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The Association Between Quantitative Measures of Dementia and of Senile Change in the Cerebral Grey Matter of Elderly Subjects

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The ageing of many populations in recent years has directed increasing attention to the social, medical and biological problems of senescence. The psychological changes associated with ageing occupy a central position in inquiries in this field. The expectation of mental disorder shows a steep increase with advancing chronological age, and beyond 75 years a large part of this increase is accounted for by disorders associated with degenerative changes in the central nervous system for which we lack remedies at the present time. Larsson *et al.* (1963) have estimated that the aggregate morbidity risk for these disorders up to the age of 70 is 0·4 per cent., up to age 75, 1·2 per cent. and up to age 80, 5 per cent. For higher ages estimates were probably less reliable, but the calculated risk up to the age of 90 was 5·2 per cent. In a survey of a random sample of elderly people aged 65 and over in the general population, Kay *et al.* (1964), found a total of 4·2 per cent. of elderly subjects to be suffering from senile dementia, 2·9 per cent. being mild cases. The condition is generally recognized as being a major cause of serious infirmity among the elderly in psychiatric, geriatric, general medical and community practice alike.

The outfall of neurones and other pathological changes associated with senile dementia were described in the early years of this century. "Plaques" in cerebral grey matter were first described by Blocq and Marinesco (1892) and related to the pathology of senile dementia by Simchowicz (1910) who first gave the "senile plaque" its name. Neurofibrillary change (Alzheimer, 1907) and granulo-vacuolar degeneration (Simchowicz) were described at about the same time. The workers who gave the earliest accounts of these changes were writing about senile dementia and Alzheimer's disease, which were regarded as specific disease entities. Difficulties in interpretation entered, however, when it was discovered that, far from being specific, such changes could be demonstrated in the brains of well-preserved old people. Isolated observations of this kind had been made for some time when Gellerstedt published his well-known studies in 1933. He found that senile plaques were present in 84 per cent., neurofibrillary change in 97 per cent. and granulovacuolar degeneration in 40 per cent. of well-preserved old people studied *post-mortem*. Although the changes were usually scanty and found in some cases only after careful search, plaque formation and other changes were sometimes just as intense in normal subjects as in cases of senile dementia. This had already been indicated by Grünthal (1927), whose findings also led him to conclude that there must be some qualitative as well as quantitative differences between the pathology of senile dementia and that of normal senescence.

The causal relationship between senile plaques and related changes in the brain and the clinical syndrome of senile dementia was also regarded as indefinite by Rothschild (1937, 1942, 1956), who considered personality factors to be important in deciding the clinical picture. He made the further point that senile dementia could occur without the presence of senile plaques; generalized cerebral atrophy with the clinical but not the histological changes generally associated with this disorder has been also reported by H. Sjögren (1952).

The situation was further complicated by the uncertainty of the role of cerebral degeneration

in the development of depressive, neurotic and paranoid disorders commencing in late life. When clinical descriptions of cases of organic psychosis in old age recorded twenty or more years ago are examined, it is evident that disorders dominated by such symptoms were often regarded as having an underlying organic basis. Post-mortem neuropathological findings were in apparent accord with this view, for Newton (1948) in the course of 150 consecutive autopsies at a mental hospital found plaques and neurofibrillary change in 32 of 76 cases of affective psychosis and in 6 out of 24 cases of schizophrenia and paranoid psychosis. The changes showed a steep increase in incidence with advancing age.

In the absence of a quantitative approach to either the clinical or neuropathological changes, the latter tended to be interpreted in "all or none" terms, some workers attributing all forms of mental disorder in old age to cerebral degenerative change, others regarding such disorders as unrelated to degeneration. Thus, in Strecker and Ebaugh's textbook (1947) paranoid and depressive states were said to constitute 15·8 per cent. and 7·4 per cent. respectively of cases of senile dementia. On the other hand, as recently as 1959, Wolf expressed the view that "no good correlation exists between the degree, distribution and the character of the various abnormal changes and the age and state of the neural function of the individual". Yet, half a century previously, Simchowicz had already begun to count senile plaques and had concluded that the number of plaques corresponded with the severity of the senile degenerative process.

Lurking behind these controversies there were at least three relatively distinct groups of problems which tended to be confused with one another:

(1) The relationship between cerebral pathology and psychiatric diagnosis in old age.

(2) The relationship between cerebral pathology and intellectual deterioration in senescence.

(3) The relationship between normal senescence and senile dementia. Is the latter an accentuation of the former or is it qualitatively distinct in a pathological sense?

These questions could not easily be answered or disentangled from one another until it had been shown that there existed several distinct nosological entities in addition to senile and arteriosclerotic dementia in old age, and that they showed relatively little overlap in symptomatology and pattern of outcome (Roth and Morrissey, 1952; Norris and Post, 1955; Roth, 1955; Kay, Norris and Post, 1956; Kay, 1962).

The prevalence of physical illness (Kay and Roth, 1955) and the expectation of life also varied in the different clinical groups. Thus, the length of survival in subjects with dementia was only about one quarter or less of the normal, and the mortality rate was at least five times as high as in the general population. On the other hand, depressive and paraphrenic patients showed mortality rates much closer to that of the general population of comparable age.

The recent observations of Corsellis (1962) have shown that, despite the many views expressed to the contrary, such clinical groupings correspond fairly well to neuropathological findings. Thus, in a study of the brains of 300 patients dying in a mental hospital, he found that the great majority of those who had been diagnosed as suffering from organic psychoses showed senile or arteriosclerotic changes of moderate or severe degree in the brain. On the other hand, only about a quarter of the subjects with functional disorders showed changes of this degree of severity, and to some extent this overlap could be accounted for by the development of organic features in late life in subjects whose initial illness had been of a "functional" kind.

