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Genetics, Ageing and Dementia

A. F. WRIGHT and L. J. WHALLEY

Summary: The contribution of genetic differences to variation in ageing and the relationship of ageing to certain types of dementia are discussed. Neuropathological changes commonly found in the ageing brain are present in more severe form in Alzheimer-type dementia, Down's syndrome, multi-infarct dementia, and a substantial number of patients with Parkinson's disease. An increased frequency of ageing-associated changes outside the brain have been reported in Alzheimer-type dementia, Down's syndrome, and multi-infarct dementia, although the evidence is generally meagre and in many cases requires further corroboration. Genetic studies of Alzheimer-type dementia support the existence of heterogeneity on the basis of family history and age of onset; early onset is associated with greater genetic risk and severity of abnormality. The increasing evidence of an association between DNA damage, premature ageing, and neuronal cell loss may provide insights into the aetiology of these and other forms of dementia.

Senile dementia is now a major public health problem. It affects about one in twenty of those over 65 years of age and one in four of those aged 80 or more. If present trends of change in the age-structure of the population continue, then the burden of caring for the demented elderly could limit our capacity to provide satisfactory standards of health care for everyone. This situation is only likely to be forestalled if substantial progress is made in understanding the aetiology of dementia. In this article some aspects of the problem are considered from a genetic perspective. The relationships between genetics, ageing, and dementia are examined and it is shown that the study of genetically determined abnormal ageing syndromes may throw some light on the aetiology of Alzheimer-type Dementia (ATD) and other forms of dementia.

Genetics and ageing

Ageing is a collective term for all those progressive, deteriorative changes which occur in mature individuals and lead to a reduced expectation of life with increasing age. What is known about the genetic contribution at ageing? Genetic factors are implicated in longevity, largely on the basis of twin and family studies (reviewed by Murphy, 1977). These studies show that identical twins are significantly more alike than fraternal twins with respect to longevity and that there is a small (about one year) increase in survival of the children for every 10 years in the parent. These findings are consistent with multifactorial inheritance and a relatively small heritable component, although with longevity it is difficult to exclude non-genetic causes of resemblance between relatives. The role of genetic factors in more specific aspects of ageing is an enormous subject (see Finch & Hayflick, 1977) in which there are few clear-cut answers, except in the case of the rare Mendelian syndromes associated with premature ageing (see below). Is there evidence of genetic influences on cerebral ageing? Jarvik and coworkers have a investigated the contribution of heritable factors to the decline in cognitive function with age. They followed up a series of 134 identical twin pairs aged 60 or more years for over 30 years, using a battery of psychometric tests (Jarvik *et al*, 1972; Bank & Jarvik, 1977; Jarvik *et al*, 1980). Considerable practical and methodological difficulties were encountered, but it appeared that subject's scores on certain tests (especially those requiring speed) declined more rapidly than their scores on other tests. A more general decline in performance was seen in the eighth and ninth decades. However, intra-pair differences in cognitive function were similar in identical and fraternal twin pairs, implying that genetic factors are not of major significance in cognitive decline, although inadvertent selection of fraternal twin pairs that were more alike for survival may weaken this interpretation (Jarvik *et al*, 1972).

On the basis of a survey of the large number of genetic syndromes known to affect man, Martin (1977) has estimated that several thousand genetic loci are capable of influencing the ageing phenotype, but of these, fewer than 100 exert major effects. Within the

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latter may be a small number of genetic loci (less than 10) which have profound effects on ageing that are manifest through the rare premature ageing syndromes. These are of potential importance in furthering our understanding of the molecular mechanisms concerned in ageing and dementia, and are discussed below in some detail. First, the role of genetic factors in the dementias is reviewed.

Genetics and dementia

Evidence for monogenic inheritance has been demonstrated in several of the less common types of dementia, including Huntington's chorea, Pick's disease, metachromatic leukodystrophy, Wilson's disease, and familial myoclonic epilepsy. These have been reviewed elsewhere (Slater & Cowie, 1971; Lishman, 1978).

