De Senectute

The F. E. Williams Lecture

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My subject is De Senectute. In truth, the title is broad enough to allow me to approach the problems of old age from any angle I choose; but perhaps at this stage I should declare my interest, which at present is a study of the pathological findings of extreme old age. I will not linger long in the realms of classical literature save to say that De Senectute, Cicero's essay on old age, written in 44 BC, has been greeted as the most famous gerontological classic of all time, but which, if accepted in its literal sense, would do little to justify the development of geriatric medicine as a specialty. It displays all the sophistry of the legal mind. Speaking of the so-called ills of old age, Cicero says that with regard to all such complaints the blame rests with character and not with age. 'Senile debility is a characteristic of not all old men but only those who are weak in mind and in will. It is our duty to resist old age, to compensate for its defects by a watchful care, to fight against it as we would fight against disease, to cultivate the principles and the practices of the virtues, for in truth it is their own vices and their own faults that fools charge to old age' (Falconer, 1946). While one could take issue with Cicero on most of these statements there is more of truth in his closing paragraph. 'Again if we are not going to be immortal, nevertheless, it is desirable for a man to be blotted out at his proper time. For as Nature has marked the bounds of everything else so she has marked the bounds of life.' This is truly a remarkable concept in 44 BC, to speak in terms of physiological death at a period when the average life expectancy was no more than 20 years and to predict that nature, in other words hereditary factors, might be concerned in its attainment.

Most workers would agree with Cicero that there is a limit to the human life span but that few if any have ever achieved it. According to Korenchevsky (1961) no human being has yet been identified whose old age, life span and death are physiologically normal. The aged individual is so subject to pathological defects that death as a natural biological phenomenon is as yet beyond his reach. At present, the maximum potential life span in Great Britain is about 113 years. There is reason to believe that this does not represent the ultimate limit but that it is not far short of it. The world record holder for fully authenticated longevity is Pierre Joubert of Quebec, who died in 1814 at the age of 113 years and 110 days and whose records were fully investigated and verified by the Chief Statistician for Canada (Ernest, 1938).

Apart from patriarchal times there are many extravagant claims to great longevity in the literature. In the words of Ernest, there are few topics of human
interest that have been more thoroughly obscured by ignorance and deliberate fraud than the subject of the extreme spans hitherto attained by man. It seems that Ireland shares with Russia the largest number of utterly baseless reports of extremely long-lived persons. For example, in a census in 1901, Ireland claimed to have more than 150 centenarians per million of the population compared with Germany which had less than one per million; with regret I read that the figures published by statistical departments on centenarians are invariably further from the truth the lower the educational standard of the country.

Of all the false claims to extreme longevity the best known is that of Thomas Parr, whose postmortem was conducted by William Harvey. He died in 1635 at the alleged age of 152 years 9 months, and because of his great age was honoured by burial in Westminster Abbey. He lived near Shrewsbury, but shortly before his death he was brought to London for the delight of King Charles I and his Court, and it was said that the change of air, diet and mode of living were too much for the old man and he withered like an uprooted tree. Apparently Parr remained a bachelor till he was 80. At the age of 100 he claimed he did penance for having begotten a bastard child and after the death of his first wife he remarried in his 120th year. It was claimed that Harvey testified to the authenticity of Parr's great age but this was not so. He simply recorded that Parr appeared to be an unusually aged individual. During his terminal illness Parr had been very breathless, and with his heart healthy, as described by Harvey, and the lungs loaded with blood, it is clear he died a respiratory death. Harvey refers to a sudden change in the 'non naturals', the chief mischief being connected with the change of air. 'In London the air is at all times rendered heavy with smoke engendered by the general use of sulfurous coal and fuel, but more so in the autumn than at any other season.' The necropsy was carried out in November and so it would appear that Parr was a victim of the London smog, but far be it from Harvey to state the simple truth. 'With the exposure of Parr to such an alien atmosphere,' he said,

'it must needs fall out that the functions of all the natural organs would become deranged, whence the stomach at length failing and the excretions long retained, the work of concoction proceeding languidly, the liver getting loaded, the blood stagnating in the veins, the spirits frozen, the heart the source of life oppressed, the lungs infarcted and made impervious to the ambient air, the general habit rendered more compact, so that it could no longer exhale or perspire — no wonder that the soul, little content with such a prison took its flight' (Willis, 1841).

In spite of the belief that Parr was an imposter, Old Parr's Life Pills, compounded upon a secret recipe obtained from one of his descendants, had a great popularity among the poorer classes for quite some time.