Despite the results of this important inquiry, the precise significance of the "senile" degenerative changes which have been described in normal subjects, individuals with functional disorders and organic psychoses alike, remained uncertain. In order to shed further light on the questions that have arisen, it is necessary to apply quantitative measures both to the phenomena of mental deterioration and to the pathological changes.

As far as pathological change is concerned, only the senile plaques could be readily quantified. When the technique of plaque counting

had been developed, three hypotheses suggested by previous findings were put to the test:

(1) That senile plaque formation is associated with all forms of psychiatric disorder commencing in old age. This hypothesis implies that subjects with psychiatric symptoms, either functional or organic, will differ significantly from subjects lacking such symptoms in respect of intensity of plaque formation.

(2) That intensity of senile plaque formation would prove to be correlated with the measures of the change that to some extent cuts across diagnostic categories, namely the decline in intellectual efficiency generally associated with old age.

(3) That in severely demented subjects pathological changes in the brain will be in some respects qualitatively distinct from those to be found in the brains of well-preserved old people.

Material and Methods

The inquiries were conducted on patients admitted to a psychiatric hospital, a geriatric hospital, and a number of wards in a general hospital. Consecutive admissions were investigated as far as possible, but it was not practicable to include every patient admitted. The clinical assessment of each patient fell into two parts. Firstly, an attempt was made to place the patient into a diagnostic category, employing the criteria outlined by Roth in 1955. In most cases a single diagnosis covered the clinical features of the illness. In a small proportion of cases, however, more than one diagnosis was applicable. The most important cases in this group were those in which functional psychoses of depressive or paraphrenic type were complicated by the development of senile dementia. These cases have been included in the category of senile dements in this report, but they are also being given separate consideration as a "mixed" group of cases. It should perhaps be pointed out that the cases studied *post-mortem* are not a representative sample of the clinical population studied: those dying of acute or chronic physical illness in general hospitals and those dying after the terminal stages of a progressive dementia in mental hospitals are over-represented.

Secondly, an attempt was made to describe in quantitative terms the degree of intellectual and personality deterioration shown by the patient. The first method of quantification was based upon the patient's ability to deal with the practical tasks of everyday life. A list of items relating to competence in personal, domestic and social activities (such as ability to perform household tasks, to cope with small sums of money, to find the way in familiar surroundings) was drawn up, and the patient's ability in respect of each item on the list was ascertained by questioning a close relative or friend about the patient's performance in these tasks during the preceding six months (see Appendix). The six-month period was chosen because it was found long enough to differentiate temporary disabilities due to transient delirious episodes from established defects. The interval was not so long, on the other hand, as to make overall assessments of performance too difficult. Total incompetence in an activity was allocated a score of 1, and partial, variable, or intermittent incapacity was given a score of $\frac{1}{2}$. The dementia score was computed by adding the scores allocated for each item, and could lie between 0 (fully preserved capacity) and +28 (reflecting extreme incapacity). The score was kept up to date as far as possible in patients who survived, by observations recorded by nursing staff on the ward in the period between the original score and the pre-terminal state. This procedure is thus a clinical evaluation made in a consistent manner and expressed in as precise a form as the situation permits.

The second method of quantification was based upon the patient's performance in a number of simple psychological tests of orientation, remote memory, recent memory, and concentration, which have been shown to differentiate groups of demented and non-demented aged persons (Roth and Hopkins, 1953; Shapiro *et al.*, 1956). In this instance a positive score was given for each item scored correctly, and the resulting test score could lie between 0 (complete failure) and +37 (representing full marks in the complete battery).

These tests were introduced after a period of trial in which groups of mentally ill and demented subjects were tested with a battery of standardized tests, such as the various indices derived

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from the WAIS, the Modified Word Learning test and the ART, which have been reported to differentiate reliably between subjects suffering from cerebral disease and normal individuals. It was then found that many subjects who were demented clinically could complete only a small part of the tests, and some were not able to register any score. It was for this reason that the dementia score was introduced, together with brief and simple tests which could be attempted even by many of the very demented patients. The dementia score was also regarded as being of value in providing a measure of competence in performance extending over relatively long stretches of time. There is, however, a substantial group of demented elderly subjects to whom a full battery of tests has been administered; in a proportion of these, pathological inquiries should become possible in the course of time.

Neuropathological Inquiries

The brain was fixed in formol saline for a period of 6–12 weeks. After weighing, the hemispheres were sectioned in the coronal plane at intervals of 8–10 mm. Each coronal slice was carefully examined and ischaemic lesions and other features such as convolutional atrophy and ventricular size noted. The extent and position of all ischaemic lesions were mapped out and drawn to scale on a series of diagrams to correspond with the coronal slices. Lesions due to cerebrovascular disease were found in all clinical groups though in the non-demented subjects these were limited. As this inquiry was mainly concerned with the "senile" type of pathological change, exclusion of cases of dementia considered to be due to unequivocal cerebrovascular disease was attempted with the aid of a quantitative criterion. A cut-off point of infarcted tissue totalling 50 c.c. or more in volume was derived from a separate study of cerebrovascular cases, in which scores for dementia were observed to rise steeply from the range found in normal elderly subjects when the total volume of ischaemic lesions exceeded this figure.

