TECHNICAL REPORT
22-75
業 績 報 告 書

A MORPHOLOGIC STUDY OF CENTRAL NERVOUS SYSTEM AGING HIROSHIMA 1961-72

中枢神経系の加齢に関する形態学的調査 広島，1961－72年

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ATOMIC BOMB CASUALTY COMMISSION

国立予防衛生研究所－原爆傷害調査委員会

JAPANESE NATIONAL INSTITUTE OF HEALTH OF THE MINISTRY OF HEALTH AND WELFARE

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中枢神経系の加齢に関する形態学的調査 広島，1961－72年

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SUMMARY

The presence of small vessel arteriosclerosis, senile plaques, neurofibrillary tangles, granulovacuolar degeneration, and hypoglossal nucleus hyaline cytoplasmic inclusions was quantified in the brains of autopsied patients from three age groups: 90-99 years old, 70-79 years old, and 50-59 years old. Neurofibrillary tangles particularly in the hippocampus were the best indicator of chronologic aging but senile plaques and granulovacuolar degeneration were also age related. Small vessel sclerosis, cerebral infarction and hemorrhage and cause of death apparently had little or no effect on the development of these aging changes. Each type of aging change appeared to be independent of the others and to progress at different rates.

INTRODUCTION

Conventional wisdom associates aging and senility with cerebral deterioration which is expressed morphologically as so-called senile changes. These include cerebral atrophy, cerebral arteriosclerosis, various types of neuronal degeneration, senile plaques, and perhaps other changes.[1-5] These indicators of central nervous system aging are correlated with chronologic age which is the criterion available to all investigators. It is generally agreed that persons more than 90 years of age have outlived the normal life-span and may be

要 約

(1) 90－99歳，(2) 70－79歳，(3) 50－59歳の三つの年齢群中の剖検例の脳における小血管動脈硬化症，老人斑，神経原線維 tangle，顆粒空胞変性および舌下神経核細胞質内硝子様封入体を数量的に調べた．特に海馬における神経原線維 tangle は暦年齢の加齢を示す最良の指標であった．さらに，老人斑および顆粒空胞変性も年齢と関係があった．小血管硬化症，脳梗塞，脳出血，ならびに死因は，これらの加齢変化の発現にほとんどまたは全然影響を及ぼさないようである．いずれの型の加齢変化も他のものと無関係であり，それぞれ異なる速度で進行するようである．

緒 言

一般の知見では，加齢および老化は，形態学的にいわゆる老人性変化で代表される脳の劣化と関連があるとされている．これには，脳萎縮，脳動脈硬化症，各種のノイロン変性，老人斑，その他の変化[1-5]が含まれる．中枢神経系の加齢を示すこれらの指標を，研究者全員に利用できる基準である暦年齢に相関させた．90歳以上の人は，通常の寿命を全うした高齢者と考えられている．このような人の脳を調べれば年齢と関係のある形態的変化の信頼

considered to be aged. Study of their brains should provide a reliable index of age associated morphologic changes. A comparative study of the brains of persons who die at a younger age may provide information on frequency and rate of development of these degenerative changes, show the relation of one to another, and provide a basis for estimating accelerated aging.

A number of investigators have reported that aging is accelerated by exposure to ionizing radiation.[6-17] Much of the evidence has resulted from animal experimentation but the interpretation of these data has recently come under methodologic criticism.[18] Warren[19] and Seltzer and Sartwell[20] found that occupational exposure of physicians to ionizing radiation produced a nonspecific life shortening effect. Mortality from cancer, cardiovascular-renal disease, and all other causes combined was increased in the high exposure groups.

Studies conducted at ABCC on premature aging of exposed atomic bomb survivors using a variety of approaches have yielded either equivocal or negative results.[21-27] Matsuyama et al[1] examined brains from autopsied survivors and studied the accumulation of both senile plaques and neurofibrillary tangles in relation to chronologic age and radiation exposure. They found no evidence of a radiation effect but confirmed the accepted teaching that these alterations are indicators of advancing age.[2-4] Since that study a large number of autopsies have been performed on A-bomb survivors including a number who were younger at the time of the bomb (ATB). This is of some significance because one theory of accelerated aging holds that an individual exposed early in life would be more likely to show radiation effects at autopsy.[28] The larger number of autopsies now available includes many subjects who were 90 or more years old at the time of death as well as a larger pool of autopsies for selection of cases for comparison.

An investigation was undertaken to study brain changes in the elderly by comparing them with selected younger subjects. A second objective was to determine if evidence of accelerated aging due to radiation could be found in the brains of exposed survivors.

METHODS AND PROCEDURES

The Study Sample. The JNIH-ABCC Life Span Study (LSS) sample consists of approximately

できる指標が得られるはずである．若年齢で死亡した者の脳に関する比較調査で，これらの変性性変化の頻度および発現率についての資料が得られれば，相互の関係ならびに加齢促進を推定する基礎が得られるかもしれない．

幾人かの研究者は，電離放射線被曝によって加齢が促進されると報告している．[6-17] 所見の多くは動物実験に基づいて得られたものであるが，最近これらの資料の解釈にあたってその方法に批判が加えられている．[18] Warren[19] ならびに Seltzer および Sartwell[20] は，医師の職業的な電離放射線被曝が，非特異的な寿命短縮性効果をもたらしていることを認めた．高線量被曝群では，癌，心臓血管—腎疾患ならびにその他あらゆる死因を合計した場合の死亡率は増大した．

ABCC において各種の方法を用いて行われた原爆被爆者の早期加齢に関する調査では，不明確ないし否定的な結果が得られた．[21-27] 松山ら[1] は，被爆者の剖検脳を検査し，老人斑および神経原線維 tangle の数量と暦年齢および放射線被曝との関係を調べた．彼らは，放射線の影響を認めなかったが，これらの変化が加齢の指標であるという一般に認められている所見を確認した．[2-4] その調査以降，原爆時若年であった者を含む多くの被爆者について剖検が行われている．加齢促進に関する一説では，若年時に被爆した者では剖検時に放射線影響が認められる可能性が多いであろうと考えられているので，このことには意味がある．[28] 現在，資料が入手されている多くの剖検例の中には，死亡時90歳以上であった者も多く含まれており，また比較のため選択に供し得る多くの他の剖検例もある．

高齢者における脳の変化を調べるため，選択した若年者との比較調査を行った．第2の目的は，被爆者の脳に放射線による加齢促進の徴候が認められるかどうか調べることであった．

方法および要領

調査集団． 予研－ABCC 寿命調査集団は，原爆被爆者お

TABLE 1 PRINCIPAL AUTOPSY CAUSE OF DEATH BY AGE GROUP

表1　剖検で認められた主要死因：年齢群別

Autopsy Cause of Death	Age Group		
	90	70	50
Cerebrovascular Disease	23	18	4
Ischemic Heart Disease	9	7	1
Hypertensive and Valvular Heart Disease	3	6	1
Cancer	9	10	31
Pulmonary Disease	15	7	10
Other	13	24	25
Total	72	72	72

100,000 A-bomb survivors and nonexposed persons.[29] An active autopsy procurement program provides autopsies on deceased members of the sample, in part for surveillance of the ascribed causes of death. During the 12-year-period 1961-72, autopsies including examination of the brain were performed in Hiroshima on 72 nonagenarians. Two other groups of autopsies were selected from the autopsy files: the first, 20 (±2) years younger and the second, 40 (±3) years younger at the time of death than the nonagenarians to which they were matched by sex (21 males and 51 females in each group), year of death, estimated (T65) radiation dose,[29] and for the nonagenarians and septuagenarians as much as possible by the presence or absence of cerebral disease as the principal anatomic cause of death (Table 1). Each of the three age groups was further subdivided into four matching groups according to the estimated amount of radiation exposure ATB; 1) no radiation and not in Hiroshima ATB (17 subjects), 2) less than 1 rad (29 subjects), 3) 1-99 rad (22 subjects), and 4) 100 or more rad (4 subjects). All autopsies were performed at ABCC in Hiroshima.