There are other interesting records of postmortem studies on allegedly very aged subjects; for example, that of John Bayles, the button-maker from Northampton, reputedly 130 years old at his death in 1703. Dr Kiell (1706), who performed the necropsy, had no doubt that the weakness of his stomach and the
hardness of his arteries were the causes of his death. He concluded that to bring a man to a full old age the essential requirements are a due conformation of all the vital parts, a healthy heart, a large chest and good lungs; and he added, 'with regard to giving rules for preventing the ill consequences of extreme old age, we can be certain only by dissections of old persons and these are not numerous enough to ground anything certain upon'.

A necropsy noteworthy for its meticulous detail was that in 1862 by Dr George Rolleston (1884) on John Pratt, reputedly 107 years old. He recorded the weather conditions at the time of examination as clear, not close. He noted the growth of the beard after death, the solitary surviving right upper canine tooth and the furfuraceous tongue. He allocated three pages of small print to the description of the skull and its contents. He even examined the tissues microscopically, noting the amylaceous bodies in the brain and the lipochrome pigment in the heart, and, failing to find spermatogenesis, promoted a philosophic discussion on the significance of spermatogenic activity in the aged. Yet he apologised for many omissions, including inadvertently forgetting to weigh the pancreas.

Coming to modern times it is apparent that studies in the morbid anatomy of old age are still scanty. In Germany, Aschoff (1937, 1938) provided detailed analysis of the pathological findings in old age and claimed that in his entire career he had not seen a natural or physiological death. In England, pioneers in this field were Piggot and Howell, but they commented on the lack of study of the pathology of old age (Howell and Piggot, 1951).

It might be appropriate to consider whether the necropsy has a significant role to play in the advancement of modern medicine, and particularly in the realm of geriatrics, where often the problem is to explain the survival of the patient against great odds rather than his demise. The purpose of a necropsy is fourfold. Firstly, to increase our knowledge of disease; most of our information in the past has been derived from this source. Secondly, to educate both the undergraduate and the practising physician. In this connection there are still pathologists who believe that their subject is the scientific basis of medicine. Thirdly, to facilitate research — and against what better background than a study of disease in relation to the individual patient? Fourthly, above all to ensure the highest standard of patient care. Despite the remarkable new investigative and diagnostic techniques that can now be applied to the living patient, the necropsy remains the final moment of truth for all medical care. Even today a significant margin of error exists between pre- and postmortem diagnosis. So long as this is the case there is no room for complacency, even where the aged are concerned. The multiplicity of disease processes in the elderly is constantly stressed; and where better can one assess the relative importance of each in contributing to the death of the patient than in the postmortem room? A study of the absence of certain diseases in old age is equally important and should throw light on their pathogenesis and possible prevention.

While commending the value of postmortem examination, one is only too well
aware of its deficiencies as at present practised. Where a low standard exists it is often the result of increasing work load, shortage of manpower, and perhaps lack of interest at the clinical as well as the pathological level. Our aim should be to improve the quality of postmortem examination and this may be achieved by ensuring close collaboration with the clinician — and the pathologist is often only as good as the clinician who drives him — by extending our observations beyond the purely morphological, and by applying new techniques as they become available. Only thus will the necropsy continue to fulfil its proper role in medical education, patient care and research.

After this eulogy I hesitate to present my own findings in a series of 100 patients, dying over the age of 90. I am only too conscious of the inadequacies of the study, and of the danger of drawing conclusions from a hospital series of cases where the broad spectrum of disease in the aged may not be fully represented. Nevertheless, the findings may reflect in this group certain features of disease that may interest the clinician.

The cases were derived from two general teaching hospitals, one with a geriatric department, under the care of Professor Adams. They comprised 60 women and 40 men, the sex incidence illustrating the usual female predominance at this time of life. Ten patients were over 95 years, one being aged 100 years and the oldest 110½ years. Acceptable documentary proof of the oldest person's age was produced for her 100th birthday and she remained in hospital thereafter. Seventy-four per cent were short-term hospital admissions (under one month), and in only 12 per cent was the period of hospitalisation longer than one year. At the outset it must be stressed that the multiplicity of pathological lesions in each patient was impressive, there being very few with less than five major pathological diagnoses. Their precise role in contributing to death was not always easy to define, but in the vast majority there was a definite cause of death. These are summarised in Table 1. It would not be possible to deal with all these groups adequately so I will summarise the main findings, and then concentrate on the lesions found in the heart and brain which may be of more general interest.