In the major dementias with late onset, such as Alzheimer-type dementia (ATD) and multi-infarct dementia (MID), the evidence is more difficult to interpret. (Alzheimer-type dementia is used to describe the clinico-pathological syndrome formerly separated into Alzheimer's disease and senile dementia.) The penetrance is expected to be reduced by the late age-of-onset and many affected relatives remain undetected in the community unless careful field surveys are carried out (Helgason, 1977). If genetic differences in ageing processes do in fact contribute to the neuropathological changes of ATD and MID, they might be expected to be of a polygenic nature, in accordance with what is known of genetic influences on other diffuse processes. The results of family studies agree with this expectation. Sjogren *et al* (1952) concluded that multifactorial inheritance is the most likely explanation for the increased risk of Alzheimer's disease in the relatives of probands with presenile onset. Larsson *et al* (1963) found a four-fold increase in the morbidity risk for dementia in the first-degree relatives of probands with senile dementia. They suggested the alternative explanation of a single dominant gene with reduced penetrance due to factors such as delayed age-of-onset. This hypothesis cannot be excluded, since single gene disorders with no selective disadvantage can reach a high population prevalence (Ling, 1963; Larsson & Sjogren, 1960). However, the small increase in the risk to relatives compared with the general population is more easily reconciled with a multifactorial hypothesis. Since certain methodological shortcomings in this study would result in an underestimate of the morbidity risk for the general population (Mortimer *et al*, 1981), the increased risk in relatives is likely to be even smaller than was demonstrated. The work of Heston *et al* (1981) avoided these difficulties and showed that the risk of ATD in the relatives of early-onset probands (<70 years) is greatly increased while that for late-onset probands (>70 years) is small.

Larsson *et al* (1963) found no evidence of genetic continuity between Alzheimer's presenile dementia and senile dementia, but the distinction between the two was made on clinical grounds which no longer seem valid (Lauter & Meyer, 1968; McDonald 1969). If age of onset had alone been used as a basis for distinguishing sub-groups, seven out of the 51 relatives with "senile dementia" had an estimated age of onset before 65 years, therefore coming into the "presenile" category. The latter figure gives a 10-20 fold higher morbidity risk for presenile-onset ATD in relatives (1.6%)[1] compared with the general population (about 0.1%). Similarly the morbidity risk for senile-onset ATD (65 years) in the relatives is found to be 10.6%, less than four times that in the general population. The study of Constantinidas *et al* (1962) also showed that there is genetic overlap between presenile and senile forms of ATD. Sjogren *et al* (1952) found eight secondary cases among the 255 first-degree relatives of 34 autopsy-confirmed patients with Alzheimer presenile dementia[2]. On the basis of the ages of onset in the secondary cases[3], the morbidity risks are 5.5% and 11.2% for early- and late-onset dementia.

1. The morbidity risks were estimated using a modification of the Weinberg short method suggested by Schulz (1932).
2. Two probands with onset after 65 years of age (Nos 50, 64) were excluded.
3. Three had onset before 65 years and five after this age (onset was known in five cases and estimated in three cases).

These risks are increased compared with general population estimates by roughly 50- and 5-fold. We have partitioned the data from the Swedish studies of Sjogren *et al* (1952) and Larsson *et al* (1963) according to onset-age, and estimated the heritabilities using the method of Falconer (1965). The results, using a cumulative liability model which assumes that early- and late-onset ATD are genetically correlated (see Smith *et al* 1972), are shown in Table I. This shows that the highest heritability estimates (0.89–1.03) are found for early-onset illness in the relatives of early-onset probands and that the heritability for all types of ATD is higher for early-onset probands. The estimates for ATD as a whole are consistent with a polygenic model, although the high estimates for early-onset probands might suggest the presence of major gene effects. Early-onset illness can be equated with a more extreme deviation and a greater genetic risk (Carter, 1969). Clinical observations also shows that early onset is associated with increased severity (Roth, 1978). Both studies of early-onset probands show genetic correlations of less than one between early and late-onset

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TABLE I

Heritability estimates (±SEM) for Alzheimer-type dementia (ATD) according to age of consent of the probands. The genetic correlation (±SEM) between early- and late-onset ATD has been calculated on the basis of the data sources indicated, using the method of Smith et al *(1972)*

Probands		Relatives			Heritability			Genetic correlation	Source
Age of onset	Number	Total	Early onset	Late onset	Early onset	Late onset	Early +late		
Early <65 yrs	34	255	3	5	0.89 ±0.17	0.44 ±0.15	0.46 ±0.09	0.59 ±0.09	Sjogren *et al*, 1952
	30	167	8	10	1.03 ±0.13	0.53 ±0.10	0.63 ±0.13	0.66 ±0.11	Heston and Mastri, 1977
Late >65 yrs	256	2421	7	44	0.83 ±0.09	0.62 ±0.07	0.32 ±0.06	1.12 ±0.13	Larsson *et al*, 1963

illness in relatives (r_G = 0.59, 0.66), suggestive of heterogeneity. Dementia in the relatives of late-onset probands, on the other hand, appears to be a genetically homogeneous disorder, since the genetic correlation between early- and late-onset forms is close to unity (Table I).