The pathologic alterations examined in this study for correlation with aging were autopsy cause of death, small vessel sclerosis (SVS), neurofibrillary degeneration or "tangles" (NFD), senile plaques, granulovacuolar degeneration (GVD), hyaline cytoplasmic inclusions (HCI) in the hypoglossal nuclei, and congophilic deposits both in the neuropil and within arteriolar walls. NFD is a neuronal change which may be found anywhere in the brain. Poorly stained by hematoxylin, it is seen in silver preparations as densely impregnated coarse fibrillary material occupying varying amounts of the neuronal cytoplasm and extending into cell processes.[1-4] Senile plaques are radially-arranged argyrophilic

よびその対照者約10万人からなるものである.[29] 活発な剖検入手計画のもとに対象集団中の死亡例の剖検が行われており，その一環として死因の調査が実施されている. 1961－1972年の12年間に広島では，90歳代の者72例について脳の検査を含む剖検を行った．剖検例のファイルから別に二つの剖検集団を選択した．その第1群は死亡時年齢が90歳代の者よりも20±2歳若く，第2群は40±3歳若い者で，90歳代の者と性(各群とも男21例，女51例)，死亡年度，T65推定放射線量[29]を一致させ，また90歳代および70歳代の者については，脳疾患が主要な解剖学的死因であったか否かによって，できるだけ一致するようにした(表1)．さらに，三つの年齢群をそれぞれ，原爆時の推定被曝線量別に次の四つに細分した．1) 非被曝者，および原爆時広島にいなかった者(17例)，2) 1 rad未満の者(29例)，3) 1－99 rad の者(22例)，4) 100 rad以上の者(4例)．剖検はそれぞれ広島ABCCで行われたものであった．

加齢との相関を求める今回の調査で調べた病理学的な変化は，剖検で認められた死因，小血管硬化症，神経原線維変化または"tangle"，老人斑，顆粒空胞変性，舌下核における細胞質内硝子様封入体，ならびに神経網および細動脈壁の双方における好コンゴ性沈着であった．神経原線維変化は，脳内のどこにでも認められるノイロン変化である．ヘマトキシリンでは十分に染色されないが，銀剤を用いれば，濃密に浸透した粗い線維性物質でいろいろな量のノイロン細胞形質を占有し，細胞突起にまで及ぶのが認められる.[1-4] 老人斑は，放射状に分布した好銀性の原線維およびいろいろな大きさの細胞残屑の集ま

collections of fibrils and cellular debris of variable size which may or may not have an amorphous argyrophilic central core. The central core may take the congo red stain (congophilic senile plaque).[1-4] GVD involves the pyramidal cells of the hippocampus, and appears as intracytoplasmic vacuoles containing a single hematoxylinophilic granule smaller than half the diameter of the vacuole. Several of these granule-containing vacuoles are often seen in the same cell. HCI are found in the neurons of the hypoglossal nucleus. They are homogeneous, ground-glass-like cytoplasmic inclusions that are stained very little, if at all, by the routine hematoxylin-eosin stain.

りであって，無形体の好銀性中心核を有したり有さなかったりする．中心核はコンゴ赤で染色できることもある（好コンゴ性老人斑）.[1-4] 顆粒空胞変性は海馬のピラミッド細胞を冒し，また空胞の直径の半分以下である一つの好ヘマトキシリン顆粒を含む細胞質内空胞として認められる．しばしば同一細胞内に顆粒を有する空胞が数個認められる．細胞質内硝子様封入体は舌下核のノイロン中にある．これらは同一構造をもつすりガラス様の細胞質封入体で，通常のヘマトキシリン・エオジン染色によってほとんど染まらない．

The formalin fixed brains were sectioned at 1cm intervals in the plane of the coronal suture and examined for the presence of hemorrhages and infarcts. In each case note was made of the size and number of gross lesions in the following 12 areas; left and right frontal, parietal, temporal, and occipital lobes, basal ganglia and thalamus, and the cerebellum and the brain stem. The amount of tissue destroyed by hemorrhage or infarction was recorded for each region and side on a scale of 0 to 5 (zero = no lesion present; 1 = a single lesion less than $0.5cm^3$; 2 = multiple lesions each less than $0.5cm^3$; 3 = 0.5 to $0.9cm^3$; 4 = 1.0 to $2.9cm^3$; and 5 = $3cm^3$ or more). Small arteries were defined as the second order and subsequent branches of the major cerebral arteries and the presence of sclerosis was based on their appearance in histologic sections. Sclerosis of meningeal and of intraparenchymal vessels was recorded separately and included proliferative, hyaline, angionecrotic, congophilic, and atherosclerotic alterations. In this study angionecrosis was observed in only six tissue blocks. Atherosclerosis was frequently observed when the anterior choroidal artery was included with the hippocampus and when the anterior cerebral artery was included with the cingulate gyrus. Otherwise atherosclerosis was not present in these sections. The status and patency of the major cerebral arteries were not recorded.

ホルマリンで固定した脳を，冠状縫合面にそって1cm間隔で切裁し，出血および梗塞の有無を調べた．各例について，次の12の部位にみられる肉眼的病変の大きさおよび数を記入した．左右前頭葉，頭頂葉，側頭葉，および後頭葉，脳底神経節および視床部，ならびに小脳および脳幹．各部位および左右別に，出血または梗塞によって損傷された組織の量を0－5の度合で記録した（0＝病変なし；1＝0.5 cm^3 未満の病変一つ；2＝それぞれ0.5 cm^3 未満の病変多数；3＝0.5－0.9 cm^3；4＝1.0－2.9 cm^3；5＝3 cm^3 以上の場合）．小動脈とは主要脳動脈よりも小さい動脈およびその分枝と定義し，硬化症の有無は組織切片における所見を基に定めた．脳膜および実質内血管の硬化症は，別々に記録し，増殖性，硝子質性，血管壊死，好コンゴ性，およびアテローム性動脈硬化性の変化をそれに含めた．今回の調査では，血管壊死は，6個の組織塊にのみ認められた．前脈絡叢動脈を海馬と共にした場合，また前大脳動脈が帯状回と共に含められた場合は，アテローム性動脈硬化症がしばしば認められた．そうでない場合は，これらの切片には認められなかった．主要な脳動脈の状態および開存については記録しなかった．

Blocks of tissue were taken for histologic sections from nine areas; the left and right superior frontal gyrus, left and right cingulate gyrus at the level of the optic chiasm, the left and right hippocampus at the level of the lateral geniculate body, the left and right calcarine cortex, and the medulla at the level of the caudal end of the 4th ventricle. Interpretation of observations of the hippocampal area was complicated because the arterial supply of the hippocampus differs from that of the rest of the

次の九つの部位から組織塊を採取し，組織切片を作成した．左右上前頭回，視神経交叉部の高さにおける左右帯状回，側方膝状帯の高さにおける左右海馬，第4脳室の下方端の高さにおける左右鳥距皮質および髄質．海馬は肉眼的観察を記録した際，側頭葉に含めたが，海馬の動脈血流は海馬を除く側頭葉の血流とは異なるので，海馬

temporal lobe with which it was included when the gross observations were recorded. Therefore, in the analyses comparisons were made between gross evidence of hemorrhage or infarct in the parietal lobe, basal ganglia, temporal lobe, and histologic evidence of SVS in the hippocampus.

Each tissue block was randomly numbered to prevent observer bias. Sections from each block were stained by three methods. NFD and senile plaques were demonstrated by the Bodian (silver) stain. GVD, HCI and intraparenchymal and meningeal SVS were recorded in hematoxylin and eosin stained sections. The congo red stain demonstrated amyloid-like material in vessel walls and in the centers of senile plaques (congophilic senile plaques). Congophilic deposits were not examined for birefringence. The number of neurons with NFD and argyrophilic and congophilic senile plaques per 102mm^2 (20 high power fields per section) was recorded but this number was limited to a maximum count of 99 per section for recording and computational purposes.

The same two observers examined each histologic section independently and were in close agreement in more than 90% of the slides. Conflicting counts were reexamined to reach a consensus.

Statistical Methods. The distributions of the senile plaques, NFD, and GVD were skewed. In addition, a count of 99 for any one observation meant that 99 or more lesions were present per 20 microscopic fields. For the most part, nonparametric methods were used. Only brain weight tended to follow a normal distribution so that parametric procedures were used in testing age and sex comparisons of brain weight.