| Table 1. Causes of death. |
|---------------------------|
| Cardiac disease           | 23 |
| Trauma                    | 16 |
| Malignancy                | 13 |
| Cerebral disease          | 12 |
| Alimentary tract disease  | 9  |
| Pulmonary infection       | 7  |
| Biliary tract disease     | 6  |
| Urinary tract disease     | 5  |
| Miscellaneous             | 9  |
| **Total**                 | 100|
Trauma was an important cause of death, accounting for 16 per cent mortality and often occurring against a background of cerebral vascular insufficiency or general frailty or debility. Falls were the major cause of accident, 6 occurring at home and 3 in hospital. Three patients were involved in road accidents, and 2 died from severe burns. Of 9 who suffered fractures, fat embolism occurred in 4. In one it was the immediate cause of death and was of such severity that almost every capillary in the lung and even in the heart was blocked with fat. Two patients died from subdural haemorrhage. One had a history of drop attacks but her terminal coma was attributed to an intracerebral vascular lesion rather than a subdural haemorrhage. In the other patient there was no definite history of injury but this could have been overlooked as she was an old hemiplegic living alone.

Malignancy accounted for 13 per cent of deaths. The sites of the tumours are recorded in Table 2. One patient with lymphosarcoma presented with prostatic enlargement due to infiltration of the gland. A correct clinical diagnosis was made in 6 cases but, as most of the patients with malignancy were admitted in the terminal stages, it was impossible to draw any conclusions about supposedly insidious onset and slow progression of tumours in this age group, except to point out that the discovery of a further 11 incidental malignancies might support this view; these were latent carcinomas of the lung, stomach, kidney and prostate. There were 4 prostatic carcinomas, 3 focal in nature and 1 diffuse, but the latter patient died from a fractured skull following a road accident and it is uncertain if there were any symptoms related to his tumour. There were many benign tumours, including 2 menigiomas, 6 pituitary adenomas, 4 uterine fibroids, 2 thecomas and 1 bronchial adenoma. The total incidence of malignant tumours was 23 per cent which is almost as high as is noted in younger geriatric groups and, indeed, if one calculates the age-specific death rate for malignant disease in this age group, it has been shown to be very much higher than in earlier decades (McHugh and Taylor, 1965).

| Carcinoma (primary site) | Number of cases |
|-------------------------|----------------|
| Stomach                 | 3              |
| Caecum                  | 1              |
| Colon                   | 2              |
| Rectum                  | 2              |
| Gall bladder            | 2              |
| Vulva                   | 1              |
| Thyroid                 | 1              |
| Lymphosarcoma           | 1              |
| **Total**               | **13**         |
Alimentary tract disease, exclusive of malignancy, caused death in 9 patients, 3 dying from complications of hiatus hernia, 3 from chronic peptic ulcer with haemorrhage, and 3 from intestinal obstruction due to diverticulitis, inguinal hernia and a Meckel's diverticulum.

Pulmonary infection caused 7 per cent of deaths. This low incidence may seem surprising but in these patients pneumonia was the main cause of death and included examples of lobar pneumonia. On the other hand, the overall incidence of pneumonia where it was regarded as a terminating event in association with other major diseases was 51 per cent.

Biliary tract disease (6 per cent mortality), apart from two patients with carcinoma of the gall bladder, was related entirely to the presence of gall-stones and their complications — cholecystitis, stones in the common bile duct and cholangitis. The overall incidence of gallstones was high at 21 per cent.

Urinary tract disease (5 per cent mortality) was remarkably unimportant. Three patients died following prostatectomy and 2 had acute pyelonephritis, one in a horseshoe-shaped kidney.

Miscellaneous cases included examples of pancreatitis, pernicious anaemia, diabetic coma, gangrene, and ruptured abdominal aneurysm. There was one remarkable case, a female patient aged 98 with hemiplegia and a discharging sinus in the neck from which she developed miliary tuberculosis complicated by a tuberculous coronary arteritis that precipitated her death.

CARDIOVASCULAR SYSTEM

It should be emphasised that when heart failure was present in these aged patients the difficulty was not in discovering the cause but in deciding which of several lesions present in the heart contributed most. Indeed, there was no case in which some cause could not be identified. However, even if it is impossible to discover the basis for heart failure, the use of the term senile cardiomyopathy is to be avoided, for the pathologist is only too well aware of the limitations of current histological techniques to suggest that senile or involutional changes alone are a possible cause of decompensation.