There are more than 30 published reports of families showing the segregation of autopsy-proven Alzheimer's disease in a manner consistent with autosomal dominant inheritance (Landy & Bain, 1970; Jacob, 1970; Slater & Cowie, 1971). The possibility of quasi-Mendelian inheritance of a transmissible dementia similar to Creutzfeld-Jakob disease or Kuru is hard to rule out (see Fine, 1977), although initial reports that inoculation of brain tissue from 2 patients with familial Alzheimer's disease into primates gives rise to spongiform encephalopathy have not been confirmed (Goudsmit *et al*, 1980): since the transmitted pathology was not that of Alzheimer's disease and transmission was inconsistent, laboratory error could not be excluded as an explanation. Familial Alzheimer's disease is still most plausibly explained on the basis of a single Mendelian gene, although such a gene could be the major factor determining susceptibility to an ubiquitous infective agent (Harper, 1977). Possible relationships between inherited immune dysfunction, Alzheimer's disease, and ageing have been discussed by Walford (1982).

There have been few satisfactory genetic studies in MID. Constantinidis *et al* (1962) showed an increased risk of MID in the relatives of probands, consistent with polygenic inheritance, but ascertainment bias, absence of field-investigations, and a lack of comparable control or general population data limit the value of this study. Akesson (1969) found a greatly increased morbidity risk in the relatives of MID probands, consistent with a high heritability, but this may in part reflect the geographical isolation of the Swedish island communities surveyed. As with ATD, studies of twins or adopted siblings with MID would help to distinguish genetic from common environmental factors. Disorders such as hypertension and degenerative vascular disease, which are themselves under some degree of genetic control (Berg, 1983), are believed to be associated with the developoment of MID (Dickinson & Thompson, 1961).

Criteria of ageing in the dementias

Ageing is by definition a highly heterogeneous phenomenon, affecting every tissue to varying degrees, so that any attempt to depict its features must inevitably use a broad brush. Martin (1977) selected 21 pathophysiological criteria of ageing, as observed in a variety of tissues and embryological germ layers. These criteria provide a useful starting-point for examining the relationship between ageing processes and the dementias. Some of the criteria proposed by Martin are unsuitable in the present context because they beg questions about the nature of ageing; for example, criteria related to the 'intrinsic mutagenesis' or 'slow virus' hyptheses of ageing. These criteria and a further 'miscellaneous' category are excluded from Martin's list, and his remaining 17 criteria can be used to identify aspects of ageing in the dementias (Table II). Ageing processes can be well marked in some tissues and barely discernable in others, so that the features of ageing could be further subdivided into those that are cell- or tissue-specific and those that affect several cell types or tissues. Unfortunately, systematic studies of structure or function outside the nervous system are scarce, so that in many instances of dementia, it is uncertain whether the features of ageing are localised to the central nervous system or not. In the following sections, the criteria in Table II are used to review the evidence for abnormal or precocious ageing in the dementias.

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TABLE II

Pathophysiological and cellular criteria of ageing, adapted from G. M. Martin (1977)

1	Increased frequency of non-constitutional aberrations
2	Increased susceptibility to certain types of neoplasm
3	Premature greying or loss of hair
4	Dementia or degenerative neuropathology related to senile changes
5	Increased amyloid deposition
6	Increased lipofuscin pigments
7	Diabetes mellitus
8	Disordered lipid metabolism
9	Hypogonadism
10	Autoimmunity
11	Hypertension
12	Degenerative vascular disease
13	Osteoporosis
14	Cataracts
15	Mitochondrial abnormalities
16	Regional fibrosis
17	Abnormal amounts/distribution of adipose tissue

