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AN AUTOPSY STUDY OF CEREBROVASCULAR DISEASE IN JAPANESE MEN WHO LIVED IN HIROSHIMA, JAPAN AND HONOLULU, HAWAII

広島および Honolulu に居住した日本人男子の脳血管疾患に関する剖検調査

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SUMMARY

Evidence of cerebrovascular disease at autopsy was compared in two groups of men, 186 long time residents of Hiroshima, Japan and 253 men of Japanese ancestry long resident in Honolulu, Hawaii. They were from 45 to 71 years of age at death.

Atherosclerosis of the circle of Willis and its major branches, sclerosis of the intraparenchymal arteries and the frequency of cerebral hemorrhage and cerebral infarct were compared in the two populations. The Honolulu subjects had significantly more atherosclerosis of the circle of Willis, but less intraparenchymal artery sclerosis and less cerebral infarction. Cerebral hemorrhage was equally frequent in the two cities. It was concluded that cerebral infarction is more frequent in Japanese men in Hiroshima than Honolulu, and that men of Japanese ancestry in Honolulu are spared an appreciable risk of cerebral infarction through decreased frequency of intraparenchymal arterial sclerosis despite higher levels of atherosclerosis of large intracranial arteries.

INTRODUCTION

It is generally reported that the mortality rate for cerebrovascular disease in Japan based on vital statistics is among the highest in the world[1-4] but that Americans of Japanese ancestry

要 約

広島に長期間居住していた者186人と Hawaii の日系人で長期間 Honolulu に居住していた者253人からなる二つの男子群を対象に，剖検時に認められた脳血管疾患の比較を行った．死亡時年齢は45—71歳であった．

この2集団について，Willis 環およびその主要分枝のアテローム性硬化，脳実質内動脈の硬化，ならびに脳出血および脳梗塞の頻度の比較を行った．Honolulu の対象群では，Willis 環のアテローム性硬化が有意に多かったが，脳実質内動脈硬化および脳梗塞は少なかった．脳出血の頻度は両市同程度であった．結局，脳梗塞は広島の男子の方が Honolulu の日系男子よりも多く，また Honolulu 集団は，頭蓋内大動脈のアテローム性硬化の率が高いにもかかわらず，脳実質内動脈硬化の頻度が低いために，脳梗塞の危険がかなり少ないとの結論に達した．

緒 言

人口動態統計によると日本人の脳血管疾患による死亡率は世界最高の部類に属し，[1-4] 米国に長期間居住している日系米人の年齢別死亡率は，それよりも

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who have lived for a long time in the United States have lower age-specific mortality rates.[5,6] The reliability and comparability of cerebrovascular disease rates by death certificate ascertainment of cause of death have been questioned[7-9] and there is suspicion that much of the difference may be the result of different "styles" of assigning the cause of death.

Since 1965, there has been a collaborative effort in the NI-HON-SAN (Nippon, Honolulu, San Francisco) project[10] to study cardiovascular and cerebrovascular diseases in Japanese men living in Japan, Hawaii, and California, using uniform criteria for diagnoses, and comparable clinical laboratory and autopsy procedures. Completed reports have dealt with differences in diet and biochemical measurements, blood pressure, certification of cause of death, and the occurrence of myocardial lesions and atherosclerosis at autopsy.[11-15] This report describes the occurrence of atherosclerosis of the circle of Willis, sclerosis of the intraparenchymal arteries, cerebral hemorrhage, and cerebral infarction as observed in autopsies of Japanese men in Hiroshima, Japan and in Honolulu, Hawaii. Intra- and inter-city comparisons are made and the relation of these observations to each other is examined.

STUDY POPULATIONS

The NI-HON-SAN project is a longitudinal study of cardiovascular disease in fixed cohorts of Japanese males living in the three study areas. The composition of and methods for selecting the study populations have been described in detail elsewhere.[10] The men in this pathology study were born during the 20-year period 1900-19 with long verified residence in either Hiroshima or Honolulu. They died between 1965 and 1971 (age range 45-71). There were 186 Hiroshima and 253 Honolulu autopsies that met these criteria and form the basis for this report.

METHOD

In Hiroshima, all brains removed at autopsy were stored in 10% buffered formalin after routine examination by the prosector. During 1972 the brains were reexamined and the findings on gross examination were recorded (LT or YM). Blocks of tissue for microscopic examination were taken from 12 areas (left frontal, motor

低いことが一般に報告されている.[5,6] 死亡診断書をもとにした死因としての脳血管疾患死亡率の信頼性および比較妥当性については異論があり,[7-9] 両者間の差の多くは死因の設定方法の差に由来するのではないかとの疑いもある.

1965年以来, NI-HON-SAN (日本, Honolulu, San Francisco) 調査[10] に基づく共同研究によって, 統一された診断基準, 比較性のある臨床検査法および剖検手法を用いて, 日本, Hawaii, および California に居住する日本人男子の心臓血管疾患および脳血管疾患に関する調査が行われている. これまでに完了している報告書は, 食餌および生化学的特性の測定,[11,12] 血圧,[13] 死因の正確性,[14] ならびに剖検時に認められる心筋の病変およびアテローム性硬化[15] などにおける差について述べている. 本報告では, 広島および Hawaii に居住していた日本人男子の剖検時に認められた Willis 環のアテローム性硬化, 脳実質内動脈の硬化症, 脳出血, および脳梗塞について述べる. それぞれの市内および両市間の比較を行い, これらの観察結果相互間の関係を考察する.

調査集団

NI-HON-SAN 調査は, 三つの調査地域に居住する日本人男子の固定集団における心臓血管疾患の縦断的調査である. 調査集団の構成および抽出方法については別に詳述されている.[10] この病理学的調査の対象男子は, 1900—19年の20年間に生まれ, 広島または Honolulu のいずれかに長期間居住したことが確認されている者で, 1965—71年の間に死亡した者であった (年齢45—71歳). これらの基準をみたし, 本報告の基礎となった剖検例は, 広島186例, Honolulu 253例であった.