The weights of the heart are shown in Fig. 1. If the upper limit of normal is accepted as 300 g in females and 400 g in males, 80 per cent of the female hearts were above this figure and 48 per cent of the male. In all, 64 per cent of hearts weighed more than normal, a figure that merely reflects the high incidence of cardiac abnormalities in this group. The smallest heart (150 g) was in a grossly emaciated female and, while it is generally accepted that in the absence of cardiac disease reduction in heart weight parallels loss of body weight and, in particular, reduction in the mass of skeletal muscle, there were many exceptions where normal or overweight hearts were found in severely emaciated individuals. The heaviest heart was 750 g, in a 91-year-old male with cardiac amyloidosis. With regard to the role of hypertension as a cause of cardiac enlargement it was possible to confirm the clinical impression that significant elevation of the blood pressure
is rare in extreme old age. Accepting the most generous upper limit of normality that is recommended, 210/110, only 3 patients (2M:1F) had blood pressure readings at or slightly above this level. Apart from minimal left ventricular hypertrophy and coronary sclerosis, 30 per cent of hearts were accepted as normal. In the remainder, multiple lesions were exceedingly common. The causes of cardiac failure are shown in Table 3.

| Causes of heart failure                  | % mortality |
|-----------------------------------------|-------------|
| Myocardial infarction                   | 13 (24)*    |
| Calcific aortic stenosis                | 2 (6)       |
| Amyloidosis                             | 2 (20)      |
| Rheumatic disease                       | 2 (3)       |
| Calcification mitral ring               | 1 (27)      |
| Aortic incompetence                     | 1 (3)       |
| Hyperthyroidism                         | 1           |
| Anaemia                                 | 1           |

* Figures in brackets represent total incidence

**Coronary disease.** Coronary atheroma, moderate to severe, was found in 75 per cent of patients. In 21 per cent it was mild, and in 4 per cent it was absent. Some workers have suggested that the absence of severe coronary atheroma is a prerequisite to the attainment of old age but these figures would not support this view. There were 13 fatal cases of coronary disease, which is exactly the same incidence as found in a much larger series in the 70 to 90 age group (McKeown, 1965). Seven patients died with recent episodes. Of these, 3 had a classical presentation with chest pain, 2 had severe dyspnoea, one had abdominal pain diagnosed as cholecystitis, and one had a silent lesion following a fracture. It is
often stated that in the very aged actual coronary thrombosis is rare and that infarction results from severe atheroma alone but in these 7 cases a thrombotic occlusion was found in 5, which is as high an incidence as in much younger age groups. Rupture of the heart is one complication believed to increase in frequency with age and it occurred in one patient in this series. It was an unusual case, a male of 94, with an infarct correctly diagnosed on admission. Seven days later severe chest pain recurred, a mitral systolic murmur was heard and he deteriorated rapidly. At necropsy not only had the left ventricle ruptured but also a papillary muscle (Fig. 2). In the other six fatal cases healed infarcts were present, one with a large ventricular aneurysm. Two of these patients had heart block, one requiring a pace-maker. In all six there was evidence of congestive failure, but contributory causes of death were pulmonary embolism and broncho-pneumonia. In all those with healed infarcts, including an additional 11 in whom the lesions were incidental, a definite history of a previous coronary episode was elicited in only one.

Valvular disease is the most common of all the lesions found in the ageing

Fig. 2. Heart showing recent infarct, with ruptured papillary muscle. There was also a haemopericardium due to left ventricular rupture.
Mitral valve ring calcification occurred in 27 patients (23F: 4M) and in one it caused heart failure. The incidence of this lesion is known to increase in frequency with age and to show a female sex preponderance. The calcium is laid down in the ring itself rather than in the cusps (Fig. 3). It is generally of no functional significance beyond giving rise to an apical systolic murmur, but with increasing severity it interferes with systolic contraction of the ring and may distort the posterior cusp, causing incompetence, or convert the cusp into a rigid shelf which causes some degree of stenosis. Extension of the calcium from the mitral annulus in the direction of the conducting system can cause heart block and this was the basis for heart failure in the one fatal case. Its increasing frequency with age suggests that it may result from some degenerative process comparable to arteriosclerosis, or represents a wear and tear phenomenon, but its predominance in the female sex and its occurrence in younger males suffering from hepatic cirrhosis have raised the possibility of other factors, perhaps hormonal, influencing its evolution (Pomerance, 1968).