In comparing the age groups, the matched nature of the data was retained. The four-fold contingency tables were tested by McNemar's method.[30] The matched triples were broken up in order to examine only those individuals who had one or more lesions for which the Mann-Whitney U-test was most often used.[31] This last procedure was also used to test for differences between sexes in density of senile plaques.

Age specific comparisons of the 165 exposed individuals for the relationship of radiation vs SVS and radiation vs infarct and hemorrhage was tested by means of the Kruskal-Wallis one-way analysis of variance by ranks.[32] The correlation of radiation with senile plaques was tested by means of Spearman's Rank Correlation Coefficient.[33]

の部分の観察結果の解釈は複雑であった．したがって，解析では a）頭頂葉，b）脳底神経節，ならびに c）側頭葉および海馬内の小血管硬化症の組織学的徴候と，出血または梗塞の肉眼的徴候の間で比較を行った．

観察者による偏りを防ぐため，各組織塊に任意に番号をつけた．各組織塊から採った切片は，三つの方法によって染色した．神経原線維 tangle および老人斑は，Bodian（銀色）染色法を用い，顆粒空胞変性，細胞質内硝子様封入体ならびに実質内および脳膜小血管動脈硬化症には，ヘマトキシリンおよびエオジン染色をほどこした．血管壁および老人斑（好コンゴ性老人斑）の中心のアミロイド様物質には，コンゴ赤染色を用いた．複屈折を調べるための好コンゴ性沈着の検査は行わなかった．神経原線維 tangle を有するノイロンの数，および 102 mm^2 当たり（組織切片当たり20の高倍率視野）の好銀性および好コンゴ性老人斑について記録したが，数は記録および計算のために，組織片当たり最大99に制限した．

同じ 2 人の観察者が，各組織切片を別々に調べたが，標本の90％以上に非常によい一致が得られた．数の一致しないものについては，一致を得るため再検討を行った．

統計学的方法． 老人斑，神経原線維変化および顆粒空胞変性の分布は一定ではなかった．その上，一つの観察について算定値99というのは，20倍の顕微鏡野当たり99以上の病変があったことを意味する．ほとんどの場合，母数によらない方法（ノンパラメトリック法）を用いた．脳の重さのみが正規分布を示す傾向があったので，年齢間および男女間における脳の重さの比較検定には，母数による方法（パラメトリック法）を用いた．

年齢群の比較では，組み合わせになっている資料の特徴をそのまま用いた．McNemar の方法[30] により，4 分割表の検査を行った．Mann-Whitney U-test[31] が最も多く用いられている病変を一つまたはそれ以上有する者のみを調べるため，組み合わせてあった 3 群を解体した．老人斑の密度における男女間の差を調べるためにも，この最後の方法を用いた．

放射線と小血管硬化症，ならびに放射線と梗塞および出血との関係を調べるのに，165 人の被爆者の年齢別比較を，Kruskal-Wallis の順位による一元配置法を用いて検定した．[32] また，Spearman の順位相関係数法[33] により，放射線と老人斑との相関をも調べた．

Mantel-Haenszel[34] procedures for combining contingency tables were used on age specific comparisons of the occurrence of SVS with the occurrence of infarct and hemorrhage. In addition, the comparison of the occurrence of senile plaques with the occurrence of SVS and the occurrence of senile plaques with the occurrence of hemorrhage and infarct were tested in a similar manner.

It should be noted that often very large plaques counts per brain were obtained when the findings of the two sides were combined. Rank procedures, which are tests of medians rather than means, tend to minimize the influence of these outliers. In some cases the sample sizes reduced to such small numbers that significance tests could not be utilized.

RESULTS

Both cerebrovascular and ischemic heart disease were increasingly frequent causes of death with increasing age and cerebrovascular disease was the more frequent cause at all ages (Table 1). Due to the number of autopsies available, it was impossible to match cause of death within each triple. Thus, in order to examine any possible effect of cause of death, the samples were divided into three cause of death groups, cerebrovascular-cardiovascular disease, cancer, and other. There was no difference in the number of brains affected or in the degree of involvement by argyrophilic and congophilic senile plaques, NFD, GVD, HCI, and intraparenchymal SVS among the three cause of death categories for each of the three age groups. Only the data for argyrophilic senile plaques and NFD are presented (Table 2). The data for the other lesions were similar. There did appear to be more meningeal SVS in the cingulate region of 90-year-olds dying of cerebrovascular-cardiovascular disease than in those dying from other causes ($P < .05$). The same was true for meningeal SVS in the occipital region of 70-year-olds.

Aside from these, the most glaring differences among the cause of death groups were found in the evaluations of hemorrhages and infarctions. There were, obviously, more cerebral hemorrhages and infarctions among those with an autopsy cause of death listed as cerebrovascular-cardiovascular disease than those dying of other causes ($P < .05$) for the 90-year-old and 50-year-old groups. This difference was not statistically significant for the 70-year-old group.

小血管硬化症の発現と梗塞および出血の発現との年齢別比較については，分割表を合計する Mantel-Haenszel 法[34]を用いた．また，老人斑の発現と小血管硬化症の発現，また老人斑の発現と出血および梗塞の発現との各関係の比較についても，同様な方法で検定を行った．

左右両側の所見を合計したため，脳に老人斑の数が非常に多かったことがしばしばあったことに注目すべきである．平均値よりもむしろ中間値の検定である順位法は，これら中心から離れたところにあるものの影響を最小限にする傾向がある．いくつかの例では，調査集団の規模が有意な検定法が利用できないほどの少数にまで減少した．

結　果

脳血管性および虚血性の心臓疾患は，年齢の増加とともにますます多くなる死因であり，脳血管性疾患はいずれの年齢にも多くみられる死因の一つであった（表１）．入手されている剖検例数の関係で，それぞれ三つの群で死因を一致させることは不可能であった．したがって，死因の影響を調べるために，調査集団を，脳血管性—心臓血管性疾患，癌およびその他の三つの死因群に分けた．三つの年齢群における三つの死因には，病変を有する脳の件数，好銀性および好コンゴ性老人斑，神経原線維変化，顆粒空胞変性，細胞質内硝子様封入体および実質内小血管硬化症の病変の程度に差はなかった．好銀性老人斑および神経原線維変化の資料のみを表２に示した．その他の病変の資料はこれに類似したものである．脳血管性—心臓血管性疾患で死亡した90歳代の者の帯状回部には，その他の原因で死亡する者のそれよりも脳膜小血管硬化症が多いようであった（$P < .05$）．70歳代の者の後頭部における脳膜小血管硬化症についても同じことが認められた．

これらのほかに，死因のうちで最も顕著な差が認められたのは出血および梗塞の評価であった．90歳代および50歳代のものにおいて，剖検で認められた死因が脳血管性—心臓血管性疾患として記載されている場合，その他の死因で死亡する者よりも，脳出血および脳梗塞の所見が明らかに多かった（$P < .05$）．70歳代のものでは，この差は統計学的に有意ではなかった．

TABLE 2 MEAN COUNTS OF ARGYROPHILIC SENILE PLAQUES AND NEUROFIBRILLARY TANGLES DIVIDED ACCORDING TO CAUSE OF DEATH AND AGE

表2　好銀性老人斑および神経原線維 Tangle の平均数；死因および年齢群別

Age Group	Cerebrovascular and Cardiovascular Disease				Cancer				Other				Test[4]
	Plaques[1]	Test[3]	NFD[2]	Test[3]	Plaques[1]	Test[3]	NFD[2]	Test[3]	Plaques[1]	Test[3]	NFD[2]	Test[3]	
90	99	A **	125	A **	91	A NS	135	A **	135	A *	131	A **	NS
70	50	B **	49	B **	42	B **	26	B **	64	B **	70	B **	NS
50	<1	C NS	1	C **	<1	C *	10	C **	<1[5]	C **	4[5]	C **	NS

1. *Mean total senile plaque count for the eight brain areas for all cases in an age and cause of death category.*
全例の脳の8部位における老人斑の平均総数，年齢群および死因別
2. *Mean total count of neurons with neurofibrillary tangles for the eight brain areas for all cases in an age and cause of death category.*
全例の脳の8部位における神経原線維 tangle を有するノイロンの平均総数
3. *Significance Tests: A = 90 vs 70, B = 90 vs 50, C = 70 vs 50; NS - Not significant; * - 0.01 <P< 0.05; ** - P<0.01.*
有意性検定　　有意でない
4. *Within each age group neither counts of argyrophilic senile plaques nor of neurons with neurofibrillary degeneration are significantly altered by the cause of death.*
各年齢群において，好銀性老人斑も神経原線維変化を有するノイロンの数も，死因によって有意に変化しない．
5. *One 50-year-old subject who died with Alzheimer's disease not included in these counts.*
Alzheimer 病で死亡した50歳の対象者1名は上記の数に含まれていない．

It should be noted that in the data here presented cerebral hemorrhage and cerebral infarction include all instances of these lesions both gross and microscopic whether or not they were considered to be the autopsy cause of death. In all areas examined, infarcts and hemorrhages were most frequent in the 70-year-old group (Table 3). In comparison with the 90-year-olds, this difference was significant only for the parietal lobe but compared with the 50-year-olds, it was significant for all areas. There were only five subjects, all 70-year-olds, with acute hemorrhage involving more than 1 cm^3 of brain. While the percentage of areas with lesions varies by age, the affected volume per affected region does not seem to.