By this criterion, 17 of the 77 cases studied were excluded from this part of the inquiry. In the remaining 60 cases a number of neuropathological changes could be selected for investigation, but of these only one, the formation of senile plaques, lends itself readily to quantification. Twelve samples of cortex, each approximately 3 cm. square, were taken for the counting of senile plaques. From these samples frozen sections of 25μ thickness were cut, and were stained by the von Braunmühl silver impregnation technique. Of the 12 samples taken from each case, two came from each frontal lobe, 2·5 cm. from the frontal pole, two from each occipital lobe, 2·5 cm. from the pole, one from each temporal lobe, 2·5 cm. from the pole, and one from each operculum immediately superior to the temporal sections. These samples included frontal and occipital parasagittal convolutions, the superior, middle and inferior frontal gyri, the calcarine cortex, and the superior, middle and inferior temporal gyri. (The hippocampus and hippocampal cortex were also examined in similar preparations for both plaque counts and Alzheimer's neurofibrillary change, though these plaque counts were not included in the calculation of the mean plaque counts.)

The slides prepared from these frozen sections were examined microscopically under low power to determine whether senile plaques were present or not, and the evenness or otherwise of the distribution of plaques was noted. If the distribution was judged to be even, 5 fields were selected at random (each field being approximately 1·3 mm. in diameter), and the number of plaques was counted in each field. Where the distribution was found to be uneven, the areas with differing density of plaque accumulation were roughly mapped out during screening, and an attempt was made to sample all the areas so plotted for counting purposes. Unevenness in plaque formation was rare in patients with high plaque counts, more common in those with low counts. Five fields were counted in each of 12 sections, giving a total of 60 fields from each brain. The pathological work was carried out without knowledge of the clinical assessments and measures, and the great majority of the counts were made by an experienced technician under the supervision of one of us (B.E.T.). A mean plaque count was calculated for each brain by dividing the total number of plaques counted by the number of fields. Sections with

small and large numbers of plaques are shown in Figs. 1 and 2.

To obtain a measure of the reliability of the plaque-counting procedure an inquiry was conducted under strictly blind conditions. Twelve slides drawn from each of 15 patients studied in the initial inquiry were re-examined by 3 different observers. The mean plaque count in 60 fields was computed by each observer for each case. The results are shown in Table I. Taking the observers in pairs, the correlation between the means so obtained was +0·99 in each case. The correlation between the recount and the original was +0·98. It may be concluded that the mean plaque count has a satisfactory degree of reliability.

Results

A total of 264 patients have been tested, and in 76 of these post-mortem investigations are complete. The findings to be described refer to 60 patients in whom neuropathological investigations have revealed no more than small amounts of cerebral infarction.

Table II shows that the patients with senile dementia registered poorer mean scores on both scales than subjects in all other groups, the difference in each case being statistically significant (Student's *t* test). On psychological testing, patients with delirium occupy an intermediate position between the control group on the one hand and the dements on the other. This accords with expectation, since these patients have functioned well until the onset of their illnesses, in the course of which their performance has been affected by clouding of consciousness. The results are broadly in accord with findings in previous studies (Roth and Hopkins, 1953; Hopkins and Roth, 1953).

Mean Plaque Count and Diagnosis

Plaques were found in all the 12 cases of functional psychosis, and the mean plaque count in this group was 2·75 ± 1·05.* This does not, however, differ significantly from the count recorded in the 8 control subjects, which was 5·13 ± 1·71 (t=1·55, d.f. 19, p<0·2>0·1),

* Owing to the small numbers the usual formula for estimating the standard error was inapplicable. Hence the fiducial limits of the population means were calculated from the formula $m = \bar{x} \pm \frac{st}{\sqrt{N}}$ (where m = the population mean, $\bar{x}$ = the sample mean, s = the standard deviation, of the sample, t the value of t at the selected level of probability, and N = the number of cases in the sample). The level of probability (p=.3) was chosen so as to make the fiducial limits closely comparable to the standard error of the mean. In the case of delirious states, for example, the fiducial limits are given by the figure of 1·2 quoted; twice this figure corresponds exactly to the fiducial limits at a probability of 1 in 20.

Table I

Results of Plaque Count Comparisons on 15 Cases. 12 Slides per Case, 5 Low Power Fields per Slide Counted

Case Number	Original	DK	BET	GB
16	1·9	2·8	2·7	4·4
20	2·5	5·3	5·8	5·6
15	28·7	36·0	36·6	35·7
26	6·0	7·3	7·0	6·9
57	13·2	14·9	13·5	13·4
2	26·8	23·5	25·6	28·7
53	9·5	7·2	8·0	8·3
25	1·6	2·0	1·5	2·1
17	2·7	4·3	3·9	3·6
28	2·4	4·6	4·0	4·9
33	40·8	45·5	41·7	41·5
65	38·5	34·6	32·4	33·9
6	21·4	26·8	27·4	25·3
41	13·0	10·1	14·5	10·4
51	12·3	13·7	13·1	11·9

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TABLE II

Mean Plaque Counts and Mean Dementia and Test Scores in Diagnostic Groups

Diagnostic Groups	No. of Cases	Mean Plaque Counts	Standard Deviation	Mean Dementia Scores	Standard Deviation	Mean Test Scores	Standard Deviation
Senile Dementia	26	20·85	12·17	13·92	5·03	10·5	9·15
Depression	7	1·14	1·22	2·14	1·35	28·6	8·42
Paraphrenia	5	5·00	4·18	2·80	1·64	25·0	6·08
Functional cases combined	12	2·75	3·33	2·42	1·44	27·1	7·45
Delirious States	14	2·64	4·16	2·00	1·71	20·8	8·28
Physically Ill Subjects ("controls")	8	5·13	4·32	2·25	1·75	31·8	4·40
	60						
				0=fully preserved capacity +28=extreme incapacity		+37=fully preserved capacity 0=extreme incapacity	

or from that in the 14 with delirious states, which was 2·64 ± 1·2 (t=0·07, d.f. 25, p< 0·95>0·9). These figures contrast with the mean count of 20·85 ± 0·25 per field recorded in those suffering from senile dementia, which differs to a highly significant degree from that of the functional cases (t=5·03, d.f. 37, p< ·001), as also from the means for the two other groups.