Fig. 3. Heart showing extensive calcification of mitral valve ring.
Aortic valve sclerosis with or without calcification occurred in 21 patients (12F : 9M) and was combined with mitral valve ring calcification in 8. In a further 6 patients it was of such severity as to give rise to calcific aortic stenosis which caused heart failure in 2. In most cases the condition is little more than the deposition of small nodules of calcium on the outflow surface of slightly sclerotic aortic cusps, resulting perhaps in a little rigidity of the leaflets, but no significant obstruction, being accountable nevertheless for an ejection type murmur often noted clinically. In the cases with calcific stenosis large deposits of calcium are laid down in the sinus pockets as well as in the leaflets, and it seems reasonable to assume that this represents a more advanced stage of the minor degrees of calcification present in the majority of cases (Fig. 4). The aetiology of calcific stenosis in old age is hotly disputed, rheumatic, congenital and degenerative factors being considered, but, in the absence of commissural adhesion, which is to be expected in rheumatic valvular disease, and the recognition of a bicuspid deformity in congenital cases, experience of the disease in the over-90 age group would support a degenerative basis in the vast majority at this time of life.

Rheumatic heart disease was found in 3 necropsies; in 2 it was a basis for heart failure and in 1 it was an incidental finding. Mitral incompetence with fibrillation was the presentation in one patient, and in the second there was mitral incompetence with tricuspid stenosis, and gross cardiac failure. The survival to advanced age of occasional patients with evidence of rheumatic heart disease is
not unusual. Its occurrence merely reflects the great prevalence of rheumatic fever during the youth of these elderly patients. In most who survive to old age a relatively benign involvement might be expected, but this is not necessarily the case, for the onset of failure in any age group with rheumatic heart disease is not as closely correlated with the degree of valvular damage as might be anticipated. That rheumatic heart disease is so well tolerated in old age has been attributed to the decline in cardiac output, but no doubt other factors, including a good coronary circulation, play a role as well.

*Isolated aortic incompetence* due to medial degeneration is a relatively recently recognised valvular lesion in old age. There were 3 cases in this series and in one it was the only detectable basis for heart failure. The aortic valve ring and proximal aorta undergo moderate dilatation due to degeneration of the elastic and muscle elements in the aortic media, and the change is similar to Erdheim’s cystic medionecrosis which predisposes to dissecting aneurysm in younger individuals. Although it is not often of functional significance its highest incidence is in the tenth decade (Bedford and Caird, 1960).

There was one example of the floppy valve syndrome or ballooning of the mitral cusps. It is a lesion that is rarely seen except in the elderly and is associated with mucoid degeneration of the normally dense fibrosa of the valve leaflets. The cusps assume a parachute-like form and may prolapse into the atrium in systole, with incompetence, but the lesion is asymptomatic in most and was well tolerated in the present case.

*Cardiac amyloidosis* was present in 20 cases (13M: 7F) and in 2 patients, one with heart block, it was responsible for cardiac failure and death. A third patient was also in failure but he died from the effects of prostatic obstruction. His heart was the heaviest in the series (750 g). In the 17 patients in whom amyloid was an incidental finding it was often associated with ischaemic heart disease, or aortic valve or mitral valve ring calcification. Senile cardiac amyloidosis is a subject that has received a great deal of attention in recent publications. Pomerance (1965) found it in 10 per cent of hearts in the ninth decade and in 50 per cent in the tenth decade. So prevalent is it that she thinks it should always be considered in the aetiology of obscure heart failure in the aged. The 20 per cent incidence in this series is not quite so impressive but it may naturally be higher in groups where it is being specifically studied. Nevertheless, if the amounts present are likely to be of any functional significance, the condition should be readily identified in routine histological examination of the heart. Cardiac amyloid may be recognisable macroscopically by enlargement of the heart with thickening of the ventricles and rigidity of their walls, especially of the atria which lose their normal pliability (Fig. 5). Endocardial nodules, 1 to 2 mm in size, may or may not be present. It can readily be identified in routine haematoxylin and eosin preparations but special stains, such as methyl violet and congo red, may be used, and the material gives a yellow fluorescence with ultraviolet light after treatment with thioflavin T. All these methods were applied to the cases in the present
study. The deposits encircle individual muscle fibres which become atrophic and, as they increase in amount, cause considerable devastation of the myocardium (Fig. 6). Vascular involvement with associated ischaemic change contributes to the myocardial damage. Pulmonary vascular amyloid is a common accompaniment, being present in 25 per cent of cases in this series, but unfortunately the distribution is otherwise generally limited and the usual biopsy sites are rarely affected, so that clinical diagnosis is virtually impossible. The ECG changes are quite non-specific. Recently it has been reported that the alkaline phosphatase may be inexplicably raised and this has been recommended as being possibly of some diagnostic value (Hodkinson and Pomerance, 1974). Digitalis sensitivity has also been noted in several cases (Pomerance, 1965).