In reviewing the data presented in Tables 1, 2, and 3 account was taken of the selection process in which nonagenarians were the index cases to which septuagenarians were matched according to the presence or absence of cerebral disease as the autopsy cause of death. A preliminary analysis of the differences between the presence of hemorrhages and infarcts in the 90-year-olds and 70-year-olds based on the 43 pairs that could be matched according to cause of death showed more involvement among the 70-year-olds ($P < .05$). In the 12 pairs in which the 70-year-olds died of cerebrovascular-cardiovascular disease but the 90-year-olds died of other causes,

今回の資料で述べた脳出血および脳梗塞には，剖検診断上の死因であった場合でもそうでない場合でも，肉眼的および顕微鏡的にこれらの病変が認められた者すべてが含まれていることに注目する必要がある．全調査を通じて，梗塞および出血が最も多かったのは，70歳代群であった（表3）．90歳代の者と比べると，この差は頭頂葉についてのみ有意であったが，50歳代群と比べるといずれの領域についても有意であった．急性出血が脳の1 cm^3 以上にわたる者はわずか5人であり，いずれも70歳代であった．病変のある領域の割合は年齢によって差があるが，障害部当たりの障害量には，差はないようである．

表1，2および3に示した資料の検討に際しては，90歳代の者を指標例とし，それに70歳代の者を，剖検で認められた死因に脳疾患が関与していたか否かによって組み合わせを行うという選択の過程に考慮を払った．死因によって組み合わせを行うことのできた43組を基に，出血および梗塞の存在についての90歳代と70歳代との差をもとに予備的解析をしたところ，70歳代の方に病変が多いことが認められた（$P < .05$）．70歳代の者が脳血管性—心臓血管性疾患で死亡し，90歳代の者がその他の原因で

TABLE 3 CEREBRAL HEMORRHAGE (CH) AND INFARCTION (CI) GROUPED ACCORDING TO AGE AND BRAIN AREA

表3　脳出血（CH）および脳梗塞（CI）；年齢群および脳の部位別

Brain Area	Age Group	CH or CI %	Significance Test	Relative Volume per Involved Area	Significance Test
Frontal	90	25	A NS	2.56	A NS
	70	39	B NS	3.43	B NS
	50	13	C **	5.44	C NS
Parietal	90	11	A **	4.38	A NS
	70	35	B NS	3.84	B NS
	50	7	C **	8.40	C *
Temporal	90	31	A NS	2.14	A *
	70	36	B *	3.62	B NS
	50	14	C **	1.40	C **
Basal ganglia	90	53	A NS	3.26	A NS
	70	58	B **	3.81	B NS
	50	14	C **	3.80	C NS
Occipital	90	19	A NS	3.64	A NS
	70	28	B NS	4.20	B NS
	50	10	C *	4.14	C NS
All Combined	90	69	A NS	6.66	A NS
	70	83	B **	9.28	B NS
	50	28	C **	9.05	C NS

Significance Tests: *A = 90 vs 70, B = 90 vs 50, C = 70 vs 50, NS - Not significant; * - 0.01 < P < 0.05,*
有意性検定 *** - P < 0.01***

Relative Volume is based on a scale of 0 (no lesions) to 10 (bilateral lesions, each side > 3.0cm^3). The scores represent the mean values of affected regions of each age group when a lesion was present in either the right or left side.

相対量は0（病変なし）から10（左右に病変あり，いずれも＞3.0 cm^3）の程度まである．評価値は病変が右または左にあった場合その障害部位の各年齢群における平均値を示す．

% - Percent of age group with CH or CI in either right or left side of area indicated.

指定部位の右または左に脳出血または脳梗塞の認められた各年齢群における百分率

there were more infarcts and hemorrhages in the 70-year-old brains. However, even in the reverse case in which the 90-year-olds were considered to have died from cerebrovascular-cardiovascular disease and the 70-year-olds died from other causes the involvement of the 70-year-old brains with hemorrhages and infarcts was greater, but in this comparison the difference was not statistically significant. There was too little involvement in 50-year-olds to conduct this preliminary evaluation.

A similar analysis of meningeal SVS in the cingulate and calcarine regions by the cause of death in both matched and unmatched pairs determined that there was consistently more involvement of 90-year-

死亡した12組では，70歳代の者の脳に梗塞および出血が多かった．しかも，90歳代の者が脳血管性—心臓血管性疾患で死亡し，70歳代の者がその他の原因で死亡している逆の場合でも，70歳代の者の脳に出血および梗塞を伴う病変の頻度が高かったが，この比較では，その差は統計学的に有意ではなかった．50歳代の群についてこのような予備的評価を行うには，病変があまりにも少なかった．

帯状部および鳥距部における脳膜小血管硬化症について，上記同様の解析を，組み合わせ群と非組み合わせ群の双方について死因別に行ったところ，90歳代の者には死因

TABLE 4 MENINGEAL AND INTRAPARENCHYMAL SMALL VESSEL SCLEROSIS (SVS) (ALL TYPES COMBINED) AND CONGOPHILIC ANGIOPATHY DIVIDED ACCORDING TO AGE AND BRAIN AREA

表4　脳膜および実質内の小血管硬化症（SVS）（全種合計）および好コンゴ性血管病変；年齢群および脳の部位別

Brain Area	Age Group	Meningeal SVS				Intraparenchymal SVS			
		H & E		Congophilic		H & E		Congophilic	
		%	Test	%	Test	%	Test	%	Test
A. Percent Involvement[1]									
Frontal	90	78	A **	29	A **	57	A NS	22	A **
	70	54	B **	7	B **	49	B **	3	B **
	50	26	C **	1	C NS	17	C **	1	C NS
Cingulate	90	71	A NS	11	A *	82	A NS	10	A NS
	70	63	B **	1	B *	69	B **	3	B NS
	50	31	C **	0	C NS	24	C **	1	C NS
Hippocampus	90	75	A *	17	A **	32	A NS	10	A NS
	70	57	B **	1	B **	25	B **	1	B *
	50	31	C **	0	C NS	10	C *	0	C NS
Calcarine	90	56	A NS	25	A **	48	A *	23	A **
	70	46	B **	6	B **	30	B **	3	B **
	50	20	C **	3	C NS	10	C **	3	C NS
All Areas	90	96	A **	37	A **	92	A *	30	A **
	70	81	B **	10	B **	78	B **	3	B **
	50	54	C **	3	C NS	38	C **	3	C NS
B. Mean Number of Areas Involved[2]									
All Areas	90	4.38	A *	1.23	A **	3.17	A NS	1.01	A **
	70	3.49	B **	0.22	B **	2.58	B **	0.08	B **
	50	1.44	C **	0.07	C NS	0.82	C **	0.08	C NS

1. *Percent based on number with at least one affected vessel present in either right or left side of indicated area.*
指定部位の左または右のいずれかに血管病変が少なくとも一つ認められる数に基づく百分率
2. *Left and right side of each area counted separately for a total of eight areas.*
各部位の左側および右側で合計八つの部位について別々に算定
3. *Significance Tests: A = 90 vs 70, B = 90 vs 50, C = 70 vs 50; NS - Not significant; * - 0.01 < P < 0.05; ** - P < 0.01.*
有意性検定

olds regardless of the cause of death. Although in no case were these results statistically significant.