(i) *Dementia and ageing*

Dementia is itself one of the most easily justified criteria of ageing since it shows the steepest age-related increase in incidence of any disorder (Burch, 1968), reaching a prevalence of about one in four in those aged 80 years or more (Katzman, 1976). These observations lend weight to the suggestion of Burnet (1974) and others (Curtis, 1966; Franks, 1974) that post-mitotic cells such as neurons are particularly susceptible to ageing processes. However, for dementia to be used as a criterion of ageing, it must be shown to bear a resemblance to the clinical, psychological, or neuropathological changes occurring in the normal aged, otherwise the argument becomes a circular one. Clinically, there is an apparent discontinuity between the features of normal ageing and of ATD, but this may be more apparent than real since the very large numbers of patients identified in community surveys with milder forms of dementia (Kay *et al,* 1964) have been relatively neglected in clinical and neuropathological studies. This view is supported by psychometric studies that have shown a large overlap in the performance of demented and non-demented elderly subjects (Miller, 1974; 1977). Neuropathological studies have consistently demonstrated that the features of ATD, such as senile plaques, neuronal loss, and neurofibrillary tangles often occur in the brains of the non-demented elderly (Corsellis, 1962; Tomlinson *et al,* 1968; Dayan, 1971; Brody, 1973; Matsuyama & Nakumara, 1978; Ulrich, 1982). Ulrich (1982) found that 25% of an unselected sample of normal brains in the age-group 55–64 years showed Alzheimer-type neuropathological changes, although the figure was lower in a group selected for being non-demented (Dayan, 1971). A progressive loss of surface area of neuronal dendrites also occurs as a prelude to neuronal loss, both in normal ageing and in senile dementia of Alzheimer type (Scheibel & Scheibel, 1977). There may, however, be specific sites where cell loss or degeneration is particularly likely to result in clinical symptoms, such as the cholinergic nucleus of Meynert (Bartus *et al,* 1982), temporal lobe, and hippocampus (Sourander & Sjogren, 1970) perhaps explaining the apparent threshold in the neuropathological signs of degeneration beyond which clinical dementia is increasingly probable (Roth, 1972). In the ageing human brain, neuronal cell loss proceeds at different rates in different areas (Brody & Vijayashankar, 1977a,b). Structures such as the noradrenergic locus coeruleus, cerebellum, and parts of the cerebral cortex are markedly affected. Other parts are relatively spared from cell loss, even although lipofuscin accumulation may be marked (eg inferior olivary nucleus). Neurochemical evidence for a relationship between ATD and ageing is difficult to interpet. Several authors highlight the relatively severe cholinergic, as compared with other, deficits in ATD (Bowen *et al,* 1979; Perry & Perry, 1982; Bartus *et al,* 1982). Significant losses affecting other neurotransmitters and neurochemical parameters have also been observed (Bowen *et al,* 1979, 1982; Bondareff *et al,* 1981; Winblad *et al,* 1981; Rossor *et al,* 1982a). Indeed, it is hard to explain the loss of about one-third of all nerve cells in the temporal lobe of Alzheimer patients (Bowen *et al,* 1979) on the basis of a single neurotransmitter system. Loss of trophic influences on innervated structures (trans-synaptic degeneration) has been suggested as a possibility (Rossor, 1981). How do these changes compare with those found in normal ageing? Several authors report mild (25% or less) changes in choline acetytransferase (CAT) activity, a cholinergic marker enzyme, in elderly human brains, although others have failed to confirm this (see Bartus *et al,* 1982). Greater continuity between CAT changes in the normal aged and in ATD may be found if patients with milder forms of dementia not requiring hospitalization are studied. Further work is also required to compare the extent and distribution of non-cholinergic losses in normal ageing and in ATD. The noradrenergic deficits reported in ATD (Adolfsson *et al,* 1979; Cross *et al,* 1981) are more readily reconciled with an ageing hypothesis in view of the known loss of locus coeruleus neurons with age (Brody & Vijayashankar, 1977a,b). The reports of a sub-population of ATD patients showing a marked loss of locus coeruleus neurons is particularly interesting in this repect (Bondareff *et al,* 1981; Tomlinson *et al,* 1981).

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The neurochemical findings in ATD are conflicting; some authors stress the selective nature of the cholinergic loss, others report significant non-cholinergic deficits suggesting dysfunction or loss of much larger populations of cells in the CNS. What does begin to emerge is that early-onset is not only associated with greater genetic risks and clinical severity but also with increased neuropathological and neurochemical severity. Cell losses, noradrenergic and cholinergic deficits are both more pronounced in early-onset ATD (Rossor, 1982). Despite the apparent clinical discontinuity between ageing and ATD, a significant degree of overlap has been shown in psychological, neuropathological, and neurochemical studies.

In MID there is also evidence for similar but more severe neuropathological changes to those found in normal ageing. In a large group of elderly normal and demented patients, there was continuity between the groups both in the extent of the cerebral infarction and in the increase in ventricular size (Tomlinson *et al,* 1968). There is again an apparent neuropathological threshold, so that the majority of demented patients have a volume of infarcted tissue greater than about 50 ml, while those below this level tend not to be demented. The volume of infarcted tissue is significantly correlated with measures of intellectual and personality impairment (Roth, 1972). Hachinski *et al* (1974) attribute the neuropathological features of MID in large part to thromboembolic disease of the heart and great vessels. Atherosclerosis of the cerebral vasculature is a variable feature in MID and often appears to be insufficient to explain the observed degree of cerebral infarction and dementia. Hypertension occurs in the majority of patients (Dickinson & Thomson, 1961; Ladurner *et al,* 1982; St Clair & Whalley, 1983) and arteriosclerotic changes are prominent in other tissues such as heart and kidney; about half of MID patients die from ischaemic heart disease (Lishman, 1978). Since hypertension and ischaemic heart disease are themselves criteria of ageing, MID fulfills three of Martin's criteria and should be regarded as a form of premature ageing when occuring in the presenium.