方　法

広島では, 剖検時に採取した脳はすべて, 執刀者が通常検査を行ったのち, 10%フォルマリン緩衝液中で保存された. 1972年には脳の再検査が行われ, 肉眼的検査所見が記録された (L. Thompson または三山吉夫). 12の部位 (すなわち, 左前頭皮質, 皮質

and visual cortex, left cingulate gyrus, hippocampus and cerebellar hemisphere, the optic chiasm, midbrain, pons, medulla oblongata, and two from the left basal ganglia) and additional sections were made of all grossly detected lesions not included in the 12 specified areas. Histologic sections taken by the original autopsy prosector were reviewed to be certain that entire lesions had not been removed previously.

In Honolulu a similar procedure was followed for examination of the brain and for taking tissue for histologic sections, but because storage space was not available, the examination and sectioning were accomplished within a few weeks after autopsy and additional tissue was not available for further study. In Honolulu one pathologist (TH) examined all cases after 1967.

The circle of Willis and its major branches from 184 of the 186 Hiroshima autopsies and from the last 88 of the 253 Honolulu autopsies were dissected from the brain, attached to plastic sheets and stored in 10% formalin.[16] In 1972, these cerebral arteries were sent to the University of Minnesota School of Medicine. Following their regular procedure,[17] Dr. Resch and his staff evaluated the degree of atherosclerosis (0 to 4 plus) at 22 separate sites. The results are usually reported as a total score (0 to 88), but for our purpose, the total was divided by the number of sites examined which provided a mean score (0 to 4.00) for each case.

Histologic sections were stained with hematoxylin and eosin (H & E). Special stains were infrequently required. Three pathologists independently examined all histologic sections collected in the two cities. Computer printouts listed all conflicting diagnoses by histologic section and subsequently, the three pathologists met together, first in Honolulu and then in Hiroshima, to reexamine the histologic sections for which diagnoses and interpretations were not in agreement. A consensus was reached in all cases and used for final analysis.

The following definitions and interpretations were employed: Using Russell's criteria,[18] massive cerebral hemorrhage was defined as an area of hemorrhage 3.0 cm or more in diameter in the cerebrum or cerebellum and 1.5 cm or more in diameter in the brain stem. Smaller hemorrhages were recorded without attempting to differentiate between small cerebral hemor-

運動領および皮質視覚領，左帯状回，海馬および小脳半球，視神経交叉，中脳，橋，延髄，ならびに左大脳基底核の２部位）から顕微鏡検査用の組織塊を採取し，さらに肉眼で探知された病変で12の特定部位に含まれていないもののすべてについても組織切片を作成した．剖検執刀者が採取した組織切片を検討し，以前に完全に除去された病変があったか否かを確かめた．

Honolulu でも同様の方法を用いて脳の検査および組織切片作製のための組織採取を行ったが，保管場所が確保できなかったため，検査および組織切片作製は剖検後２，３週間以内に完了し，再調査に利用できる組織はなかった．Honolulu では，1967年以後は１人の病理研究員（T. Hayashi）が全例の検査を行った．

広島の剖検186例中184例，Honolulu の剖検253例中最近の88例の脳から，Willis 環およびその主要枝を切除し，プラスチック板に取り付けて，10%のフォルマリン溶液中で保存した．[16] 1972年にこれらの脳動脈は Minnesota 大学医学部へ送られた．同大学の通常要領[17]に従って Resch 博士とその教室員が22か所の部位におけるアテローム性硬化の程度（０－４以上）を評価した．結果は通常総合評価値（０－88）として報告されたが，本調査ではその総合評価値を被検部位の数で割り，それによって各例の平均値（０－4.00）を求めた．

組織切片の染色にはヘマトキシリンおよびエオジン（H & E）を用いた．特別の染色はまれにしか必要でなかった．両市で収集された組織切片のすべてを，３人の病理研究員が別々に検査した．コンピューター・プリントアウトは，矛盾のある診断のすべてを組織切片別に列記したので，３人の病理研究員は，最初 Honolulu，次に広島で会合をもち，診断および解釈が一致していない組織切片について再検討を行った．すべての例について意見の一致が得られ，最終解析にはこれを用いた．

次のような定義と解釈が採択された．すなわち，Russell の基準[18]に従い，大量出血は，大脳または小脳における出血範囲が直径3.0㎝以上，脳幹で直径1.5㎝以上と定義した．小量出血の場合は，小量の脳出血と出血性梗塞との鑑別を試みることなく

rhage and hemorrhagic infarction. Cerebral infarctions were defined as circumscribed areas of parenchymal necrosis due to ischemia. Hemorrhagic and anemic infarcts were not recorded separately. Lacunae were included as representing tiny areas of infarction[19] but peripheral necroses of pseudolaminar type and focal recent necrosis less than 0.2 cm in diameter were excluded as possibly being nonischemic or agonal in origin. Infarcts were listed as recent or old, based on histologic findings. Sclerosis of intraparenchymal arteries was a histologic finding (Figure 1) and included fibrinoid and hyaline degeneration, splitting of the vessel wall with and without foam cells, intimal fibrosis, thrombosis, and microaneurysmal formation.[20-22]

Blood pressure records or other clinical evidence of hypertension were not available for most Hiroshima cases.[23] The heart weight was taken as a crude indicator of the absence or presence of hypertension.[24] Body weight at autopsy was available for 180 of the Hiroshima and 99 of the Honolulu subjects including 46 of the 88 Honolulu patients with circle of Willis evaluation.

Statistical analysis was directed at four main questions: 1) Was there bias in the selection of autopsies? 2) Did the autopsy observations suggest cerebrovascular disease was more frequent in Hiroshima than in Honolulu? 3) Were the specific lesions of cerebral hemorrhage, cerebral infarct, circle of Willis atherosclerosis and intraparenchymal artery sclerosis more frequent in either city? 4) What was the relation of the specific lesions to each other and were these relations the same in the two cities?