Senile degenerative change is unlikely, therefore, to play any significant part in the development of the "functional" psychoses of old age, although the possibility that it releases pre-existing tendencies to psychiatric disorder in isolated cases is not excluded.

It is of interest that the mean plaque count in patients with unequivocal cerebrovascular disease (0·6) falls at the lower end of the range of means for "control" subjects and functional cases. This finding suggests that there is no causal relationship between the processes responsible for plaque formation and cerebrovascular disease The observation is in accord with those of Arab (1954), Corsellis (1962) and Sjögren *et al.* (1966).

Age in Diagnostic Categories

The mean age of patients in each diagnostic group was greater than 70 (see Table III). Although the functional cases were slightly younger than cases with senile dementia, the age difference was not significant (t=1·82, d.f. 33, p<0·1>0·05). Indeed, none of the groups differed significantly for age. In view of the tendency for plaque counts to increase with increasing age in subjects dying from injury or physical disease (Tomlinson, 1966), the correlation of age with the mean plaque count in this series was examined. The coefficient of correlation was +0·13, which was not significant statistically. Hence the effects of age are presumably overshadowed in this material by the influence of other factors.

The Relationship between Plaque Count and Measures of Intellectual Deterioration

In Fig. 3 mean plaque count has been plotted against dementia score. It reveals a general tendency for functional incapacity to increase as the mean plaque count is increased. The trend appears to be broadly linear, and the extent of the relationship is revealed by a coefficient of correlation of +0·770, which is highly significant statistically (p<·001). In Fig. 4, mean plaque count has been plotted against test score, and a tendency for performance on the test to decline with increasing

TABLE III

Mean Age in Diagnostic Groups

Diagnostic Groups	Number of Cases	Mean Age	Standard Deviation
Senile Dementia	26	78·15	8·17
Physically ill (controls) ..	8	76·88	6·08
Depression	7	71·86	4·14
Paraphrenia	5	75·00	7·58
Functional cases combined ..	12	73·17	5·73
Delirium	14	76·36	8·26

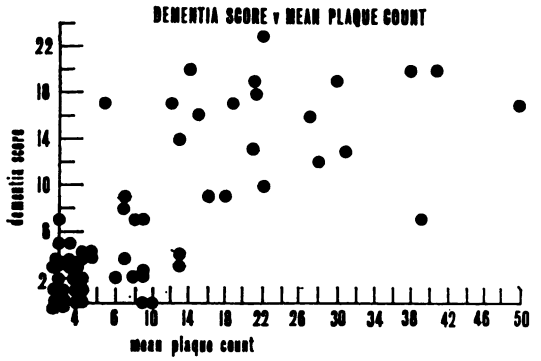

FIG. 3.—Relationship of dementia score to mean plaque count in 60 aged subjects.

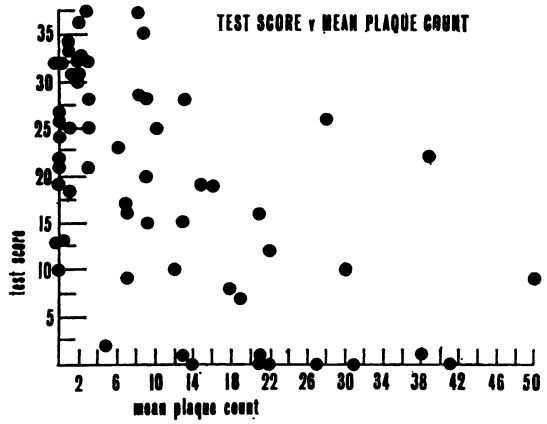

FIG. 4.—Relationship of test score to mean plaque count in 60 aged subjects.

plaque formation is revealed. The correlation coefficient in this case is −0·591, which again is highly significant ($p < \cdot 001$).

The hypothesis that the intensity of plaque formation is closely related to the degree of intellectual deterioration in elderly subjects is upheld. As plaque counts provide only a crude measure of a complex neuropathological process, and as the evaluation of intellectual and personality functioning was also along simple lines, the correlations between the two groups of measurements are very high.

Another way of describing the relationship between mean plaque counts and dementia scores is to examine in greater detail the range in the value of mean plaque counts found in subjects with little or no deterioration on the one hand (dementia scores of less than 4) and more definite and marked deterioration on the other (scores of 4 or more). In the former group (26 cases) no plaques were seen in any part of the cortex in 8 patients, and in a further 5, plaques were extremely scanty, the mean count being less than 1 per field; in 2 of these the mean was 0·2 plaques per field. Six cases showed very few plaques widely scattered, with a mean count of 2 per field or less, and in these subjects more than half the fields examined were completely free from plaque formation. Seven cases showed some plaques in most of the fields counted, with mean counts ranging from 5 to 14, 2 of the patients having counts of 10 to 14. Even in these subjects it was usually possible to find fields containing no plaques at all. Among the 34 subjects with dementia scores of 4 or over, however, 18 had plaque counts of 15 or more, 14 of these having a mean count of 20 or over,

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and 6 a mean count of 30 or more. Three subjects had plaque counts of 10 to 14, and 6 of 5 to 9. Only 7 patients had plaque counts of 3 or less, and in 2 of these no plaques were found in any field. To summarize, 73 per cent. of the group with little or no dementia and only 9 per cent. of the demented group had a mean plaque count of 2 or less. The mean count of the first group is 3·0 and of the second 16·9 per field, the difference being highly significant statistically.