Idiopathic Parkinson's disease (PD) also shows features of ageing. The prevalence of PD rises steeply with age, reaching 1 in 100 over the age of 50 years (Pearce, 1978). In PD, there is loss of neurons in the substantia nigra and other sites including the locus coeruleus and dorsal motor nucleus of the vagus. About one-third of affected subjects show features of dementia (Boller *et al,* 1980: Sroka *et al,* 1981) and Alzheimer-type neuropathological changes are present to a greater extent than in matched controls (Hakim & Mathieson, 1978). It is important to establish that this does not arise because of the coincidence of ATD and PD in a patient leading to a greater likelihood of being identified. Jellinger & Grisold (1982) showed that there is a good correlation between the degree of dementia and the severity of Alzheimer-type neuropathological changes in PD. Features of Parkinsonism are present in ATD (Pearce, 1974) so that there is both clinical and pathological overlap between these two disorders. Cortical cholinergic and noradrenergic abnormalities are also found in Parkinsonian patients who develop dementia (Rossor, 1981; Ruberg *et al,* 1982). Dopaminergic cells in the substantia nigra (McGeer *et al,* 1976) and noradrenergic cells in the locus coeruleus (Brody & Vijayashankar, 1977a,b) show sharp decreases in number with age; an acceleration of ageing processes may therefore be involved in PD. The absence of significant dementia or Alzheimer-type changes in other cases of PD shows that the overlap is only partial, but it becomes more prominent with increasing age (Jellinger & Grisold, 1982). The empirical risks to the relatives of PD probands are increased (20–30%) in the case of younger-onset probands, but much less so (3–4%) for older-onset probands (Martin *et al,* 1973; Jeston, 1981). This is consistent with the value that in PD, as in ATD, genetic factors are more prominent the earlier the onset. The little available evidence suggests that genetic factors in ATD and PD are largely independent, but in older age-groups, where most of the neuropathological overlap occurs, these genetic factors are less evident.

(ii) *Chromosomes and dementia*

A second criterion of ageing relates to chromosomal aberrations (Table II). An increase in the spontaneous occurrence of chromosomal aneuploidy (gain or loss of a chromosome) is known to occur in somatic cells as a function of age (Schneider, 1978). Either gain or loss of a chromosome can occur with age, but loss (hypodiploidy) is the predominant change. The frequency of hypodiploid cells increases slowly in both sexes up to the age of 45 years, after which there is a marked increase in frequency in females, while in males the increase continues at the same rate as before (Jacobs *et al,* 1963). The increased aneuploidy of ageing cells may arise either from increased *de novo* formation or from decreased removal of these cells by immunological or other selective mechanisms. Genetic differences do not appear to have a significant effect on the frequency of aneuploidy with ageing; a study of senescent twins by Jarvik & Kato (1970) could not demonstrate any within-pair differences in aneuploidy between elderly monozygotic and dizygotic twins. The marked sex difference in aneuploidy after the age of 45 years also implies a non-genetic, perhaps hormonal, basis for changes in aneuploid frequency with age. The

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TABLE III

Chromosomal aneuploidy and aberrations in females with Alzheimer-type dementia

Reference	Patients	Diagnosis	Aneuploidy (%)		Spontaneous aberrations
			Patients	Age controls	
Nielsen, 1968	10	SD	18.0***	11.9	NR
Nielsen, 1970	3	PSD	10.3	11.9	NR
Bergener and Jungklaas, 1970	NR	PSD	—	—	Increased
Jarvik, *et al*, 1971	8	OBS	21.9***	13.7	NR
Jarvik, *et al*, 1974	36	OBS	17.0	15.6	NR
Ward *et al*, 1979	3	PSD	8.7**	2.6	NR
White *et al*, 1981	2♀+10♂	PSD	2.2	2.1	Normal
Nordenson *et al*, 1980	5♀+5♂	PSD	11.3**	7.8	Increased
Martin *et al*, 1981	46	SD	10.8	11.1	Normal
Buckton *et al*, 1982	23	PSD	8.9	4.5	Increased

***Difference significant at P<0.001
**Difference significant at P<0.01
*Difference significant at P<0.05

causes of somatic cell aneuploidy are largely obscure, but may include abnormal spindle dynamics and chromosomal or DNA damage (Bond & Chandley, 1983).