BIAS

The possibility of bias in the selection of autopsies was a major concern. In both cities, membership in the study cohort and not diagnosis was the basis for efforts to obtain autopsy consent. However, the samples did differ in some respects. Clinical records and a history of the terminal illness were generally available in Honolulu. Several hospitals and the medical examiner collaborated by sending the intact brain to one pathologist (TH) for examination. In Hiroshima, the subjects were all members of the Life Span Study sample, a fixed population of A-bomb survivors and non-exposed controls selected for the study of delayed radiation effects. A comparable medical

記録した．脳梗塞は，虚血により限局された実質性壊死と定義した．出血性および貧血性梗塞は，分けて記録しなかった．裂孔は小さい梗塞[19]として含めたが，偽層性の末梢性壊死および直径0.2cm未満の新鮮な限局性壊死は，本来非虚血性あるいは死戦期性と考えられるとして除外された．梗塞は組織学的所見に基づき，新鮮または陳旧性と記載された．実質内動脈の硬化は組織学的所見であり（図1），類線維素性および硝子変性，泡沫細胞の有無を伴う血管壁の分裂，動脈内膜線維症，血栓および微細動脈瘤形成を含めた．[20-22]

広島の症例の大多数については，血圧の記録や高血圧に関する他の臨床的所見は入手されていなかった．[23]高血圧症の有無の大まかな指標として心臓の重さを用いた．[24] 剖検時の体重は広島180人，Honolulu 99人の対象者から得られており，その中にはWillis環の評価の行われたHonoluluの対象者88例中46例が含まれていた．

統計学的解析では，主として次の四つの問題を目標とした．1）剖検の選択に偏りがあったか，2）剖検観察では，脳血管疾患はHonoluluよりも広島の方に多いことが示唆されたか，3）脳出血，脳梗塞，Willis環のアテローム性硬化および脳実質内動脈硬化症などの特定病変は，いずれかの市に多かったか，4）特定の病変相互間の関係はどうであったか，またこれらの関係は両市とも同じであったか．

偏り

剖検例の選択に当たって偏りがあったかどうかは重大な関心事であった．両市とも，剖検承諾を得る基本条件となったのは，調査集団の対象者であることであって，診断名ではなかった．しかし，対象集団にはいくつかの面で差異があった．Honoluluでは，おおむね最終疾患の臨床記録や病歴は入手されていた．いくつかの病院や監察医は病理研究員（TH）に脳を完全な状態で提供して調査に協力した．広島では，全対象者は寿命調査集団，すなわち，放射線の晩発性影響調査のために選択された原爆被爆者とその対照である非被爆者からなる固定集団に属するものであった．Honoluluと同様の監察医制度はなく，大部

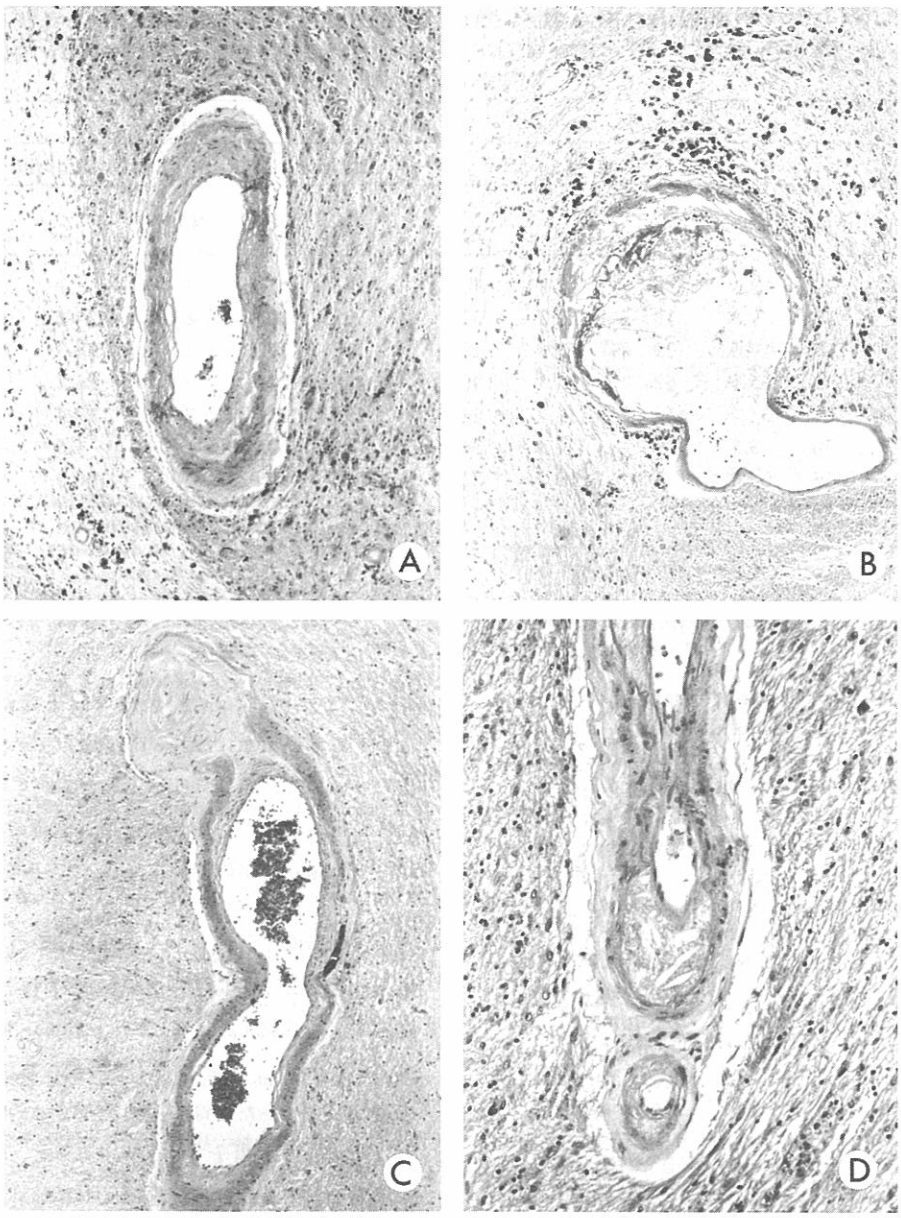

FIGURE 1. A: Sclerosed intraparenchymal artery at margin of a collapsed cerebral infarct (age 70, Hiroshima, ×175). B: Intraparenchymal artery sclerosis with microaneurysm formation & early perivascular hemorrhage (age 69, Honolulu, ×70). C: Intraparenchymal artery sclerosis with thrombosis (age 66, Honolulu, ×70). D: Intraparenchymal artery sclerosis with cholesterol clefts & foam cell in subintima (age 66, Honolulu, ×175).