For a long time cardiac amyloid has been regarded as representing the primary or idiopathic form with no known predisposing factor, but there is considerable interest in inherited types of the disease occurring in different parts of the world, in some areas in a cardiopathic form (Frederiksen et al., 1962). Accordingly, the
suggestion has been made and is gaining acceptance that amyloid disease may be genetically determined and, therefore, that the elderly who suffer from it may be sporadic examples of the inherited form. If this is so, cardiac amyloidosis may be regarded as an expression of an inborn error of metabolism with some biochemical mutation-induced aberration affecting the structure of the fibrous proteins (Gafni et al., 1964).

CENTRAL NERVOUS SYSTEM

Certain changes in the brain are so frequently present in old age that they have come to be regarded as morphological expressions of ageing. However, as some of these changes occasionally occur prematurely and in association with certain disease states and may yet prove to have a pathological background, it is probably more correct to interpret them as changes occurring with age rather than due to ageing.

There is general agreement that there is reduction in weight of the brain in old
In this series, 75 per cent of brains were below the normal average of 1250 g. The smallest was 900 g. There was only a loose correlation with reduction in body weight and none with the degree of cerebral atheroma. A mild degree of dilatation of the ventricular system was often noted; nerve cell loss, believed to be an accompaniment of ageing, was difficult to assess in routine histological examination but could be suspected because of the accompanying gliosis. This is one change that might be challenged as due to age alone as it would be difficult to exclude the possibility that the reduction in cerebral blood flow that occurs with age did not play a contributory role. Accumulation of lipochrome pigment was constantly present in the nerve cells and, although occupying a large part of the cytoplasm, it is stated to be compatible with normal function. Perivascular atrophy with loss of parenchyma around the blood vessels (état criblé) was frequently noted and reflected the degree of cerebral atrophy. Senile plaques and neurofibrillary tangles within the nerve cells are other changes that are believed to increase in frequency with age. The plaques are peculiar argyrophil structures best seen in the frontal cortex and cornu ammonis. They are 50 to 80 μ in size and often have a central core with a halo of silver staining fibrils (Fig. 7). The tangles occur within the nerve cells as fibres heavily impregnated with silver and are probably separate from the normal intracellular neurofibrils (Fig. 8). With the electron microscope the nucleus of the plaques frequently contains fibrils that resemble amyloid but the neurofibrillary tangles do not. It is therefore uncertain how closely they are related to each other in their development, and their exact

Fig. 7. Senile plaque, with central core and surrounding fibrils showing argyrophilia (von Braunmüller x 430).

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Table 4. Incidence of senile plaques and intracellular neurofibrillary tangles.

| Percentage incidence of plaques and tangles |
|---------------------------------------------|
| Senile plaques and tangles                  | 78            |
| Tangles only                                | 3             |
| No plaques, no tangles                      | 19            |

nature has yet to be clarified. The incidence of these lesions is shown in Table 4.

It is interesting that they were absent in the oldest patient of the series. Although so frequently present in old age, an argument against the specificity of these lesions as evidence of ageing is their association with definite pathological states such as Alzheimer’s disease and senile dementia, where they occur in great abundance, and with tangles, where they are particularly numerous, especially in the cornu ammonis (Dayan, 1970). It is believed that it is this very profusion that distinguishes these pathological states from the ageing process where, it is claimed, they are more sparse. However, the problem of interpretation of their significance was illustrated by three cases in the present series where plaques and tangles were present in large numbers; one patient had a clinical diagnosis of senile dementia, a second had some degree of cerebral incompetence in the absence of significant vascular disease, and a third had been in excellent health till his death from trauma. Perhaps an explanation lies in the individual’s response to degenerative

Fig. 8. Neurofibrillary tangles in nerve cells in cornu ammonis (von Braunmühl × 260).
change, bearing in mind that a degree of degeneration that produces dementia in one person may be well tolerated by another.

Vascular changes in the brain with advancing age are not very clearly defined. Reduplication of the internal elastic lamina was the most consistent arterial change found and in the intracerebral arteries down to vessels of arteriolar size some degree of medial fibrosis was common but to what extent this is purely an age change is not clear. In the globus pallidus and to a lesser extent elsewhere a peculiar impregnation of arterial walls with iron is sometimes found, pallidal siderosis. It is accepted as characteristic of ageing and of no functional significance, but it was present in only 15 per cent of this series.