The possibility has to be considered that the very high correlations between plaque counts and measures of dementia are mainly due to the large cluster of individuals with few or no plaques and very low dementia scores in the lower left-hand corner of Fig. 3. These may be normal individuals qualitatively distinct from those at the other extreme of the distribution. In other words, the question raised here is whether correlations between plaque counts and dementia scores would remain significant if the group of 19 subjects with plaque counts of less than 3 and dementia scores of under 4 were excluded. When the correlation coefficient in the remaining 41 subjects was computed, it proved to be 0·64, which is highly significant statistically ($p<\cdot001$). A further test sought to ascertain whether the correlations between plaque counts and dementia scores would remain significant when the markedly demented subjects at the opposite extreme of the distribution, i.e. the 18 subjects with dementia scores of 10 and above in whom dementia was clinically obvious, were excluded. (The correlation coefficient for this excluded group is 0·11, which is not significant statistically.) In the 42 remaining cases with dementia scores of 9 or less the correlation coefficient is highly significant; a proportion of these are clinically demented to a mild or moderate degree.

A similar procedure was followed in relation to the results for test scores and plaque counts. When the small relatively distinct group of cases (14) with a test score of greater than 28 was excluded, the correlation coefficient within the remaining 46 subjects was still highly significant ($r=-0\cdot52$, $p<\cdot001$). Among the 14 cases the correlation coefficient was not significant ($r=+0\cdot216$).

Pathological Differences between Cases with Senile and "Presenile" Dementia and Other Subjects

Finally, attention was directed towards that group of patients in whom a definite diagnosis of senile dementia could be made. It has to be stressed that this "all or none" clinical judgment is relatively crude and subjective. It does not imply that those not judged senile dements lacked all evidence of intellectual deterioration. The subjects regarded as senile dements were those in whom a process of progressive dilapidation of intellectual and personality functioning could be identified on clinical grounds. Twenty-six patients were judged to be in this group. Two of these, aged 69 and 65, could probably be regarded on clinical grounds as examples of Alzheimer's disease, and in two others the progressive dementia had followed a chronic confusional state in a setting of physical disease without interruption. Four of the patients initially presented with a functional psychosis (2 manic depressive and 2 paraphrenic). In each of the last six cases mentioned, when the dementia supervened it was of a gradually progressive type identical in clinical picture with senile dementia.

It is in senile dementia and in the specific forms of presenile dementia that qualitative differences from the normal senium have been claimed by some authors. In the 26 cases that fell into this category the correlation coefficient between dementia score and mean plaque count proved to be $+0\cdot401$, which is statistically significant at the 5 per cent. level; that between test score and mean plaque count is $-0\cdot263$, which is not significant.

Although the trends within this group are in the same direction as in the total group of 60 subjects, there can be no doubt that the correlations between psychological and pathological measures decline sharply as we enter the severely demented group, or those broadly defined as "senile dements". This may be due to the fact that when the degenerative process measured by plaque counts develops beyond a certain threshold point it has already done nearly maximum damage. The possibility that severely demented cases are separated from the rest by

qualitative changes therefore deserves careful examination.

Many of the severely demented subjects did, in fact, have changes which were very rare among those with low dementia scores. These included the fusion of plaques to form large aggregations in which separate elements could not be defined, and the presence of patchy, ill-defined argyrophilic areas of abnormal fibrillary appearance which were too diffuse to be counted as individual plaques. Further, in the severely demented, plaques tended to be distributed throughout the full thickness of the cortex, extending into the deepest cortical layers, whereas among those with low dementia scores they were often confined to the superficial layers. Alzheimer's neurofibrillary change tended also to be generalized in the severely demented, but in the others largely confined to the hippocampus. However, there was every gradation between these two extremes, and the patients within the intermediate ranges in dementia scores fell on the whole between the extremes in relation to depth of cortex affected by plaque formation, the clumping of plaques and other changes. Moreover, there was no one kind of pathological change peculiar to the severely demented individuals; senile plaques, neurofibrillary change, granulovacuolar degeneration were all found to some extent in normal subjects, in patients with functional disorder, and in those with low dementia scores in general. In other words, as far as can be judged with the aid of existing techniques, the differences between the "senile dements" and other subjects reflect a quantitative gradation of a pathological process common in old age, rather than qualitative differences.

However, the possibility that in a proportion of severely demented subjects there are qualitatively distinct pathological changes inaccessible to available techniques of examination cannot be excluded. The possible existence of changes of this nature is implied in the conclusion recently drawn by Larsson *et al.* from their studies of the heredity of senile dementia; they consider that it is determined by a major gene difference, probably a simple Mendelian dominant.