図1. A：閉塞性脳梗塞の辺縁における脳実質内動脈硬化症；70歳，広島，175倍. B：微小動脈瘤形成および初期の血管周囲出血を伴う脳実質内動脈硬化症；69歳，Honolulu, 70倍. C：血栓症を伴う脳実質内動脈硬化症；66歳，Honolulu, 70倍. D：動脈内膜下のコレステロール裂および泡沫細胞を伴う脳実質内動脈硬化症；66歳，Honolulu, 175倍.

TABLE 1 DISTRIBUTION OF DEATHS, ALL STUDY AUTOPSIES, & PROPORTION OF DEATHS INCLUDED IN THE AUTOPSY STUDIES, BY AGE AT DEATH & CITY

表 1　死亡，調査対象全剖検例の分布，および剖検調査に含まれる死亡例の割合：死亡時年齢および都市別

Age at Death	Hiroshima					Honolulu				
	All Deaths		Study Autopsies			All Deaths		Study Autopsies		
	No.	%	No.	% of Autopsies	% of Deaths	No.	%	No.	% of Autopsies	% of Deaths
<50	22	2.6	9	4.8	40.9	53	5.7	13	5.1	24.5
50-54	83	9.8	19	10.2	22.9	192	20.8	61	24.1	31.8
55-59	149	17.6	29	15.6	19.5	205	22.2	59	23.3	28.8
60-64	298	35.1	62	33.3	20.8	256	27.7	72	28.5	28.1
65-69	267	31.4	58	31.2	21.7	198	21.4	44	17.4	22.2
70 +	30	3.5	9	4.8	30.0	21	2.3	4	1.6	19.0
Total	849	100.0	186	100.0	21.9	925	100.0	253	100.0	27.4

Test Results: Within each city; homogeneity of study autopsies vs other deaths as to age at death; not significant in both cities. Between cities; homogeneity of percent of deaths in the study autopsy sample; for each age group, not significant, for all ages together $P < 0.01$.

検定結果：　両市では，調査対象剖検例とその他の死亡例との死亡時年齢別の均質性については，有意差はみられなかった．両市間では，調査対象剖検集団における死亡の百分率の均質性は，各年齢群別には有意でないが，全年齢合計の場合は $P < 0.01$ である．

examiner system was not used and, in most cases, medical records and history of terminal illness were not available. Evaluation of circle of Willis atherosclerosis was performed for almost all of the Hiroshima autopsies, but for only the last 88 Honolulu autopsies.

The distribution of autopsies in each city was compared for age at death within the entire cohort of deaths in that city and between cities (Table 1). The autopsy rate was higher in Honolulu (27.4%) than in Hiroshima (21.9%). Approximately 70% of Hiroshima men in the entire cohort of deaths and in the autopsy cohort were over 60 years of age compared with 50% of the Honolulu men. With the exception of the small group below age 50 in Hiroshima, in neither city did the autopsy rate vary significantly by age.

In Honolulu, autopsies with and without an evaluation of the circle of Willis were compared and no significant difference in distribution was found for height, body weight, cerebral hemorrhage, cerebral infarct or intraparenchymal artery sclerosis. However, Honolulu subjects with circle of Willis evaluation, when compared with those without evaluation, were older ($P < 0.01$) and had lower heart weight ($0.01 < P < 0.05$), thus approaching the Hiroshima subjects in these categories.

分の者については，最終疾患の臨床記録や病歴も入手されていなかった．Willis 環のアテローム性硬化については，広島ではほとんどすべての剖検例の評価が行われたが，Honolulu では最近の88例のみについて実施された．

両市の剖検例について，全死亡集団中の死亡時年齢の分布を都市別にそして両市間で比較を行った（表１）．剖検率は，広島（21.9%）よりも Honolulu（27.4%）の方が高かった．死亡集団および剖検集団の全例中，60歳以上であったのは広島の男子では約70%であるが，Honolulu の男子では50%であった．広島の50歳未満の小集団を除けば，両市とも年齢別の剖検率に有意な差はなかった．

Honolulu では，Willis 環の所見の有無を基に剖検例の比較をしたが，両者間に身長，体重，脳出血，脳梗塞または脳実質内動脈硬化症の分布に有意な差は認められなかったが，Willis 環の所見がある者は同所見のない者より年長で（$P < 0.01$）心臓の重さも軽かった（$0.01 < P < 0.05$）．これらの所見は広島の対象者に認められたものに近似していた．

TABLE 2 THE FREQUENCY OF CEREBRAL HEMORRHAGE, CEREBRAL INFARCTION, & INTRAPARENCHYMAL ARTERY SCLEROSIS IN 186 HIROSHIMA & 253 HONOLULU AUTOPSIES

表 2　広島186例，Honolulu 253例の剖検例における脳出血，脳梗塞，および脳実質内動脈硬化症の頻度

Lesion	Hiroshima		Honolulu		Test (Age-adjusted)
	No.	%[1]	No.	%[1]	
Cerebral hemorrhage					
Recent massive	14	7.8	26	10.4	NS
Other	15	8.1	10	4.2	NS
Cerebral infarction					
Recent	14	6.4	15	7.0	NS
Old[2]	93	44.3	59	24.9	**
$<$0.2 cm	15	7.4	7	2.6	*
0.2-1.0 cm	45	20.9	32	13.6	*
$\geqslant$1.0 cm	33	16.0	20	8.7	*
Intraparenchymal artery sclerosis	105	52.4	78	32.8	**

[1] *Age-adjusted: Performed with the direct method of adjustment using the combined population as the standard population.*
年齢訂正は，合計集団を標準集団として用いる直接法によった．

[2] *Only the largest infarct present is recorded.* 最大の梗塞のみを記録した．

NS = not significant, 有意でない　*$0.01 < P < 0.05$,　** $P < 0.01$.