Based on the above, all the pairs whether matched or not according to cause of death were combined for the remaining analyses. Although the selection process in which 90-year-olds were the index cases to which the 70-year-olds were matched did not apparently significantly affect the results, the data are characteristic of the groups under study and should not be considered characteristic of a randomly selected autopsy population in Hiroshima.

と関係なく病変が一貫して多かった．しかしながら，これらの結果は統計学的に有意ではなかった．

上記に基づき，死因別に組み合わせたものであると否とにかかわらず，すべての組み合わせ群を合計して，残りの解析を行った．90歳代の者を指標例とし，70歳代の者をそれに組み合わせるという選択過程は，結果に有意な影響をもたらさないようであったが，その資料は調査対象群の特性を表わしており，広島で無作為に選択された剖検集団の特性を表わしていると考えることはできない．

TABLE 5 ARGYROPHILIC AND CONGOPHILIC SENILE PLAQUES ACCORDING TO AGE & BRAIN AREA
表5 好銀性老人斑および好コンゴ性老人斑；年齢群および脳の部位別

Brain Area	Age Group	Argyrophilic Plaques %[1]	Test[4]	Density[2]	Test	Congophilic Plaques %[1]	Test	Density[2]	Test[4]
Frontal	90	51	A **	32	A NS	46	A **	13	A *
	70	25	B **	55	B NS	19	B **	6	B NS
	50	4	C **	69	C NS	3	C **	4	C NS
Cingulate	90	57	A **	29	A NS	46	A **	12	A *
	70	24	B **	41	B NS	18	B **	5	B –
	50	4	C **	58	C NS	0	C **	0	C –
Hippocampus	90	76	A **	68	A NS	53	A **	10	A NS
	70	35	B **	58	B NS	15	B **	10	B –
	50	6	C **	50	C NS	0	C **	0	C –
Calcarine	90	55	A **	47	A NS	51	A **	28	A NS
	70	19	B **	55	B NS	17	B **	19	B NS
	50	4	C *	67	C NS	1	C **	13	C NS
All Areas	90	77	A **	141	A NS	61	A **	51	A NS
	70	40	B **	135	B **	21	B **	32	B NS
	50	11	C **	98[3]	C NS	3	C **	10	C NS

1. *Percent with one or more senile plaques in left or right side of area indicated.*
指定部位の左側または右側に一つ以上の老人斑が認められる者の百分率.
2. *Mean number of plaques per 102mm² (twenty 40X field for both left and right side of area indicated) in brains with at least one plaque in the designated area (i.e., involved cases only).*
指定の部位に少なくとも一つの老人斑がある脳（すなわち，病変のある例のみ）における102 ㎜² （指定部位の左右両側で40Xのもの20枚）当たりの老人斑の平均数.
3. *One 50-year-old subject died with Alzheimer's disease. If this case were dropped the mean density for the 50-year-old group would be three.*
50歳の対象者1人は Alzheimer 病で死亡している．この例を除外すると，50歳群の平均密度は3になる.
4. *Significance Tests: A = 90 vs 70, B = 90 vs 50, C = 70 vs 50; NS - Not significant; * - 0.01 < P < 0.05;*
有意性検定 *** - P < 0.01.*

Sclerosis of both meningeal and intraparenchymal small vessels increased with age and significantly so in most areas (Table 4). The change was greater between the 50- and 70-year age groups than between the 70- and 90-year age groups. However, small vessel congophilia was infrequent below age 90 and the difference between the 90-year-group and the other two groups was large and consistently significant.

Argyrophilic senile plaques were most frequently found in older persons although when present the number of plaques did not differ significantly in the three age groups (Table 5). The presence of congophilic senile plaques also was significantly related to age. When present, they were most numerous in the calcarine cortex. There was no

脳膜および実質内の双方における小血管の硬化症は年齢とともに増加し，ほとんどの領域においてその傾向が有意に認められた（表4）．この変化は，50歳代群と70歳代群の間の方が，70—90歳代群間の変化よりも大きかった．しかし，小血管の好コンゴ性変化は90歳未満の者には少なく，90歳代群とその他の2群との差も大きく，一貫して有意であった.

好銀性老人斑は，老齢者に最も多く認められたが，その存在が認められる場合，老人斑の数では三つの年齢群間に有意な差はなかった（表5）．好コンゴ性老人斑の存在と年齢との関係も有意であった．この病変がある場合は，鳥距皮質に最も多く認められた．好銀性老人斑もしくは

TABLE 6 NEUROFIBRILLARY DEGENERATION ACCORDING TO AGE & BRAIN AREA
表 6　神経原線維変化：年齢群および脳の部位別

Brain Area	Age Group	Neurofibrillary Degeneration			
		% [1]	Test [4]	Density [2]	Test [4]
Frontal	90	13	A NS	3	A NS
	70	10	B *	31	B NS
	50	3	C NS	100	C NS
Cingulate	90	35	A **	9	A NS
	70	7	B **	45	B *
	50	3	C NS	113	C NS
Hippocampus	90	100	A NS	125	A **
	70	93	B **	51	B **
	50	34	C **	26	C *
Calcarine	90	3	A NS	3	A NS
	70	1	B NS	3	B NS
	50	1	C NS	16	C NS
All Areas	90	100	A NS	128	A **
	70	94	B **	57	B **
	50 [3]	34	C **	45	C *

1. *Percent with one or more neurons with neurofibrillary tangles in either left or right side of area indicated.*
指定部位の左側または右側に神経原線維 tangle をもつノイロンが一つ以上認められる者の百分率.

2. *Mean number of neurons with neurofibrillary tangles per 102mm² (twenty 40X fields for both left and right side of indicated area) in brains with at least one such lesion in the designated area (i.e., involved cases only).*
指定の部位に病変が少なくとも一つある脳（すなわち，病変のある例のみ）において，102 mm² （指定部位の左右両側で40X のもの20枚）当たり神経原線維 tangle を有するノイロンの平均数.

3. *One 50-year-old subject died with Alzheimer's disease. If this case were excluded the mean density for the 50-year-old group would be 21.*
50歳の対象者 1 人は Alzheimer 病で死亡した．この例を除外すると50歳群の平均密度は21となる.

4. *Significance Tests: A = 90 vs 70, B = 90 vs 50, C = 70 vs 50; NS - Not significant,*
有意性検定 ** - 0.01 < P < 0.05, ** - P < 0.01*

significant difference in occurrence of either argyrophilic senile plaques or congophilic senile plaques by sex but when either of the two forms was present they were more numerous in women than men in each age group.

Both the presence and density of neurons with NFD in the hippocampus increased with age (Table 6) and NFD was found in the hippocampus of every nonagenarian. The occurrence of NFD increased with age in other areas also but the findings were less consistent and in some areas the density of cells with NFD was less in older persons. In no case was NFD observed in another area of the brain when it was not present in the hippocampus. There was no consistent difference between males and females in the density of neurons with NFD.

好コンゴ性老人斑の出現には，性別に有意な差はなかったが，いずれかが認められる場合，その数量は各年齢群とも女の方が男よりも多かった.

海馬における神経原線維変化を伴うノイロンの存在および密度は，年齢とともに増加し（表 6），90歳代の各例の海馬に認められた．神経原線維変化の出現はその他の領域でも年齢とともに増加したが，その所見の一貫性は幾分低く，高齢者ではいくつかの領域でそれのある細胞の密度が薄かった．海馬に認められなかった場合は，脳のその他の部分にこれが認められることは決してなかった．これを伴うノイロンの密度には，男女間に一貫した差はなかった.