A number of factors may have contributed to the absence of any significant association between plaque count and dementia score among those identified as definite "senile dements" and those with severe grades of dementia in general. In the first place, the technique of plaque counting used takes no account of aggregations of several plaques which were reckoned as one plaque, nor of the neurofibrillary changes and ill-defined argyrophilic areas to which reference has been made. The severity of the pathological process is therefore almost certainly under-estimated in subjects with high plaque counts. The psychological measures that have been used are relatively crude, and it has previously been found that differences in psychological performance among the severely demented group are difficult to define objectively; the distribution of scores tends to cover a very narrow range (Roth and Hopkins). A further point is that patients who have come to *post mortem* are not a representative sample of the population in whom the senile degenerative processes that are the object of this inquiry are taking place. Particularly among patients with severe dementia, those with rapidly progressive forms of illness and those who have reached the terminal stage of their disorder are likely to be over-represented. Cases with less rapidly progressive forms of illness are perhaps less likely to enter hospital, and in any event will survive for a longer period. That dementia scores are negatively correlated with the period of survival is shown in Fig. 5 ($r = -0{\cdot}396$, $p < {\cdot}01$). The small positive correlation between dementia score and plaque count among the senile dements suggests that when degenerative change advances beyond the threshold point for the development of dementia there is some tendency for it to produce further clinically observable deterioration. However, there may well be a point in the degenerative process beyond which the effects on intellectual and personality functioning may be negligible.

In summary, although the existence of changes beyond the reach of our present methods of investigation cannot be wholly excluded, the evidence obtained here is consistent with the view that the process we have measured, albeit imperfectly, with the aid of plaque counts, and the deterioration of intellectual and personality function quantitatively

assessed during life, are closely and causally related to one another over the whole of the range of variation studied.

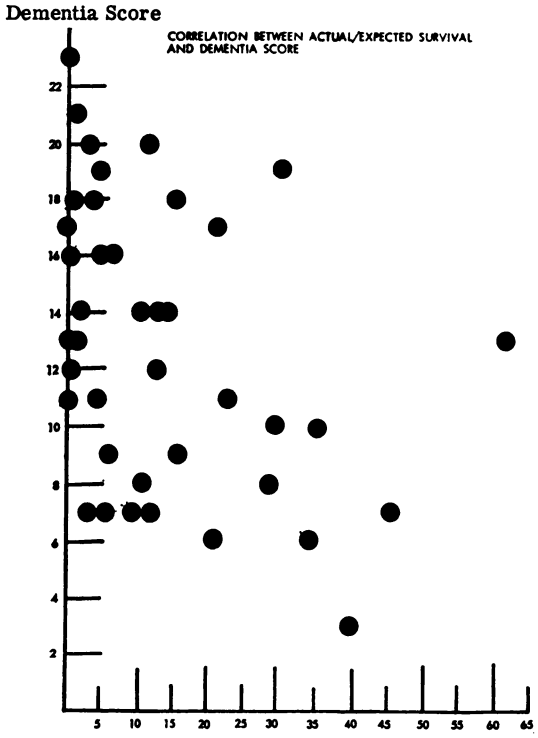

FIG. 5.—Correlation between actual/expected survival in months and dementia score for 40 subjects diagnosed clinically as suffering from senile dementia including the 26 who came to post-mortem.

DISCUSSION

Some possible sources of error. Before evaluating the significance of the results a number of possible sources of error have to be considered. Thus, plaque formation may have been a pre-terminal phenomenon in patients with physical illness of rapid progression. However, most such patients were in the functional or normal groups, and the great majority had low mean plaque counts. A number had carcinomas with secondary deposits, and in others a long-standing metabolic disturbance had preceded death; mean plaque counts were low without exception in these subjects. Although the mean age of the senile dements was greater by four years than that of the remaining subjects, the difference was not significant statistically, nor was there any significant correlation ($r=+0\cdot13$), between chronological age and mean plaque count in this population. Any effect due to chronological age can only have been a very small one. However, in studies of a large number of subjects of all ages coming to *post mortem* in general and psychiatric hospitals a progressive increase in mean plaque count with advancing age beyond 40–50 years was found (Tomlinson, 1966; Newton, 1948). These observations are, incidentally, consistent with a quantitatively graded phenomenon linked in the normal population with ageing.

Some Discrepancies between Psychological and Pathological Measures

Although the association between measures of dementia and mean plaque count was generally close, in a few cases some degree of discrepancy between the two measures was noted. Thus one subject with a dementia score of 17 had a mean plaque count of only 5. In addition to a marked degree of cerebral atrophy, histological examination revealed unusually widespread Alzheimer's neurofibrillary change. In another patient a similar discrepancy was probably explained by the presence in the right temporal lobe of a single infarct which had not declared itself clinically. Infarcts of similar size had also been found in control subjects, but in the presence of low plaque counts. The incomplete association between plaque counts and measures of dementia is, therefore, partly explained by the fact that only one relatively crude index of senile cerebral degeneration has been used in measurement, other cerebral changes being very difficult to quantify at the present time. Another factor is that, although cases with clear-cut cerebrovascular disease were singled out for separate inquiry, and the majority of the patients in the present study had only minimal lesions, plaque counts take no account of these. However, although some degree of overlap between cerebrovascular disease and the degenerative process associated with senile dementia undoubtedly exists, it will be remembered that the mean plaque count in patients with

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unequivocal cerebrovascular disease was almost identical with that in "functional" cases and physically ill subjects. Any overlap is, therefore, presumably due to the fortuitous association of two relatively common disorders.

Variation in the Distribution of Plaques

The significance of variations in the distribution of plaques requires brief comment. In subjects with high plaque counts plaques were invariably distributed in a diffuse manner. In those with low counts, variations in the intensity of plaque formation in different cortical areas were more common, but there was no suggestion from a preliminary analysis that changes in some areas were more closely related to dementia than changes in others. In physically ill controls, plaque formation was often confined to the hippocampal region, an observation also made by Gellerstedt in normal elderly subjects. Test and dementia scores did not suggest intellectual deficits in these subjects, but in view of the evidence linking memory functioning with the hippocampal-fornix-mammillary system (Scoville and Milner, 1957) investigations in a more extensive material to ascertain whether there is any relationship between measures of memory deficit and measures of damage confined to this anatomical system should prove of interest.