RESULTS

The distribution of autopsy subjects by height was almost identical for the two cities, but there was a highly significant difference in body and heart weight (Figure 2). The age-adjusted mean body weight was 45.0 kg for Hiroshima and 61.1 kg for Honolulu subjects, and the age-adjusted mean heart weight was 327.0 g for Hiroshima and 366.7 g for Honolulu subjects.

Table 2 gives the frequency of massive and other hemorrhage, recent and old infarction, and intraparenchymal artery sclerosis by city. Since the Hiroshima sample was appreciably older and the frequency of these lesions was age related, tests of significance were made on age-adjusted values. Cerebral hemorrhage and recent cerebral infarction were no more frequent in one city than in the other. However, old infarcts and intraparenchymal artery sclerosis were significantly more frequent ($P < 0.01$) in Hiroshima subjects.

Atherosclerosis of the circle of Willis increased in severity with age at death. Although the trends with age were very similar in the two cities, the age-adjusted mean atherosclerosis score was significantly greater at all ages for Honolulu

結　果

剖検対象者の身長別分布は両市ともほとんど同一であったが，体重および心臓の重さにはきわめて有意な差があった（図 2）．年齢訂正平均体重は，広島の対象者で45.0kg，Honolulu の対象者で61.1kgであり，年齢訂正平均心重量は，広島 327.0 g，Honolulu 366.7 gであった．

表 2 は，大量出血およびその他の出血，新鮮および陳旧性梗塞ならびに脳実質内動脈硬化症の頻度を都市別に示したものである．広島の集団はかなり高齢で，これらの病変の頻度は年齢と関連があったので，有意性検定は年齢訂正を行った値について行った．脳出血および新鮮な脳梗塞の頻度は，両市同様であった．しかし，陳旧性梗塞および脳実質内動脈硬化症は，広島の対象者の方が有意に多かった（$P < 0.01$）．

Willis 環のアテローム性硬化の程度は，死亡時年齢とともに増加した．年齢増加に伴う傾向は両市ともほとんど同様であったが，アテローム性硬化の年齢訂正平均値はいずれの年齢においても Honolulu 対象

FIGURE 2 DISTRIBUTION OF AUTOPSIES BY HEIGHT, BODY WEIGHT, & HEART WEIGHT – HIROSHIMA & HONOLULU

図 2　剖検の分布；身長，体重，および心重量別－広島および Honolulu

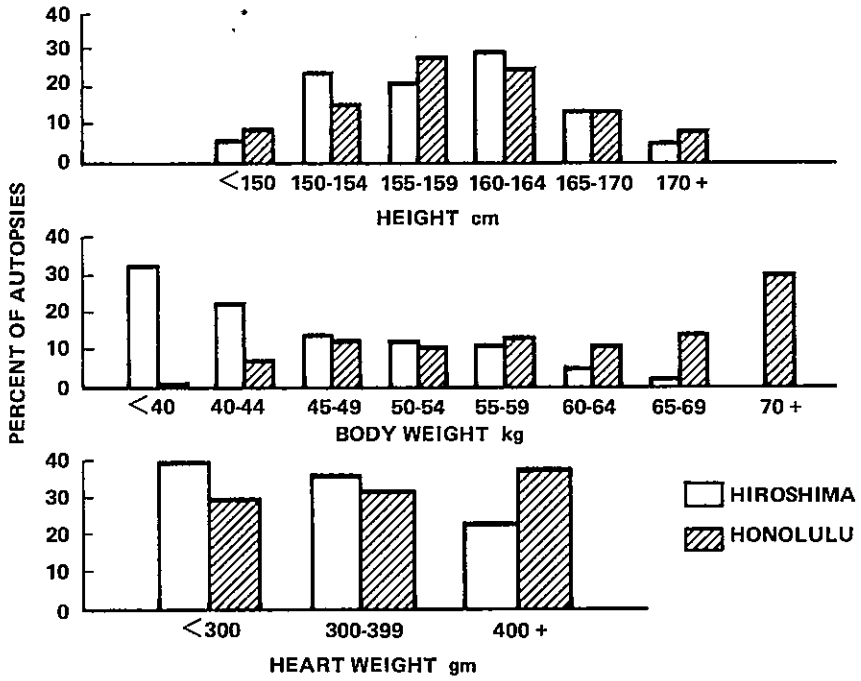

FIGURE 3 MEAN CIRCLE OF WILLIS ATHEROSCLEROSIS SCORE BY AGE AT DEATH & CITY WITH 95% CONFIDENCE INTERVALS

図 3　Willis 環のアテローム性硬化の平均値；死亡時年齢および都市別，95%信頼区間

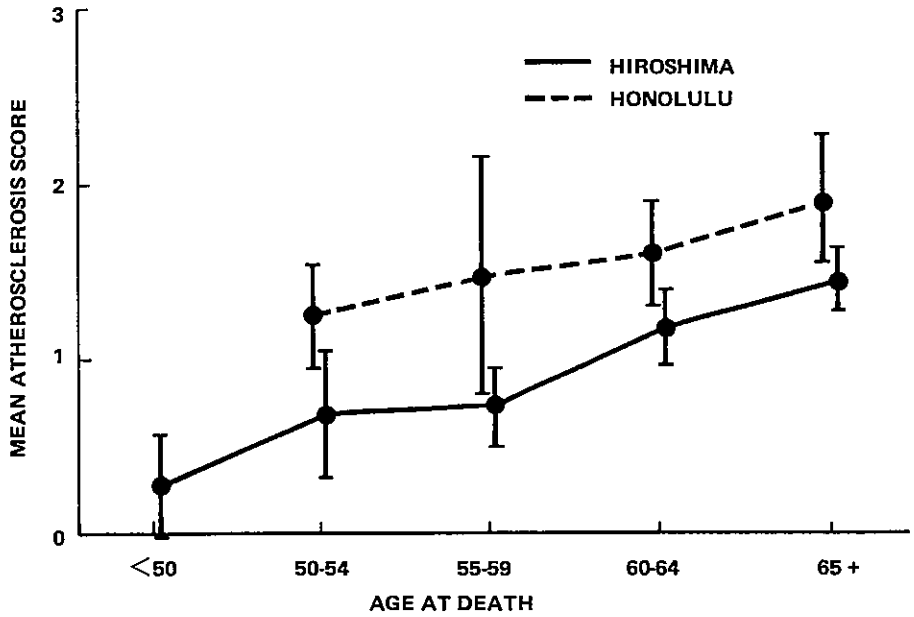

TABLE 3 CEREBRAL HEMORRHAGE, CEREBRAL INFARCTION, & INTRAPARENCHYMAL ARTERY SCLEROSIS BY AGE AT DEATH & CITY
表 3　脳出血，脳梗塞，および脳実質内動脈硬化症；死亡時年齢および都市別

