constitutional and combined risk factors to explain the differences between the subjects with and without myocardial infarcts.

Because of the age limits in this study, it is difficult to compare frequency distribution of the different tissue lesions with other published data. Myocardial infarcts were found in 12 cases (10.3%) and were the cause of death in 4 (3.4%). The rate for myocardial infarcts at autopsy in metropolitan areas in Japan has recently been estimated to be about 10%. In a recent autopsy series from Tokyo, death was attributed to myocardial infarction in 6 of 232 cases (3.4%).

All cases in the present study with myocardial infarcts had marked coronary atherosclerosis and stenosis. Of interest is the correlation of surface involvement and stenosis (+0.85). This finding confirms the validity of surface area grading in the assessment of coronary atherosclerosis. The correlation between the two appraisal techniques confirms the findings of Strong and McGill in supporting the hypothesis that coronary atherosclerosis is the most significant factor in determining the risk of ischemic heart disease in a population.

Cerebrovascular lesions were present in 46 cases (41.4%) and were responsible for death in 22 (19.9%). According to the Vital Statistics of Japan in 1962, cerebrovascular disease accounted for about 24% of the deaths in Japan; this high death rate from cerebrovascular disease is generally ascribed to the high frequency of cerebral hemorrhage. Based on mortality rates the ratio of cerebral hemorrhage to cerebral thrombosis has been given as 12.4:1.

In this autopsy series, cerebral infarcts (cerebral thrombosis) are the commonest cerebrovascular lesions (Table 7). When lesions responsible for death are considered separately, there are 10 cases of intracerebral hemorrhage, 7 cases of cerebral infarction and 5 cases of ruptured aneurysm. If the 4 cases in which aneurysms ruptured directly into the brain as cerebral hemorrhage are included the ratio of cerebral hemorrhage to cerebral infarct is 2.0:1. This relationship is difficult to interpret since the age group is restricted (40-69). In the experience of the ABCC Department of Pathology, however, the proportion of cerebral infarcts increases with age. Thus, if all ages were considered, a further reduction in this ratio could be

心筋梗塞の有者において、冠状動脈のアテレーム性硬化症および大動脈のアテレーム性硬化症の重症度は非常によく似ている（表3, 6）。これらの症例における傾向は、米国とそれをよく似ている。心筋梗塞の有者との差を説明するために、体質的因子および複合因子の作用を考慮することも必要であろう。

本調査に年齢限制を設けたので、各病変の頻度を他の発表資料と比較することは困難である。心筋梗塞が12例（10.3%）に認められ、これが死因であった者は、4例（3.4%）であった。日本の主要都市では、剖検で認めた心筋梗塞の頻度は、最近約10%と推定されている。東京における最近の剖検例では、222例中8例（3.4%）の死因が心筋梗塞であった。

脳血管病変が46例（41.4%）に認められ、22例（19.9%）の死因であった。1962年日本人死亡統計によれば、脳血管病変が日本の死亡の約24%を占めていた。脳血管病変による死因は、一般に脳出血の高頻度によるものといわれる。死亡統計によれば、脳出血対脳血管病変の比率は12.4:1である。

本剖検例では、脳血管病変のうち、脳の梗塞（脳血栓症）が最も多い（表7）。死因となった病変を別々に取り上げれば、脳内出血10例、脳の梗塞7例、および、破裂した動脈瘤5例である。脳内で直接破裂した動脈瘤4例を脳出血として扱った場合、脳出血対脳の梗塞の比率は2.0:1である。この関係は、年齢群（40-69歳）に制限を加えたので、解釈することは困難である。しかし、ABCC病理部の資料では、脳梗塞の割合は、年齢とともに増加する。したがって、全年齢を考慮すれば、この比率はさ
expected. Recent studies from ABCC, and by Katsuki and Hirota in a defined population cast further doubt on the alleged high frequency of cerebral hemorrhage in Japan.

The data here support the expected relationship between cerebral atherosclerosis and cerebrovascular lesions (Table 8). This association is statistically significant when compared with subjects without brain lesions. The degree of atherosclerosis is greatest in subjects with cerebral infarcts and ruptured aneurysm. The acknowledged association of hypertension and cerebrovascular lesions is also confirmed. The rates of occurrence of cerebral infarction and intracerebral hemorrhage among the hypertensive subjects are significantly higher than those in normotensive subjects (Table 9).

Experience with intracranial aneurysms raises several interesting points. Although racial differences have not generally been considered an important factor in the occurrence of saccular intracranial aneurysms,31 many Japanese pathologists consider these lesions quite rare. Both the prevalence of aneurysm (10.8%) and the occurrence of multiple lesions in 75% of cases in the present study are higher than generally reported.31,32 In four of the five cases of ruptured aneurysm, a diagnosis of primary intracerebral hemorrhage may have been made had the vessels not been removed during dissection. If the prevalence of aneurysm is actually higher in Japan than elsewhere, its possible role in the pathogenesis of cerebral hemorrhage is of interest especially in view of the large proportion of cases with multiple lesions. However, until carefully controlled studies are made on different populations, it must be assumed that the prevalence of cerebral aneurysm at autopsy is largely related to the interest and care of the examiner. Data presented here (Table 10) suggest that hypertension and advanced cerebral atherosclerosis may have a role in the rupture of saccular aneurysms.