Relationship between Plaque Counts and the Psychological Measures

The results of this inquiry appear to support only the second hypothesis formulated in the first part of this paper. There is a very highly significant association between the average number of plaques in cerebral grey matter and measures of intellectual and personality functioning in old age, when cases of unequivocal cerebrovascular disease are omitted from consideration. This suggests that differences between well-preserved, mildly impaired, and unequivocally demented subjects are, as far as can be determined, of a quantitative nature. Further, since there are 6 subjects in whom a dementia score of near to zero (2 or less) was associated with a mean plaque count of 6 or more, it would appear that a certain amount of the change estimated by plaque counts may be accommodated within the reserve capacity of the cerebrum without causing manifest intellectual impairment.

The Possible Effects of Bias

The patients in this study formed a biased sample of the normal population, and the bearing of this fact on the findings must be considered. Since the chance of being sent to hospital for treatment would be increased by the combination of physical with mental disease, a population such as this could be expected to contain an excessive proportion of patients with illnesses complicated in this manner. Among them would be "mixed" cases of mental disorder (Kay, 1962) in whom functional psychiatric disorder had been released by the early stages of cerebral disease. These cases could be expected to blur the distinction between severe and minimal cerebral degenerative disease, since somatic disease might impair behaviour and psychological performance without corresponding cerebral change, while "mixed" cases have cerebral changes with little or no measurable psychological deficit. The correlations between measures of cerebral and psychological change might therefore prove to be even greater in post-mortem material derived from a sample of the normal population than those elicited in the present study of hospital patients. However, although it seems unlikely that the results reported here owe anything to bias in the sample of patients investigated, a population study would be of great interest.

Correlations between Plaque Counts and Psychometric Scores among Senile Dements

The third hypothesis implies a qualification of the second, in that it suggests that severely demented subjects are a distinct population separated from the remainder by some specific pathological process. Although the findings provided little support for this hypothesis, it is not wholly excluded. Plaques may merely provide evidence of neuronal degeneration which might arise from a variety of causes.

The situation is in some respects analogous to that which obtains in relation to mental sub-

normality and essential hypertension. Specific pathological variants analogous to phenylketonuria, epiloia or primary aldosteronism and phaeochromocytoma may await discovery. It is improbable, however, that phenomena of this nature will account for more than a fraction of cases of a disorder as common as senile dementia—one, moreover, for which the morbid risk in the general population shows a rapid increase with advancing age (Larsson *et al.*).

Some General Implications of the Findings

The markedly diminished life expectation of patients in whom a definite diagnosis of senile dementia can be made deserves special consideration (Roth; Kay; Larsson *et al.*). In Kay's inquiry it was shown that the expectation of life of individuals with senile dementia was only one-quarter of that of the population of comparable age. This diminished life expectation of senile dements gives a wider significance to the process of which plaque formation is only one expression. The brain is an organ with a fixed cell population and therefore particularly susceptible to the changes of senescence. Many views have been expressed about the nature and derivation of senile plaques, but their association with the outfall of neurones has long been suspected, and recent electronmicroscopic studies have tended to substantiate this theory. Liss (1960) has stated that plaque formation is always secondary to neuronal degeneration, while the plaques seen in authenticated cases of Alzheimer's disease (and indistinguishable on light microscopy from those investigated in this study) are reported by Kidd (1964) and Terry *et al.* (1964), on the basis of electron microscopic studies, to consist of degenerative nerve cell processes, intercellular amyloid and reactive microglia, and astrocytosis. If the conclusions drawn in this study are valid, the differences between grossly demented, mildly demented, and well-preserved old people may well lie in a different rate of progression of one and the same process assessed, albeit crudely, by plaque counts.

Summary

1. The association between plaque counts in sections of cerebral cortex and measures of intellectual and personality functioning undertaken in elderly subjects during life has been studied.

2. There was no evidence that degenerative changes had contributed significantly to the causation of illness in patients with "functional" psychiatric disorders or delirious states.

3. There is a highly significant correlation between mean plaque counts and scores for dementia and performance in psychological tests. The findings suggest that psychological and pathological indices are closely related to one another, possibly through their common association with the underlying degenerative process in the brain.

4. Among severely demented subjects and those diagnosed clinically as "senile dements", correlations between psychological and pathological measures decline sharply. However, pathological differences between normal, mildly demented, and severely demented subjects appear to be of a quantitative nature. The possibility that there are qualitative differences in this group, inaccessible to present methods of examination, cannot be excluded.

Appendix I

Dementia Scale

Information obtained as far as possible from relative in close and continual contact with patient. Inquiries were directed towards defining changes in capacity, habits and personality. Allowance was made in scoring for physical disabilities that would restrict activities.

Changes in Performance of Everyday Activities

1.	Inability to perform household tasks	1 ½ 0
2.	Inability to cope with small sums of money	1 ½ 0
3.	Inability to remember short list of items, e.g. in shopping	1 ½ 0
4.	Inability to find way about indoors	1 ½ 0
5.	Inability to find way about familiar streets	1 ½ 0
6.	Inability to interpret surroundings (e.g. to recognize whether in hospital, or at home, to discriminate between patients, doctors and nurses, relatives and hospital staff, etc.)	1 ½ 0
7.	Inability to recall recent events (e.g. recent outings, visits of relatives or friends to hospital, etc.)	1 ½ 0
8.	Tendency to dwell in the past	1 ½ 0