TABLE 7 GRANULOVACUOLAR DEGENERATION AND HYALINE CYTOPLASMIC INCLUSIONS BY AGE GROUP

表7　顆粒空胞変性および細胞質内硝子様封入体；年齢群別

Lesion	Brain Area	Age Group	%[1]	Test[3]	Density[2]	Test[3]
Granulovacuolar Degeneration	Hippocampus	90	81	A **	19	A NS
		70	33	B **	20	B NS
		50	6	C **	14	C NS
Hyaline Cytoplasmic Inclusions	Medulla	90	39	A NS	1.4	A NS
		70	26	B NS	1.3	B NS
		50	23	C NS	1.3	C NS

1. *Percent with one or more lesions in area indicated.*
指定部位に一つ以上の病変が認められる者の百分率

2. *Mean number of affected neurons per histologic section from brains with at least one such lesion in the designated area (i.e., involved cases only).*
指定部位に病変が少なくとも一つある脳（すなわち，病変のある例のみ）から採取した組織切片当たりの障害ノイロンの平均数.

3. *Significance Tests:* *A = 90 vs 70, B = 90 vs 50, C = 70 vs 50; NS - Not significant,*
有意性検定 *** - $P < 0.01$*

The occurrence of GVD in the pyramidal neurons of the hippocampus increased with increasing age but when present the density of cells per brain with GVD did not increase significantly with age (Table 7). There was no significant age relationship in the distribution of HCI in the hypoglossal nucleus (Table 7).

海馬のピラミッド型ノイロンにおける顆粒空胞変性の出現は年齢の上昇とともに増加したが，それが存在する場合には，脳あたりの細胞の密度は年齢とともに有意に増加しなかった（表7）．舌下核にみられる細胞質内硝子様封入体の分布には年齢との有意な関係はなかった（表7）．

Brain weight at the time of autopsy decreased significantly with increasing age (1370g for 50-year-old males and 1265g for 90-year-old males) and at all ages was lower in women.

剖検時に測定された脳の重量は，年齢の増加とともに有意に減少し（50歳の男では1370g，90歳の男では1265g），女では全年齢にわたって男より軽かった．

The number of subjects in this study exposed to 100 or more rad was too small to produce conclusive data. However no preliminary evidence was obtained showing a relation between radiation exposure ATB and any morphologic changes associated with aging. There was no significant relation between the amount of atomic radiation received and the subsequent development of cerebral infarct, cerebral hemorrhage, SVS, senile plaques, NFD, GVD or, HCI.

本調査の対象者で100 rad以上の線量に被曝した者の数は，確定的な資料を得るにはあまりにも少なかった．しかし，原爆時の放射線被曝と加齢に伴う形態的変化との関係を示す予備的な徴候は認められなかった．原爆放射線の被曝線量とその後の脳梗塞，脳出血，小血管硬化症，老人斑，神経原線維変化，顆粒空胞変性または細胞質内硝子様封入体との間には，有意な関係はみられなかった．

Cerebral hemorrhage or infarction was more frequently found if SVS was present then when the comparative histologic section did not show SVS (Table 8). However, in a significant number of cases cerebral hemorrhage and infarct were not accompanied by SVS and in only 8 of 24 brain area comparisons were both found together in a majority of the cases.

組織切片に小血管硬化症が認められる場合は，認められない場合よりも，脳出血または脳梗塞が多くあった（表8）．しかし，相当多くの例においては，脳出血および脳梗塞は小血管硬化症を伴わず，また，大部分の例において脳内の24の比較部位のうち，両者が同時に認められたのは八つの部位にすぎなかった．

TABLE 8 PRESENCE OR ABSENCE OF MENINGEAL AND INTRAPARENCHYMAL SMALL VESSEL SCLEROSIS IN THE PRESENCE OF CEREBRAL HEMORRHAGE OR INFARCT

表8　脳出血（CH）または脳梗塞（CI）がある場合の脳膜および実質内の小血管硬化症（SVS）の有無

CH or CI Present		Meningeal SVS		Intraparenchymal SVS	
Gross Area	Histologic Area	% Present[1]	% Absent[2]	% Present[1]	% Absent[2]
L. Frontal	L. Sup. Frontal	23[3]	13	26	13
R. Frontal	R. Sup. Frontal	27[3]	13	20	18
L. Frontal	L. Cingulate	23[3]	12	24[3]	10
R. Frontal	R. Cingulate	22	16	27[3]	9
L. Parietal	L. Hippocampus	11	9	13	9
R. Parietal	R. Hippocampus	21[3]	8	16	13
L. Basal Ganglia	L. Hippocampus	34	25	30	28
R. Basal Ganglia	R. Hippocampus	47[3]	16	50	26
L. Temporal	L. Hippocampus	12	11	20	10
R. Temporal	R. Hippocampus	29[3]	13	34	17
L. Occipital	L. Calcarine	20	11	33	10
R. Occipital	R. Calcarine	18	9	11	12

1. *Percentage of brains with SVS in which CH or CI was also found.*
小血管硬化症があり，出血または梗塞の認められた脳の百分率．
2. *Percentage of brains in which SVS was not present but CH or CI was found.*
小血管硬化症はなかったが出血または梗塞が認められた脳の百分率．
3. *Comparison in which more than 50% of areas with CH or CI also had SVS.*
部位の50%以上に脳出血または梗塞のある部位における小血管硬化症の存在についての比較．

TABLE 9 OCCURRENCE AND DENSITY OF ARGYROPHILIC SENILE PLAQUES IN THE PRESENCE AND ABSENCE OF SMALL VESSEL SCLEROSIS (SVS) BY AGE AND BRAIN AREA

表9　小血管硬化症（SVS）の有無と好銀性老人斑の出現率および密度；年齢群および脳の部位別

Brain Area	Meningeal SVS								Intraparenchymal SVS							
	%[1]		Plaque Density[2]						%[1]		Plaque Density[2]					
			90		70		50				90		70		50	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
L. Sup. Frontal	36[3]	16	16	18	29	32	99	7	31	21	19	15	26	27	0	53
R. Sup. Frontal	36[3]	16	17	19	40	26	99	1	35	20	14	20	17	42	99	1
L. Cingulate	33[3]	20	17	15	17	34	82	5	37[3]	15	15	19	23	27	82	5
R. Cingulate	25	19	19	19	23	27	2	85	32[3]	11	18	27	29	21	85	2
L. Hippocampus	44[3]	27	39	33	54	18	34	1	53	31	42	35	54	25	0	26
R. Hippocampus	41[3]	24	48	31	34	54	0	99	47	28	59	36	68	36	0	99
L. Calcarine	29	17	26	27	42	22	99	0	42	16	24	28	6	27	99	0
R. Calcarine	37	18	37	24	40	38	99	1	41	19	49	19	58	30	99	1

1. *% = Percent of cases with (+) or without (−) SVS in histologic sections in which argyrophilic plaques were observed (all age groups combined).*
好銀性老人斑が認められた組織切片に小血管硬化症がある例（＋）とない例（−）の百分率（全年齢群の合計）．
2. *Density = Mean number of senile plaques in the presence (+) or absence (−) of small vessel sclerosis.*
密度＝小血管硬化症がある場合（＋）とない場合（−）の老人斑の平均数．
3. *Those comparisons in which more than 50% of areas with senile plaques also had SVS.*
部位の50%以上に老人斑がある部位における小血管硬化症の存在についての比較．

TABLE 10 OCCURRENCE AND DENSITY OF NEUROFIBRILLARY DEGENERATION AND GRANULOVACUOLAR DEGENERATION IN THE HIPPOCAMPUS IN THE PRESENCE AND ABSENCE OF SMALL VESSEL SCLEROSIS (SVS) BY AGE

表10　小血管硬化症（SVS）の有無別にみた海馬の神経原線維変化および顆粒空胞変性の出現率および密度；年齢群別

	Meningeal SVS								Intraparenchymal SVS							
	%[1]		Density[2]						%[1]		Density[2]					
			90		70		50				90		70		50	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
NFD																
Left	80	59	72	61	30	32	41	14	90	64	79	64	45	27	3	20
Right	79[3]	54	60	58	31	32	3	23	88	61	73	56	37	30	4	21
GVD																
Left	41[3]	23	15	7	14	11	23	0	50	27	17	10	8	14	0	23
Right	41[3]	27	15	7	6	22	0	8	47	31	20	9	8	17	0	8

1. *% = Percent of cases with (+) or without (−) SVS in histologic sections in which NFD or GVD was observed (all age groups).*
神経原線維変化または顆粒空胞変性が認められた組織切片に小血管硬化症がある例（＋）またはない例（−）の百分率（全年齢群の合計）.
2. *Density = Mean number of neurons with NFD or GVD in the presence (+) or absence (−) of small vessel sclerosis.*
密度＝小血管硬化症のある場合（＋）またはない場合（−）に神経原線維変化または顆粒空胞変性を有するノイロンの平均数.
3. *More than 50% of sections with neuronal degeneration also contained SVS.*
ノイロン変性を有する組織片の50％以上に小血管硬化症があった.