Age at Death	Hiroshima			Honolulu		
	CH	Old CI	IAS	CH	Old CI	IAS
<50	11.1 %	33.3 %	33.3 %	7.7 %	–	–
50-54	21.1	15.8	31.6	9.8	16.4	19.7
55-59	10.3	24.1	41.3	15.3	20.3	28.9
60-64	19.4	58.1	61.3	18.1	26.4	37.5
65 +	13.4	65.7	68.6	14.6	37.5	45.8
Linear trend with age	NS	**	**	NS	**	**

CH: Cerebral hemorrhage, all types. 脳出血，全種類.
CI: Old cerebral infarcts. 陳旧性脳梗塞.
IAS: Intraparenchymal artery sclerosis. 脳実質内動脈硬化症.
*Test Results: NS=not significant, *0.01 <P <0.05, **P <0.01. Inter-city: homogeneity of the two city regression coefficients for each lesion, not significant.*
検定結果：NS =有意でない，　*0.01< P <0.05，　**P <0.01.　両市間：両市における各病変別の回帰係数の均質性については有意性がみられない.

TABLE 4 CIRCLE OF WILLIS ATHEROSCLEROSIS SCORE BY PRESENCE OF CEREBRAL HEMORRHAGE, CEREBRAL INFARCTION, & INTRAPARENCHYMAL ARTERY SCLEROSIS, 184 HIROSHIMA & 88 HONOLULU AUTOPSIES
表 4　広島184例，Honolulu 88例における Willis 環のアテローム性硬化の評価値；脳出血，脳梗塞および脳実質内動脈硬化症の有無別

Lesion	Circle of Willis Atherosclerosis Score						Inter-city Test
	Hiroshima			Honolulu			
	No.	Mean[1]	SE	No.	Mean[1]	SE	
Total autopsies	184	1.01	0.06	88	1.58	0.10	**
Cerebral hemorrhage[2]							
Absent	155	0.92	0.06	73	1.49	0.10	**
Present	29	1.42	0.16	15	2.09	0.35	NS
Test (absent or present)		**			NS		
Cerebral infarct (old)[3]							
Absent	92	0.63	0.05	65	1.41	0.11	**
<0.2 cm	15	1.36	0.17	2	1.35	–	NS
0.2–1.0 cm	45	1.03	0.06	13	2.21	0.20	**
⩾1.0 cm	32	1.97	0.17	8	2.64	0.15	**
Test (⩾ 1.0 cm vs absent)		**			**		
Intraparenchymal artery sclerosis							
Absent	80	0.70	0.06	57	1.46	0.12	**
Present	104	1.29	0.12	31	1.84	0.15	**
Test (absent vs present)		**			**		

[1] *Age-adjusted means by direct method of age-adjustment using the combined population in the two cities as the standard population.*
両市の合計集団を標準集団として用いる直接訂正法による年齢訂正平均値.
[2] *Presence of any cerebral hemorrhage.* 脳出血の有無.
[3] *Based on largest infarct recorded.* 記録されている最大の梗塞が基準.
*NS = not significant, **P <0.01.*
有意でない

TABLE 5 CEREBRAL HEMORRHAGE, CEREBRAL INFARCTION, INTRAPARENCHYMAL ARTERY SCLEROSIS, & MEAN CIRCLE OF WILLIS ATHEROSCLEROSIS SCORE BY HEART WEIGHT & BY CITY
表5　脳出血，脳梗塞，脳実質内動脈硬化症およびWillis環のアテローム性硬化の平均評価値；心重量および都市別

	Hiroshima					Honolulu				
	No.	CH %	CI %	IAS %	C/W	No.	CH %	CI %	IAS %	C/W
Heart weight										
<300 g	75	10.4	34.7*	47.1**	0.76**	75	3.1	17.5	17.3	1.25
300-399 g	67	16.0	47.1**	62.3	1.22	82	14.1	21.5	40.6	1.31
400+ g	44	22.0	51.6	42.0	1.01**	95	24.2	34.7	39.6	2.06
Number of autopsies	186	29	93	105	184	252	36	59	78	88
Linear trend with heart weight		**	**	NS	**		**	**	**	**

CH: Cerebral hemorrhage. 脳出血.
CI: Cerebral infarction. 脳梗塞.
IAS: Intraparenchymal artery sclerosis. 脳実質内動脈硬化症.
C/W score: Circle of Willis mean atherosclerosis score. Willis 環のアテローム性硬化平均評価値.
All data age-adjusted by direct method of age-adjustment using the combined population in the two cities as the standard population.
両市の合計集団を標準集団として用いる直接訂正法によって年齢訂正を行った全資料.
Significance Tests: Inter-city differences indicated by asterisks on the Hiroshima data; (no asterisk indicates no significant inter-city difference).
有意性検定：広島の資料では，両市間の差を星印で示した（星印のないものは両市間に有意な差のないことを示す）.
NS=not significant, *$0.01 < P < 0.05$, **$P < 0.01$.
有意でない.

subjects (Figure 3). Cerebral infarction and intraparenchymal artery sclerosis also increased in frequency with advancing age. Although the slopes for these changes also did not differ significantly in the two cities, both cerebral infarction and intraparenchymal artery sclerosis were more frequent in Hiroshima subjects and at all ages, except for cerebral infarcts in the 50-54 year group (Table 3).