Table III summarises the results from a number of studies reporting the frequency of aneuploid cells in mitogen-stimulated lymphocytes from female ATD patients, compared with age- and sex-matched controls. When the data are pooled from all those studies scoring adequate number of cells from defined ATD and control groups (Nielsen, 1968, 1970; Jarvik *et al*, 1971, 1974; Ward *et al*, 1979; Martin *et al*, 1981; Buckton *et al*, 1982), the percentage of aneuploid cells is slightly greater in female Alzheimer patients (weighted mean, 13.4%) than in age-matched female controls (11.1%). Studies of male ATD patients have failed to show significant differences from age-matched controls. Buckton *et al* (1982) also compared ATD patients with non-demented senescent controls, on average 18–20 years older than the patients, and found that the ATD females showed more aneuploidy than age-controls but less than the senescent controls. This finding, when taken together with the findings in males, suggests that lymphocyte aneuploidy does not correlate with the degree of dementia and is probably an index of age-related changes occurring independently of the neuropathological processes. This interpretation differs from that proposed by Jarvik and her co-workers, who provide evidence for a close relationship between chromosomal aneuploidy and specific psychometric test performance (Jarvik & Kato, 1969; Bettner *et al*, 1971) but these studies have been criticised by Cohen (1976). Too few studies on multi-infarct dementia have been performed to allow reliable conclusions, but so far there is no evidence that cell aneuploidy is increased in this condition (Nielsen 1970; Jarvik *et al*, 1971, 1974; Martin *et al*, 1981). It is not yet known if middle-aged patients with Down's syndrome, most of whom have neuropathological features of ATD (see below) also show altered frequencies of hypodiploid cells with age.

The frequency of chromosomal aberrations other than aneuploidy also increases with age (Hirsch, 1978). These consist of chromosome or chromatid breaks, gaps, fragments or other distortions. Curtis (1966) has argued that they are a reflection of the increased accumulation of somatic mutations with time and that this is one of the fundamental causes of age-associated decline. Three authors have reported increases in the frequency of chromosome aberrations in ATD (Bergener & Jungklaas, 1970; Nordenson *et al*, 1980; Buckton *et al*, 1982; Table III). Other authors (Mark & Brun, 1973; Martin *et al*, 1981; White *et al*, 1981) have been unable to confirm these findings. However, several syndromes associated with premature ageing show a normal spontaneous chromosome aberration frequency, but a marked increase in the frequency of aberrations induced by mutagens or irradiation (see Arlett & Lehman, 1978). It remains to be seen whether this is the case in ATD.

In Down's Syndrome, patients show normal spontaneous chromosome aberration frequencies, but increases in mutagen and irradiation-induced chromosome aberrations are well established (Countryman *et al*, 1977; Preston, 1981; Vijayalaxmi & Evans, 1982). Irradiation-induced aberrations may be increased in

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TABLE IV

Summary of neuropathological findings in patients with Down's Syndrome (DS) compared with non-DS mentally retarded controls. ATD, Alzheimer-type neuropathological changes. Data from Malamud (1972) and Whalley (1982)

Patients	Age-group	N	With ATD changes	
			N	%
Down's Syndrome	<40 yrs	331	13–17	4–5
	>40 yrs	91	87–89	96–98
Non-DS mentally retarded controls	<40 yrs	588	0	0
	>40 yrs	225	31	14

Down's Syndrome (DS) as a result of abnormal DNA repair mechanisms (Countryman *et al*, 1977; Preston, 1981). These findings are relevant to the aetiology of ATD because of the well-established link between DS and this condition (see below).

(iia) *Down's syndrome, ageing and Alzheimer's disease*

Neuropathological changes typical of ATD were first reported in a patient with Down's Syndrome by Struwe (1929). Since then, there have been numerous reports strengthening this association (reviewed by Whalley, 1982; Lott, 1982). Only a small proportion of DS patients reach the fourth and fifth decades of life because of premature deaths (Smith & Berg, 1976), but of these the majority show many of the neuropathological features of Alzheimer's disease. Table IV summarises the neuropathological data from 422 DS patients examined at autopsy and reported in the literature, in comparison with a series of 813 mentally handicapped control subjects without DS reported by Malamud (1972). The comparison shows that only 4 or 5% of those patients dying before the age of 40 years have Alzheimer neuropathological changes at autopsy. After the age of 40 years, 96–98% of DS patients show these changes, compared with 14% of control subjects (data from Malamud, 1972; Whalley, 1982). These differences are very striking and support the view that virtually all middle-aged DS patients have Alzheimer-type changes.