TABLE 11 OCCURRENCE AND DENSITY OF SENILE PLAQUES IN THE PRESENCE AND ABSENCE OF CEREBRAL HEMORRHAGE AND INFARCT BY AGE AND BRAIN AREA

表11　脳出血および脳梗塞の有無別にみた老人斑の出現率および密度；年齢群および脳の部位別

Brain Area	Equivalent Histologic Section	%[1]		Average Number of Plaques[2]					
				90		70		50[3]	
		+	−	+	−	+	−	+	−
L. Frontal	L. Sup. Frontal	25	24	19	16	18	33	0	53
R. Frontal	R. Sup. Frontal	30	23	19	17	23	36	0	50
L. Frontal	L. Cingulate	25	25	17	16	14	28	0	44
R. Frontal	R. Cingulate	23	22	25	18	11	29	0	44
L. Temporal	L. Hippocampus	56	31	28	37	20	38	0	26
R. Temporal	R. Hippocampus	37	30	52	38	19	54	0	99
L. Occipital	L. Calcarine	30	19	13	31	35	24	0	99
R. Occipital	R. Calcarine	19	24	30	31	0	39	0	34

1. *% = Percent of cases with (+) or without (−) cerebral hemorrhage or infarct in which senile plaques were observed (all age groups combined).*
老人斑が認められ，脳出血または脳梗塞がある例（＋）またはない例（−）の百分率.
2. *(+) = Mean plaque count when both CH or CI and plaques are present; (−)= Mean plaque count when CH or CI are absent and plaques are present.*
（＋）＝脳出血または脳梗塞と老人斑がともに認められた場合の平均老人斑数；（−）＝脳出血または脳梗塞がなく老人斑が認められた場合の平均老人斑数.
3. *Includes one subject who died of Alzheimer's disease.* Alzheimer 病で死亡した者1例を含む.

Argyrophilic senile plaques were found more frequently in the presence of small vessel sclerosis than in its absence but in only 7 of 24 area comparisons did a majority of the sections that contained senile plaques also contain SVS (Table 9). There was no consistent relationship between the number of senile plaques and the presence of SVS.

In all cases NFD and GVD in the hippocampus were found more frequently in the presence of intraparenchymal SVS than in its absence but with almost no statistically significant correlation between the presence of neuronal degeneration and arteriosclerosis (Table 10). In only one of the four comparisons did a majority of the sections of hippocampus that showed NFD also show SVS. There was no consistent relation between SDS and the number of neurons with NFD or GVD found in the hippocampus. There was no relation between the occurrence of senile plaques and cerebral hemorrhage or infarction (Table 11).

DISCUSSION

Nonagenarians were selected for study based on the belief that specific central nervous system degenerative changes (SVS, NFD, senile plaques, GVD, and HCI) would reflect the "aging" process in these aged individuals. The two comparative age groups were chosen to test this hypothesis. Cause of death varies with age and it was not possible to avoid this variable in selecting autopsies for comparison. However, it was obvious even within the limited selection of autopsies available for this study that the occurrences of the major target changes was independent of the cause of death.

Sclerosis of small meningeal and intraparenchymal arteries was most frequent in nongenarians but was already present in an appreciable number of 50-year-olds and the increase in frequency was much greater between 50 and 70 than between 70- and 90-year-olds. Congophilic deposits in these sclerosed vessels, however, were infrequent below age 90. Sclerosis of these vessels even in the nonagenarians often was present in the absence of hemorrhage, infarction, senile plaques, and neuronal degenerations. Sclerosis of intraparenchymal vessels was least frequent within the hippocampus where some of these changes were most frequent.

Senile plaques increased in frequency with advancing age and were not often found in 50-year-olds. However, even in the nongenarians they were not

小血管硬化症が認められる場合は，認められない場合よりも，好銀性老人斑が多く認められたが，24の比較部位のうちで老人斑のある切片の大部分に小血管硬化症が認められたのは，わずか7か所であった（表9）．老人斑の数と小血管硬化症との間には，一貫した関係はみられなかった．

すべての例において，実質内小血管硬化症が存在する場合は，存在しない場合よりも，海馬に神経原線維変化および顆粒空胞変性が認められることが多かったが，ノイロン変性と動脈硬化症の存在との間には統計学的に有意な相関はほとんど認められなかった（表10）．神経原線維変化を示した海馬の切片の大部分に小血管硬化症が併せて認められたのは，四つの比較のうちわずか一つだけであった．海馬に神経原線維 tangle または顆粒空胞変性が認められたノイロン数と，小血管硬化症との間には，一貫した関係はなかった．老人斑と脳の出血または梗塞との関係は認められなかった（表11）．

考　察

特定の中枢神経系の変性性変化（小血管硬化症，神経原線維変化，老人斑，顆粒空胞変性および細胞質内硝子様封入体）は高齢者における「加齢促進」を反映するとの考えに基づき，調査対象には90歳代の者を選択した．この仮説について検定するために，二つの比較年齢群を選択した．死因は年齢に伴って変動するものである．しかも比較のための剖検例選択に際しては，この変数をさけることはできなかった．しかし，今回の調査に役立つ剖検例の限られた範囲から選択されたものでも，主要な目標となる変化の出現は死因とは無関係であることが明らかであった．

脳膜および実質内の小動脈硬化症は，90歳代の者に最も多かったが，50歳代の者にもすでにかなりの例数が認められ，また50－70歳代の者における頻度の増加率は70－90歳代の者の場合よりもはるかに高かった．これらの硬化した血管における好コンゴ性沈着は，90歳未満の者ではまれであった．90歳代の者において出血，梗塞，老人斑およびノイロン変性が認められなかったのに，これら血管の硬化が認められることはしばしばあった．実質内の小血管硬化症は上述の変性のいくつかが最も多くみられる海馬には最も少なかった．

老人斑は年齢の増加とともに頻度は増加したが，50歳代では多くの場合認められなかった．しかし，90歳代の場合でも，常に認められたわけではない．老人斑がある場

always present. When senile plaques were present the number in each area except for the hippocampus did not vary significantly among the three age groups suggesting that perhaps plaques were found as a single crop or that the rate of formation was fairly constant and reached a steady state with the rate of removal, if indeed they are removed with time. Congophilic deposits in senile plaques were less frequent at all ages but increased in number with increasing age supporting the opinion that this is a late stage in the progressive development of senile plaques.

Of all the indicators of chronologic aging, NFD in the hippocampus appeared to be the most reliable for not only did these lesions occur at an earlier age and increase in frequency with age but the number of neurons with NFD in the hippocampus increased with age. This is in contrast to the number of neurons with GVD and the number of senile plaques which appeared to reach a maximum density before age 90.

In the present study cerebral hemorrhage and infarcts were less frequent in the nonagenarians who had more widespread sclerosis of small cerebral vessels. As previously indicated by Tomlinson et al,[2] no association was found between the occurrence of cerebral hemorrhage or infarction and the presence of senile plaques of NFD in the same area. Evidently cerebral hemorrhage and infarction are not satisfactory indicators of aging.

There were too few autopsies in subjects exposed to high radiation doses for much weight to be attached to the fact that none of the observed changes increased as a result of prior radiation exposure. This was also the conclusion reached in the 1962 study.[1] A still larger number of autopsies must be examined before this negative conclusion can be asserted with confidence.

It is evident from the analyses that sclerosis of small meningeal and intraparenchymal arteries and congophilic alteration of these vessels, development of argyrophilic senile plaques with subsequent appearance of congophilia, occurrence of NFD and GVD all increase with advancing age. However, the various neuronal degenerations appear to be independent of the vascular lesions and to the cause of death. They progress at different rates and perhaps each is a response to a different combination of physiologic and metabolic process.