In each city higher degrees of circle of Willis atherosclerosis were accompanied by cerebral hemorrhage, old cerebral infarcts, and intraparenchymal artery sclerosis than were found in the absence of these alterations (Table 4). However, even among individuals with each of these lesions, Honolulu subjects had higher circle of Willis atherosclerosis scores. There was also a relation between the size of the cerebral infarct and the severity of atherosclerosis; in Hiroshima subjects this was true for the larger infarcts (≥ 1.0 cm), and in Honolulu for infarcts greater than 0.2 cm.

Cerebral hemorrhage, cerebral infarction, and atherosclerosis of the circle of Willis were associated with increase in heart weight in each

者の方が有意に高かった（図3）．脳梗塞および脳実質内動脈硬化症の頻度も，年齢の上昇に伴って増加した．これらの変化の勾配にも両市間で有意な差はなかったが，脳梗塞および脳実質内動脈硬化症の頻度は，50—54歳群の脳梗塞を除けば，いずれの年齢においても広島の方が高かった（表3）．

両市とも，Willis環のアテローム性硬化の程度は，脳出血，陳旧性脳梗塞，および脳実質内動脈硬化症を伴う場合の方が伴わない場合よりも高かった（表4）．しかし，これらの病変をそれぞれ有する者においても，Honoluluの対象者におけるWillis環のアテローム性硬化の値の方が高かった．脳梗塞の範囲とアテローム性硬化の程度との間に関係が認められた．この関係は，広島対象者では広範囲の梗塞（≧1.0cm），Honoluluでは0.2cm以上の梗塞のある場合に認められた．

両市とも，脳出血，脳梗塞，およびWillis環のアテローム性硬化がある場合は，心臓の重さが増加

TABLE 6 INTRAPARENCHYMAL ARTERY SCLEROSIS & CEREBRAL INFARCTION BY MEAN CIRCLE OF WILLIS ATHEROSCLEROSIS SCORE

表 6　脳実質内動脈硬化症および脳梗塞：Willis 環のアテローム性硬化平均評価値別

Mean C/W Score	Hiroshima			Honolulu		
	No.	IAS	CI	No.	IAS	CI
0.00 – 0.99	87	37.8%	24.3%	23	28.3%	14.2%
1.00 – 1.99	66	68.9**	53.0**	38	14.6	14.4
⩾2.00	31	86.0*	98.3**	27	56.9	42.8
Total	184	52.4**	44.3**	88	33.1	24.9
Test: ⩽0.99 vs ⩾2.00		**	**		*	**

IAS: Intraparenchymal artery sclerosis. 脳実質内動脈硬化症.

CI: Cerebral infarction. 脳梗塞

All data age-adjusted by the direct method of age-adjustment using the combined population in the two cities as the standard population.

両市の合計集団を標準集団として用いる直接訂正法によって年齢訂正を行った全資料.

Significance tests: Inter-city differences are indicated by asterisks on Hiroshima data (no asterisk indicates no significant inter-city difference).

有意性検定：広島の資料では，両市間の差を星印で示した（星印のないものは両市間に有意な差のないことを示す）.

*NS=not significant, *0.01 <P<0.05, **P<0.01.*

有意でない.

TABLE 7 CEREBRAL HEMORRHAGE & CEREBRAL INFARCTION BY INTRAPARENCHYMAL ARTERY SCLEROSIS

表 7　脳出血および脳梗塞：脳実質内動脈硬化症の有無別

Intraparenchymal Artery Sclerosis	Hiroshima			Honolulu		
	No.	CH	CI	No.	CH	CI
Absent	81	8.9 %	24.9** %	175	7.3 %	11.2 %
Present	105	24.3	59.6*	78	32.7	48.9
Total	186	15.9	44.3**	253	14.6	24.9
Test: Absent vs present		*	**		*	**

CH: Cerebral hemorrhage. 脳出血

CI: Cerebral infarction. 脳梗塞

All data age-adjusted by the direct method of age-adjustment using the combined population in the two cities as the standard population.

両市の合計集団を標準集団として用いる直接訂正法によって年齢訂正を行った全資料.

Significance tests: Inter-city differences are indicated by asterisks on Hiroshima data (no asterisk indicates no significant inter-city difference).

有意性検定：広島の資料では，両市間の差を星印で示した（星印のないものは両市間に有意な差のないことを示す）.

**0.01 <P<0.05, **P<0.01.*

city (Table 5). The frequency of intraparenchymal artery sclerosis did not vary significantly with heart weight in Hiroshima subjects, but did in the Honolulu autopsies. There were inconsistent but significant inter-city differences in the degree of circle of Willis atherosclerosis in small and enlarged hearts (i.e., more severe in Honolulu). Cerebral infarction and intraparenchymal artery sclerosis were more frequent in Hiroshima at different heart weights.

していた（表 5）. 広島の対象者では，脳実質内動脈硬化症の頻度に，心臓の重さの増加に伴う有意な差は認められなかったが，Honolulu の剖検例では認められた. 小さい心臓および肥大した心臓では Willis 環のアテローム性硬化の程度に両市間に一貫性はないが有意な差が認められた（すなわち，Honolulu の方が重篤であった）. 心重量別では，脳梗塞および脳実質内動脈硬化症の頻度は広島の方が高かった.

In both cities, the frequency of intraparenchymal artery sclerosis and cerebral infarction increased significantly as the severity of atherosclerosis of the circle of Willis increased (Table 6) and in each case, the values were significantly greater in Hiroshima than in Honolulu subjects. In both cities cerebral hemorrhage and cerebral infarction increased significantly when intraparenchymal artery sclerosis was present (Table 7).

DISCUSSION

In this study, we avoided the problems associated with allocating death certificate and autopsy cause of death by recording only objective evidence of cerebrovascular disease; namely, extent of atherosclerosis of large extraparenchymal arteries (the circle of Willis and its major branches), sclerosis of intraparenchymal arteries, massive and other cerebral hemorrhages excluding those not due to cerebrovascular disease, and cerebral infarcts. Although not directly pertinent and not recorded in the data, we also noted the presence of massive subarachnoid hemorrhage (Hiroshima 1.6%, Honolulu 2%) and senile histologic changes (Hiroshima 17.7%, Honolulu 10.7%) and found no significant inter-city differences in the frequency of these changes.