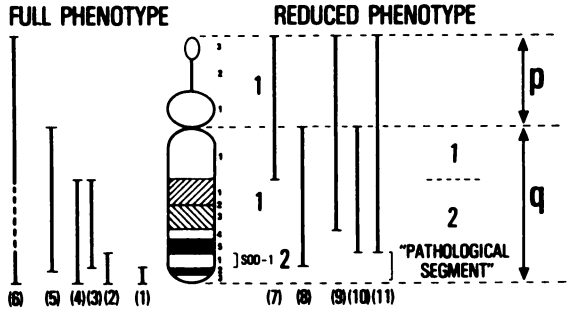
The possibility of bias towards the reporting of cases with Alzheimer changes cannot be excluded, although the majority are from the extensive series by Malamud (1972) which appears to have been systematic. There are two reported exceptions to the association between DS and Alzheimer neuropathology. Both cases were studied by Maloney and reported by Whalley (1982). One patient, a female aged 55, proved to be a chromosomal mosaic (46, XX, 47, XX trisomy 21/22) and the other, a female aged 49, was a full trisomy 21. The brain weight of these patients was greater than other DS patients of the same age and although no senile plaques or neurofibrillary tangles were seen, histological studies were not sufficiently extensive to exclude Alzheimer changes definitively. This observation raises the possibility that the association between DS and ATD is not an invariable one. The karyotype is stated in only 17 of the DS patients shown in Table IV, and with the exception of the mosaic patient mentioned above, all karyotypes reported so far have shown free trisomy 21. Electron microscopic studies of the neuropathological changes observed in DS have shown that these are identical to those seen in ATD (O'Hara, 1972; Ellis *et al*, 1974). Ball & Nuttall (1981) found that the frequencies of neurofibrillary tangles and neuronal loss in five DS brains exceeded those from aged subjects, but were comparable with those from eight ATD patients. Ropper & Williams (1980) commented that the regional distribution of plaques and tangles in the hippocampus of DS patients differed from that reported in ATD patients, but this remains to be confirmed. Neurochemical similarities between DS and ATD have also been demonstrated. Yates *et al* (1980; 1981) showed that the activity of choline aetyltransferase, acetylcholinesterase, and noradrenaline concentrations are markedly reduced in post-mortem brain samples for DS patients showing Alzheimer-type neuropathological changes.

It has been more difficult to demonstrate evidence of cognitive decline in middle-aged DS patients. Several authors have found clinical evidence of dementia in some, but not necessarily all, DS patients surviving beyond the age of 40 years (Jervis, 1970; Lott, 1982). Quite subtle cognitive and behavioural changes occur with age in DS, but this may not be an invariable feature of the condition. Ropper & Williams (1980) retrospectively compared the clinical and neuropathological features of 20 DS patients dying after the age of 30 years. All patients showed neuropathological changes of ATD, but only three showed clear-cut evidence of dementia. However, the clinical assessments were retrospective so that this probably represents a minimum estimate. Wisniewski *et al* (1978) compared the neuropsychiatric features of 50 DS patients above and below the age of 35 years. The older subjects showed evidence of greater memory impairment, aphasia-agnosia, personality change, and subtle neurological deficits than the younger subjects. Changes in neurological reflexes, evoked responses and electroencephalograms suggestive of deterioration have been reported to occur with age in DS patients (Dalton *et al*, 1974; Callner *et al*, 1978; Tangye, 1979). The only reported prospective study of cognitive function in DS did show a progressive decline in learning ability with age (Dalton *et al*, 1974). When

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these patients were later examined at autopsy, the severity of Alzheimer-type neuropathological changes could be correlated with the extent of cognitive deterioration (Crapper *et al*, 1975).