合は，各領域におけるその数は，海馬を除けば，三つの年齢群間で有意な差はなかった．これにより，老人斑が一度に形成されるか，形成の速度がかなり一定したものであって，時の経過とともに除去されるとすれば，その除去速度が一定であることも示唆される．老人斑中に認められる好コンゴ性沈着の頻度は，すべての年齢において低いが，年齢の増加とともにその数は増加した．このことは，老人斑の漸進的出現の最終段階であるとする意見を支持するものである．

暦年齢に基づく加齢の指標の中で，海馬中の神経原線維tangleが，最も信頼性のおけるものであると考えられた．というのは，これらの病変が比較的若年に発生し．年齢とともに増加するものであるばかりでなく，海馬において神経原線維変化を有するノイロンの数も年齢とともに増加するからである．これは顆粒空胞変性を有するノイロンの数ならびに90歳になる以前に最高密度に達する老人斑の数と異なるものである．

本調査では，脳の小血管に広範な硬化症を有する90歳代の者に，脳の出血および梗塞が少なかった．Tomlinsonら[2]が以前に指摘したように，脳出血または脳梗塞の発現と，同一領域における老人斑または神経原線維変化の存在との間には関係が認められなかった．脳出血および脳梗塞は加齢の指標としては満足なものでないことは明らかである．

以前の原爆放射線被曝の結果として観察された変化が増加していないという事実に多大のウェイトをおくには，高線量被曝者の剖検例数があまりに少なかった．1962年の調査[1]でもこれと同じ結論に到達している．この否定的な結論が確信をもって主張できるまでには，なお多数の剖検例について調べる必要がある．

脳膜および実質内の小動脈硬化症，これら血管の好コンゴ性変化，好銀性老人斑の出現とその後の好コンゴ性変性の出現，神経原線維性および顆粒空胞性ノイロン変性が，ことごとく加齢とともに増加することは解析によって明らかである．しかし，各種のノイロン変性は，血管病変および死因とは関係がないように思われる．これらは異なる速度で進行し，またそれぞれ別々の生理学的および代謝的過程の組み合わせに対して反応したものであると思われる．

REFERENCES

参考文献

1. MATSUYAMA H, NAMIKI H, WATANABE I: Senile changes in the brain in the Japanese. Incidence of Alzheimer's neurofibrillary change and senile plaques. Proceedings of the 5th International Congress of Neuropathology, Zurich, 1965. pp 979-980

2. TOMLINSON BE, BLESSED G, ROTH M: Observations on the brains of nondemented old people. J Neurol Sci 7: 331-356, 1968

3. DAYAN AD: Quantitative histologic studies on the aged human brain. I. Senile plaques and neurofibrillary tangles in "normal" patients. Acta Neuropathol 16:85-94, 1970

4a. TERRY RD, WISNIEWSKI H: The ultrastructure of the neurofibrillary tangle and the senile plaque. Ciba Foundation Symposium on Alzheimer's Disease and Related Conditions. Ed by Wolstenholme GEW and O'Conner M. London, Churchill, 1970. pp 145-168

4b. HIRANO A: Neurofibrillary changes in conditions related to Alzheimer's disease. Ciba Foundation Symposium on Alzheimer's Disease and Related Conditions. Ed by Wolstenholme GEW and O'Conner M. London, Churchill, 1970. pp 185-207

5. MENDELL RD, MARKESBERY WR: Neuronal intracytoplasmic hyaline inclusions. J Neuropathol Exp Neurol 30: 233-239, 1971

6. BLUMENTHAL RT: Radiation and aging. Scientist and Citizen 9:21, 1967

7. LAMSON BG, BILLINGS MS, MEEK RA, BENNETT LR: Late effects of total-body roentgen irradiation. III. Early appearance of neoplasms and life-shortening in female Wistar rats surviving 1000 r hypoxic total body irradiation. Arch Pathol 66:311-321, 1958

8. UPTON AC, FURTH J, CHRISTENBERRY KW: Late effects of thermal neutron irradiation in mice. Cancer Res 14:682-690, 1954

9. ALEXANDER P, CONNELL DI: Shortening of life span of mice by irradiation with x-rays and treatment with radiomimetic chemicals. Radiat Res 12:38-48, 1960

10. FURTH J, UPTON AC, CHRISTENBERRY KW, BENEDICT WH, MOSHMAN J: Some late effects in mice of ionizing radiation from an experimental nuclear detonation. Radiology 63:562-570, 1954

11. BENNETT LR, CHASTAIN SM, FLINT JS, HANSEN RA, LEWIS AE: Late effects of roentgen irradiation. I. Studies on rats irradiated under anoxic anoxia. Radiology 61:411-419, 1953

12. WALBURG HE JR: Longevity as influenced by irradiation in germfree mice. In *Radiation and Aging.* Ed by Lindop PJ and Sacher GA. London, Taylor and Francis, 1966. pp 361-365

13. CASARETT GW: Similarities and contrasts between radiation and time pathology. Adv Gerontol Res 1:109-163, 1964

14. ALEXANDER P, CONNELL DI: Differences between radiation-induced life-span shortening in mice and normal aging as revealed by serial killing. In *Cell Basis and Aetiology of Late Somatic Effects in Ionizing Radiation.* Ed by Harris RJC. New York, Academic Press, 1963. pp 277-283

15. MOLE RH: Does radiation age or produce nonspecific life shortening? In *Cell Basis and Aetiology of Late Somatic Effects in Ionizing Radiation.* Ed by Harris RJC. New York, Academic Press, 1963. pp 273-275

16. UPTON AC: Ionizing radiation and the aging process, a review. J Gerontol 12:306-313, 1957

17. UPTON AC, KIMBALL AW, FURTH J, CHRISTENBERRY KW, BENEDICT WH: Some delayed effects of atom-bomb radiation in mice. Cancer Res 20(8) pt 2:1-60, 1960

18. WALBURG HE JR: Radiation-induced life-shortening and premature aging. Adv Rad Biol 5:145-177, 1975

19. WARREN S: Longevity and cause of death from irradiation in physicians. JAMA 162:464-468, 1956

20. SELTZER F, SARTWELL PE: The influence of occupational exposure to radiation on the mortality of American radiologists and other medical specialists. Am J Epidemiol 81:2-22, 1965

21. ANDERSON RE, YAMAMOTO T, ISHIDA K, THORSLUND T: Aging in Hiroshima and Nagasaki A-bomb survivors: Accumulation of cardiac lipofuscin. J Am Geriatr Soc 19:193-198, 1971

22. STREHLER BL, NISHIMURA ET, GEE MV, SHOCK NW: Influence of a single exposure to radiation on accumulation of lipofuscin (age pigment) in cardiac tissue of atomic bomb survivors. ABCC TR 35-59

23. HOLLINGSWORTH JW, HASHIZUME A, JABLON S: Correlation between tests of aging, Hiroshima, an attempt to define physiologic age. Yale J Biol Med 38:11-26, 1965

24. ANDERSON RE: Aging in atomic bomb survivors. Arch Pathol 79:1-6, 1965

25. HOLLINGSWORTH DR, HOLLINGSWORTH JW, BOGITCH S, KEEHN RS: Neuromuscular tests of aging, Hiroshima. J Gerontol 24:276-283, 1969

26. OMORI Y, ASHLEY FW, BELSKY JL: Achilles tendon reflex and aging in atomic bomb survivors, Hiroshima. J Chronic Dis 25:111-120, 1972

27. ANDERSON RE: Longevity in radiated human populations, with particular reference to the atomic bomb survivors. Am J Med 55:643-656, 1973

28. STORER JB, SANDERS PC: Relative effectiveness of neutrons for production of delayed biological effects. 1. Effectings of single doses of thermal neutrons on life span of mice. Radiat Res 8:64-70, 1958

29. BEEBE GW, USAGAWA M: The major ABCC samples. ABCC TR 12-68

30. MCNEMAR Q: Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 12:153-157, 1947

31. MANN HB, WHITNEY DR: On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statistics 18:50-60, 1947

32. KRUSKAL WH, WALLIS WA: Use of ranks in one-criterion variance analysis. J Am Statistical Assn 47:583-621, 1952

33. HOTELLING H, PABST MR: Rank correlation and tests of significance involving no assumption of normality. Ann Math Statistics 7:29-43, 1936

34. MANTEL N, HAENSZEL W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719-748, 1959