Four questions were listed as objectives of this study. Was there a selection bias among the study cases? There were differences in the two cities which are more likely due to the characteristics of the two study populations than to bias in case selection. In Hiroshima, exposure to radiation at the time of the bomb was known to produce central nervous system changes in fetuses exposed in utero, but no evidence of other central nervous system effect has been demonstrated.[25,26] Consequently, the radiation experienced by some of the Hiroshima subjects can be disregarded.

In some important respects the autopsied subjects differed in the two cities, but there is internal evidence that these differences were true divergences in population characteristics rather than due to autopsy selection bias. The body height was remarkably similar in the two cities, but in Honolulu, body weight was significantly greater, age at death younger, and heart weight heavier. There was significantly more severe coronary heart disease in Honolulu and more cerebral infarction in Hiroshima subjects.

脳実質内動脈硬化症および脳梗塞の頻度は，両市ともWillis環のアテローム性硬化の増加とともに有意に増加し（表6），いずれの例においても，広島の対象者の方がHonoluluの対象者よりも有意に高い値を示した．両市とも脳実質内動脈硬化症が認められた場合は，脳出血および脳梗塞は有意に増加した（表7）．

考　察

今回の調査では，死亡診断書記載の死因と剖検時に認められた死因とを分けることに伴う各種の問題を回避し，脳血管疾患の客観的所見，すなわち，脳実質外大動脈（Willis環およびその主要枝）のアテローム性硬化の程度，脳実質内動脈の硬化，脳血管疾患によらない脳出血を除く大量脳出血および他の脳出血，ならびに脳梗塞を記録した．直接関係がないため資料として記録しなかったが，大量のクモ膜下出血（広島1.6%，Honolulu 2%），および老人性組織変化（広島17.7%，Honolulu 10.7%）を認めたが，これらの変化の頻度には両市間に有意な差は認められなかった．

本調査の目標として四つの問題を挙げた．調査対象例の選択に偏りがあったか．両市には，症例選択上の偏りというよりも二つの調査集団の性格によると思われる差があった．広島では，原爆時の放射線被曝は胎内被爆児の中枢神経系に変化をもたらすことが知られていたが，その他の中枢神経系の影響は認められていない．[25,26] したがって，広島対象者の一部が体験した放射線被曝は無視できる．

剖検を行った対象例には，若干の重要な点で両市間に差があったが，これらの差は剖検選択上の偏りによるものでなく集団の特性における本質的な差異によるものであったことを示す．身長は両市間で著しく酷似していたが，Honoluluでは広島より体重は有意に重く，死亡時年齢が若く，心臓は重い．また，Honoluluでは重度の冠動脈性心疾患が有意に多く，広島では脳梗塞が多かった．死因としての癌の頻度は

Cancer was an equally frequent cause of death in the two cities. It is concluded that the autopsy samples were representative of Hiroshima and Honolulu men of their age who died during the period of this study.

The second and third questions concerned the prevalence of objective evidence of cerebrovascular disease in the two autopsy cohorts. In age-adjusted comparisons, statistically significant inter-city differences were seen in the extent of atherosclerosis of the circle of Willis, the presence of intraparenchymal artery sclerosis and of cerebral infarcts, but not in the occurrence of cerebral hemorrhage. These inter-city differences were not only large but were also consistent when the samples were examined in a variety of ways. The scores for atherosclerosis of the circle of Willis were higher in Honolulu subjects when compared by age at death, heart weight, presence of old cerebral infarcts, and intraparenchymal artery sclerosis. In contrast, both cerebral infarcts and intraparenchymal artery sclerosis were more frequently observed in Hiroshima subjects. This dichotomy in the direction of change for atherosclerosis of the circle of Willis and intraparenchymal artery sclerosis was an outstanding feature in the comparison of the findings in the two cities.

The fourth question concerned the relation of the specific lesions to each other. Evidently these alterations are interrelated but, for reasons not apparent, it appears that Japanese migrants in Honolulu are spared an appreciable risk of cerebral infarction through decreased frequency of intraparenchymal artery sclerosis despite high levels of major cerebral vessel atherosclerosis. The data are also consistent with the hypothesis that in Japanese men in Hiroshima, intraparenchymal artery sclerosis plays at least as great a role in the pathogenesis of cerebral infarction as does atherosclerosis of the major cerebral vessels.

両市同等であった．剖検集団は，本調査の期間中に広島およびHonoluluで死亡したその他の同年齢男子を代表するものであるとの結論に達した．

第2および第3の問題は，両剖検集団における脳血管疾患の客観的所見の有病率に関するものであった．年齢訂正による比較では，Willis環のアテローム性硬化の程度，脳実質内動脈硬化症および脳梗塞の有無では，両市間に統計学的に有意な差が認められたが，脳出血の発生率にはそれが認められなかった．これらの両市間の差は単に大きかったばかりでなく，各種の方法でこの集団について検討を行った場合でも不変であった．死亡時年齢，心重量，陳旧性脳梗塞および脳実質内動脈硬化症の有無別に比較を行った場合は，Honoluluの対象者の方がWillis環のアテローム性硬化の率は高かった．それに対して，脳梗塞および脳実質内動脈硬化症は，いずれも広島対象者に多く認められた．Willis環のアテローム性硬化と，脳実質内動脈硬化症とが異なった変化を示すことは，両市の所見の比較で認められた顕著な特徴であった．

第4の問題は，特定の病変相互間の関係に関するものであった．これらの変化には相関関係があるようであるが，理由ははっきりしないながらも，Honoluluの日本人移住者は，主要脳血管のアテローム性硬化の値が高いにもかかわらず，脳実質内動脈硬化症の頻度が低いために脳梗塞の危険率がかなり低いようである．この資料からはまた，広島在住の日本人男子では，脳実質内動脈硬化症は脳梗塞の成因として，少なくとも大きな脳血管のアテローム性硬化と同等の役割を果たすという仮説とも一致している．

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