In presenting the findings in the over-90 age group it should be emphasised that for many reasons, and in particular the small size of the sample examined, it would be unwise to draw any conclusions about the true incidence or range of pathological lesions in the brain of the aged, but, if the results do nothing more, they illustrate the difficulties inherent in full examination of the nervous system and in interpretation of the findings in this age group. In the ideal situation the pathologist should have a clear indication of the cerebral status of the patient prior to death. This is sometimes not possible through no fault of the clinician. In this series there was clinical evidence of cerebral incompetence in 34 per cent. Twenty-three per cent were described as in good health till their terminal illness, but in 43 per cent, many of whom were short-stay terminal patients, among them surgical emergencies or traumatic cases, there was little information about the pre-admission state. Furthermore, when there is evidence of organic brain disease it is of the utmost importance in this age group, who are subject to multiple pathological conditions, to give due consideration to all those extracranial systemic factors that may affect the cardiac output or alter the composition or quality of the circulating blood. Furthermore, having narrowed down the problem to one of cerebral vascular disease, its study is incomplete in the absence of examination of the extracranial caroticovertebral system of vessels. This is a very time-consuming procedure and is not possible in routine hospital pathology. It was carried out in only two cases in this series. It entails removal of the aorta with the great vessels and the cervical spine in one block, followed by angiography and dissection. Following dissection the extracranial vessels are sectioned transversely, their patency is further studied and blocks taken for histology. Similarly, the intracranial vessels are injected, X-rayed, cleared and dissected. The sites of occlusion and corresponding areas of infarction are demonstrated in one of the two cases examined by this method (Fig. 9). Taking all these factors into account it is apparent that the study of the brain as routinely carried out postmortem is of limited value in the interpretation of the pathogenesis of the various types of vascular lesion that may be found.

In the current series, eight brains could be described as normal, showing no cerebral atheroma, no plaques or tangles, no parenchymal or deep vessel change. The incidence of atheroma is as shown in Table 5. The findings confirm the
increasing frequency and severity of cerebral atheroma with advancing age and there is no evidence to indicate that survival to extreme old age is in any way dependent on a resistance to its development. The results with respect to cerebral vascular accidents are summarised in Table 6. In eight patients the infarcts were multiple. The most frequent site was the basal ganglia, but cortical, pontine and cerebellar infarcts were also found. They were clinically silent in 7 cases, including the oldest patient who had a recent occipital lesion. The remainder had signs of some neurological deficit. In all patients with infarcts there was moderate to severe atheroma of the intracranial vessels. There was no reason to suspect that

Table 5. Incidence of cerebral atheroma.

| Degree of atheroma | Incidence (%) in over-90 age group | Incidence (%) in 70-90 age group |
|--------------------|-----------------------------------|---------------------------------|
| Moderate to severe | 58                                | 22                              |
| Slight             | 23                                | 43                              |
| Absent             | 19                                | 35                              |
embolism was a factor in any case. In one patient the development of a minor stroke coincided with the onset of a myocardial infarct and was presumably due to a hypotensive episode.

The cerebral haemorrhage occurred in a female aged 90 with a history of sudden collapse and a fall which resulted in a fracture of the skull. With a heart weight of 650 g due to gross left ventricular hypertrophy it is more likely that the lesion had a hypertensive rather than a traumatic origin. The ruptured aneurysm was in a female aged 96, rupture occurring in the intracavernous course of the internal carotid artery. The patient was recovering from a coronary thrombosis in hospital when she suddenly developed proptosis and a pulsating exophthalmos. Ligature of the vessel was carried out but she deteriorated and died.

Histological examination of the brain was carried out in all cases, and, apart from confirming the presence of infarcts and recognising the changes which have already been discussed as possibly related to the ageing process, there were other parenchymal and vascular changes observed that undoubtedly make a contribution to the neuropathology of old age. They are listed in Table 7.

### Table 7. Range of cerebral vascular lesions, mostly at the microscopic level.

| Nature of lesion           | % Incidence |
|----------------------------|-------------|
| Small softenings           | 21          |
| Sclerosis deep vessels     | 45          |
| Arteriolosclerosis         | 12          |
| Capillary fibrosis         | 10          |

The small softenings ranged from recent necroses of microscopic size consisting of collections of compound granular corpuscles to larger necroses just recognisable macroscopically. Older lesions were represented by cystic micro-infarcts or larger lacunar lesions. Such lesions were clinically silent, a cause of minor strokes, or even of hemiplegia. When lacunar lesions occur in younger age groups there is a very close association with hypertension, but in the aged, and in this group in
particular, no such relationship existed. Their multiplicity and small size suggested that disease of nearby intracerebral vessels played an important role in their genesis and when serial sections were prepared it was usually possible to demonstrate some degree of arterial disease in their vicinity. Hyaline fibrosis of the arterial walls was almost constantly present and with recent necroses in the parenchyma thrombotic occlusion was often found. Other vessels showed fibrinoid necrosis with or without thrombosis, and in older lesions vessels were recanalised. Aneurysmal dilatation comparable to the Charcot Bouchard aneurysms of cerebral haemorrhage was also often a feature. Although these deep vessel changes were generally accompanied by atheroma of the circle of Willis the lesion itself is not atheromatous, for the main degenerative process is in the media.