Changes in Habits

9. Eating:	
Cleanly with proper utensils	0
Messily with spoon only	2
Simple solids, e.g. biscuits	2
Has to be fed	3
10. Dressing:	
Unaided	0
Occasionally misplaced buttons, etc.	1
Wrong sequence, commonly forgetting items	2
Unable to dress	3
11. Complete sphincter control	0
Occasional wet beds	1
Frequent wet beds	2
Doubly incontinent	3

Changes in Personality, Interests, Drive

No change	0
12. Increased rigidity	1
13. Increased egocentricity	1
14. Impairment of regard for feelings of others	1
15. Coarsening of affect	1
16. Impairment of emotional control, e.g. increased petulance and irritability	1
17. Hilarity in inappropriate situations	1
18. Diminished emotional responsiveness	1
19. Sexual misdemeanour (appearing *de novo* in old age)	1
Interests retained	0
20. Hobbies relinquished	1
21. Diminished initiative or growing apathy	1
22. Purposeless hyperactivity	1
Total	

Information-Memory-Concentration Test

Information Test

Name	1
Age	1
Time (hour)	1
Time of day	1
Day of week	1
Date	1
Month	1
Season	1
Year	1
Place—Name	1
Street	1
Town	1
Type of place (e.g. home, hospital, etc.)	1
Recognition of persons (cleaner, doctor, nurse, patient, relative; any two available)	2

Memory:

(1) personal	
Date of birth	1
Place of birth	1
School attended	1
Occupation	1
Name of sibs or Name of wife	1
Name of any town where patient had worked	1
Name of employers	1
(2) non-personal	
*Date of World War I	1
*Date of World War II	1
Monarch	1
Prime Minister	1
(3) Name and address (5-minute recall) Mr. John Brown 42 West Street Gateshead	5

Concentration

Months of year backwards	2 1 0
Counting 1–20	2 1 0
Counting 20–1	2 1 0

* ½ for approximation within 3 years.

Appendix 2

Depression

Seven patients—five female and two male—were regarded as suffering from depressive illnesses. Both males had psychotic depression with previous attacks responding to E.C.T. Two sibs of one of the patients had similar illnesses.

Only one of the females had undoubted depressive psychosis. Previous attacks had responded to E.C.T. on three occasions and her brother was also a sufferer. The patient in addition suffered from hypertension (250/150), hypertensive heart disease, and a right sided hemiparesis. A second probably had a psychotic depression. There was a positive family history, and she had made a calculated and determined suicidal attempt which indirectly led to her death a few weeks later. Three of the females had non-psychotic illnesses. Two were hypochondriacal, anxious, dependent women who had been depressed on and off for years, the other became depressed after a long and debilitating physical illness.

Delirious States

Patients who had become acutely confused for any reason were placed in this category. Patients who were mentally clear when seen, had no history of confusion, and became clouded only shortly (a day or two) before death were not included in this group. There were 10 males and 4 female patients. Definite physical illness was detected in twelve cases. "Double" pathology was common, but is mentioned

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only when each illness detected could possibly cause confusion in its own right. The illnesses present were:

Intestinal Obstruction	- 2 cases
Gangrene of limb	- 2 cases (1 + pneumonia)
"Strokes"	- 3 cases (1 with uraemia)
Malignant disease	- 2 cases
Retention + Uraemia	- 2 cases
Congestive Cardiac Failure	- 2 cases

This hospital population showed a relatively low incidence of infection, probably because we are dealing here only with those who failed to recover.

Paraphrenia

Three females and two males were placed in this category. Only one of the males was a true late onset paraphrenic, the other having suffered from chronic schizophrenia for 25 years. He was included as he had been seen at the request of the geriatrician and died a few days after being assessed. Two of the females were spinsters—one a life-long eccentric and solitary lady, the other, being the last survivor of a family, had lived alone for eleven years before developing her illness. One female patient was married. She had fairly severe hypertension (B.P. 220/130, controlled on methyldopa and thiazides to 150/70) and was also very deaf.

Cases with Physical Disease and no Mental Abnormality

These were patients who appeared mentally well preserved when seen. Some became confused shortly before they died, and some possibly felt depressed but did not admit to this on the day of assessment. There were six females and two males. Malignant disease was present in half the cases, two died from gangrene of a limb and one each from a stroke and intestinal obstruction.

Senile and Presenile Dementia

Some clinical facts about these cases have already been given on page 804. The diagnosis of Alzheimer's disease made in two of the 26 cases was confirmed in both pathologically. It seemed logical to include them in an enquiry concerned with the relationship between intensity of plaque formation and psychological deficit. In addition to the four cases that had initially presented with a functional psychosis some years previously (page 804), a further case had had successful treatment for a depressive illness in the past. In all of these patients the features indicative of a functional psychosis became progressively more inconspicuous with the progress of dementia.

As was to be expected, some overlap between senile dementia and arteriosclerotic dementia was found in respect of both clinical features and pathological findings. The pathological criterion by means of which the line of demarcation between these two disorders was decided has been described on page 800. Clinically speaking, 8 of the patients had had sharply defined episodes of cerebral dysfunction or other clinical features (e.g. epileptic fits, emotional incontinence, etc.) of an isolated kind that could have suggested arteriosclerotic dementia, had they not been related to the general course of the illness. In 6 of these cases no evidence of ischaemic lesions was found *post mortem*, or else the lesions were minimal in character and of a kind also found in the "control" subjects. The suggestion is that in the presence of senile degenerative change the effect of transient cerebral ischaemia tends to be potentiated. It seems likely also that if attention is concentrated on isolated episodes or symptoms, arteriosclerotic psychosis is liable to be diagnosed to excess. The detailed clinical analysis of this material and the relationships of clinical and pathological findings will be published in full elsewhere.

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