Although this study is limited in that it represents a relatively short experience, it has been found of great value to relate clinical information, often obtained long before the terminal illness, with quantitative pathological findings. Autopsy series or clinical studies alone have limitations which are often related to the unrepresentative nature of the sample, whereas ABCC has a defined population, unselected for disease, and continuously surveyed for instances of death. The ABCC pathology contactors routinely seek permission for post-mortem examination for all deaths. More important is the gift of cooperation during and after life of the citizens of Hiroshima and Nagasaki.

らに減少するであろう。固定集団を対象にした最近のABCC調査、藤木および広田30による調査は、日本におい
て脳出血の高頻度にさらに疑問を投じた。

予想のとおり脳動脈のアテローム性硬化症と脳の血管病変との間に関係があることが明らかになった（表8）。こ
の関連性は、脳病変のない者の比較において、統計的
に有意である。アテローム性動脈硬化症は、脳の梗塞お
よび破裂した動脈瘤を有する者において最も重い、髙血
圧症と脳血管病変との間に一般に認められている関連性
も確認された。高血圧者における脳梗塞と脳出血の発
生率は、正常血圧者のそれよりも有意に高い（表9）。

頭蓋内動脈瘤について行なった観察は、いくつかの興味ある点を提起した。人種の差は、小脳性頭蓋内動脈瘤の
発生に重要な因子とは一概に考えられていないが31、日本
の多くの病理学者は、これらの変化はなおはまだである
という。本調査において、動脈瘤の有病率（10.8%）お
よび75%の例に多発性病変が発生したことは、従来報告
されているものよりも高い31,32。破裂した動脈瘤5例の
うち4例では、剖検において脳血管を切断しなかったか
ら、原発性脳内出血との診断が下されていたかもしれない。
もし日本の動脈瘤の有病率が実際に高いならば、脳
出血の発生には関与されるかと思われる動脈瘤の役割は興
味深い問題である。特に多発性動脈瘤をもつ例が多いの
で、興味深い、異った集団を対象に、注意深く管理し
た調査が実施されるまでは、動脈瘤の有病率は、主に
として研究者の関心に注意によって左右されるものとい
ざるを得ない。ここに示した資料（表10）では、高血圧症
および重症性脳動脈のアテローム性硬化症が、小脳性頭
蓋瘤の破裂に役割をもつかもしれないことを思わせる。

本調査は、比較的短い期間にわたるもので、制限されて
はいるが、死因となった疾患の発生よりはるか前に入手
された臨床資料と数冊的な病理学的所見との関係をみると
上に非常に価値があった。剖検調査または臨床調査を単
独に行なった場合、対象標本が代表的でないので制限が
あるが、ABCCでは、疾患によって選択されていない固
定集団を対象にして、死因を絶えず探求している。その
対象に死亡があれば、ABCの病理連絡員は、剖検の承
諾を求めることになっている。さらに重要なことは、ABCC
は、広島・長崎市の市民から存命中も死後も協力を受
けていることである。
At present, studies in vascular disease continue in cooperation with the Honolulu Heart Program being conducted by the USNaH. By comparable methodology it is sought to identify the pattern and to quantitate the increment in atherosclerosis occurring in Japanese migrating or born outside Japan.

SUMMARY

During the period of approximately 1 year, 132 male and female subjects, aged 40-69, were examined postmortem. Systematic grading of aorta, coronary, and cerebral arteries was performed and results are reported. The subjects were members of a defined population and were representative for age and sex of all persons dying during the period of study.

In general, atherosclerosis increased in severity with age and correlated positively with antecedent hypertension and cholesterol levels exceeding 200 mg/100 ml. Similarly, the proportion of fibrous plaques and complicated lesions were related to those factors.

The relative sparing of the coronary arteries in the Japanese, manifested by consistently greater involvement of the aorta compared to the coronary arteries, has been confirmed in this study.

Myocardial infarcts were demonstrated in 10.3% of the cases and were the cause of death in 3.4% of the subjects. All infarcts were associated with marked coronary atherosclerosis.

Cerebrovascular lesions were very common, occurring in 41.4% of the subjects and causing death in 19.9%. Intracerebral hemorrhage was a common cause of death in the age group studied, occurring in 10 of 111 subjects (9.1%). Cerebral hemorrhage, however, did not occur as frequently in relation to cerebral infarction as often as reported in mortality data for Japan. Cerebral aneurysms, often multiple, were unusually common in the study sample.

The value of combined clinical and pathologic findings in a defined population, unselected for disease and continuously surveyed, is noted.
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