Hyaline arteriolosclerosis was found in 12 per cent of brains, mainly in pial and cortical vessels. Although this is the hall-mark of hypertension in the kidneys in younger age groups, there is a much less close association when it occurs in the aged brain. In no case in the present series could it be claimed to be the sole organic basis for any neurological disturbance but its cortical distribution and the small linear softenings associated with it may combine to produce a clinical picture that is distinctive, with a gradual onset of progressive mental change and only minor recurring apoplectiform attacks rather than major strokes. Finally, at the capillary level, sclerosis was found in 10 per cent, mainly in the cortical zone. This is a change that is believed to increase with age but it is rather inconstant in its development and could have pathological effects in that it might interfere with oxygen transfer to the nerve cells and in a minor way contribute to neuronal degeneration.

It is evident that much of the neuropathology of old age is attributable to disease of the cerebral blood vessels and that in its assessment one must consider the influence of lesions at all levels of the vascular tree, from the origin of the great vessels right down to the capillary level. It must not be forgotten that it is often the reserve capacity of the collateral circulation that has an important mediating influence on the effects of occlusive vascular disease at any level.

CONCLUSIONS
From this survey of some of the postmortem findings in the over-90 age group it has been found that the main causes of death are circulatory disorders, trauma and malignancy. It cannot be claimed that these findings have much statistical significance and accurately reflect the incidence of fatal disease in the age group as a whole. Nevertheless, in the few comparable studies that are available, the picture is very much the same. The results as presented take no account of the many
conditions, degenerative or otherwise, that contribute to a great deal of chronic disability in the very elderly and are an integral part of the total pathology of old age.

Individuals who survive to extreme old age are often referred to as the biologically élite, the supernormals, the physical aristocracy of old age, as if they were a unique group who were born physically stronger and better endowed than their shorter-lived brethren, and some studies have shown that throughout their life they have had significantly fewer illnesses and less hospitalisation than younger geriatric patients (Pritchard, 1967). Whether their long survival is attributable to chance alone dictating their freedom from major illnesses, perhaps combined with environmental factors, or whether hereditary influences are of prime importance is not clear. Longevity often shows a familial incidence but as yet there is no known gene shown to be directly associated with it. Evidence would suggest that it is very often the short life with the attendant diseases that commonly cause premature death that may be capable of genetic selection. Yet in considering the actual causes of death in the aged they are not very different from those found in younger geriatric groups. The increasing role of trauma is a distinctive feature, and perhaps the frequency with which major illnesses are terminated by respiratory tract infection. The degenerative vascular disorders dominate the pathological if not the clinical picture. What is so essentially different about pathological processes in this age group is their clinical expression which is so frequently modified in symptomatology and physical findings. This is one of the outstanding characteristics of disease in this age group and is only too familiar to every geriatrician.

Apart from identifying causes of death, this study fully confirms the multiplicity of disease processes in old age, some unrelated to each other, others interrelated, some combining to cause death, others being merely incidental. These diseases are often superimposed on a background of a more general process of deterioration related to the involutionary changes associated with ageing and which, it is claimed, increase the vulnerability of the elderly patient to disease, lowering the lethal threshold for disorders that would have been of less consequence in younger age groups. However, since age changes alone are poorly defined and variable in their time of onset — and indeed there is doubt as to what extent they are uncomplicated expressions of senescence — their influence on the evolution of disease is far from clear.

Another feature of the diseases of extreme old age is their insidious onset and often silent progression. This is what makes their recognition so difficult and their treatment often ineffective. The question of the prevention of the common killing disorders rarely arises, for the geriatrician is merely dealing with their terminal stages. In particular, onset of the degenerative vascular disorders dates from adult life or even earlier and with their relentless progression it is clear that their effective control will rest not only in their early detection but in the anticipation of their onset.
What of the future? If we believe that no one is ill merely because he is old, that old age need not necessarily be a period of physical and mental decline, and these are statements that constantly appear in geriatric literature, then we are accepting the challenge that ultimately it may be possible not only to alleviate but to eliminate many of the diseases of old age, and every advance that is made brings us nearer to the time when man may yet achieve a natural biological death. No matter how unattainable this goal may now seem, and to the geriatrician in his daily round it must seem very remote, we must work towards this end hoping that the day may not be too far distant 'When man shall come to his grave, in a full age. Like as a shock of corn cometh in, in his season.'

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