Other features of accelerated or pathological ageing in DS have been reported (Martin, 1977; Goldstein, 1978; Tolksdorf & Wiedemann, 1981; Lott, 1982). Martin used his 21 criteria of ageing (see above) to roughly quantify the features of ageing in 162 syndromes with potential relevance to ageing identified from the 2336 genetic conditions listed in the McKusick's (1975) catalogue. He gave a rank order to each syndrome on the basis of the number of criteria satisfied and found that 10 syndromes had a score of six or more, including the classic progeroid syndromes (Progeria, Werner and Cockayne syndromes). Surprisingly, the syndrome scoring higher than any other was DS (Martin, 1977). Other features of premature or accelerated ageing in DS include increases in chromosome aberrations, malignancy, premature greying or hair loss, ageing pigment deposition, hypogonadism, diabetes mellitus, autoimmunity, degenerative vascular disease, cataract, skin and adipose tissue changes (see Martin, 1977 & Lott, 1982). These observations support the view that ageing and Alzheimer-type



(1) Habedank and Rodewald, 1982; Taysi et al.,1982 (21q 22.2→ q ter)
(2) Sinet et al.,1976; Schmidt et al.,1972; Wahrman et al., 1976 (21q 22)
(3) Sinet et al.,1976 (21q 21→ q22.1)
(4) Pueschel et al.,1980; Williams et al.,1975; Pfeiffer et al.,1977 (21q 21→ qter)
(5) Cantu et al.,1980 (21q 11→ q22.2)
(6) Cervenka et al.,1977 (21p ter→ q11::q22→ q ter)
(7) Williams et al.,1975; Chen et al.,1976 (21p→ q11)
(8) Couturier et al.,1979 (21q 11→ q22.1)
(9) Sanchez et al.,1977 (21p ter→ q21.3)
(10) Niebuhr, 1974 (21 q11→ q21)
(11) Sinet et al.,1976; Hagemeijer et al.,1977; Pfeiffer et al.,1977 (21p ter→ q21)

FIG 1.—Schematic representation of chromosome 21 (G-banding) showing the distribution of some reported partial trisomy 21 chromosomes that are associated either with the full phenotype of Down's syndrome or with a reduced phenotype. The references are shown below, with the trisomic segment in parenthesis. (Adapted from Hagemeijer and Smit, 1977).

neuropathological changes are closely related. Although some of the neuropathological features of ATD are occasionally found in toxic, infective, traumatic, and other degenerative disorders (Corsellis, 1976), they are not known to occur secondarily to any of the consequences of the chromosome anomaly. The causes of ageing-associated changes in DS are not well understood, but a number of possible explanations have recently been put forward and are discussed below.

Several authors have attempted to link specific segments of chromosome 21 with the clinical features of DS on the basis of studies on patients with partial trisomies (Figure 1). In these patients, varying lengths of the long arm of chromosome 21 are present in triplicate, either as translocated or as free chromosomal fragments. It is known that the distal euchromatic segment of chromosome 21 (21q22) is largely responsible for the major phenotypic features of DS (Niebuhr, 1974; Wahrman *et al*, 1976) and Sinet *et al* (1976) have suggested that the superoxide dismutase (SOD–1) locus, in a particular sub-band of this region (21q22.1) is responsible for many of these features. Sinet and others (1976; 1982) suggest that since this enzyme shows increased activity in DS (by gene dosage), there may be corresponding increases in free (hydroxyl) radical formation, which could give rise to increased irradiation-induced chromosomal damage and accelerated ageing. A comparison of these features in patients with partial trisomies that do and do not involve the SOD–1 locus may help to clarify this question. An alternative hypothesis put forward by Shapiro (1983) suggests that the development and maintenance of complex characters such as these involved in the DS phenotype require the coordinated, interactive activity of genes on many chromosomes, and is disturbed by the genetic imbalance imposed by the trisomic state. This argument could be extended to explain the enhanced ageing found in DS, since the integrity of a tissue is maintained by the interaction of many genes and environmental influences, which if disturbed could lead to enhanced ageing. This suggests that enhanced ageing, which is present in the sex chromosomal aneuploidies (Martin, 1977) may also arise in other types of chromosome imbalance (eg unbalanced translocations) and be associated with Alzheimer-type neuropathology.

Heston and co-workers (Heston & Mastri, 1977; Heston *et al*, 1981) have reported a previously unrecognised association between Alzheimer's disease and DS. They found a roughly five-fold excess of DS patients amongst the relatives of Alzheimer probands compared with the general population (Heston & Mastri, 1977). In an expanded study, the excess was reduced to 2.5-fold, but remained significant (Heston

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et al, 1981). The authors argued, on the basis of this finding and an excess of malignant and other disorders in the Alzheimer relatives, for a common genetic diathesis underlying these disorders and suggested that this might be related to a disturbance of microtubular function (Heston & Mastri, 1977). Because the incidence of DS has a clear relationship with increased maternal age, the authors reported maternal ages for 9 of the 11 mothers of DS children identified in their survey. The mean maternal age was 34 years and the authors inferred that this did not represent an increase over expected. This may not be the case; when these figures are compared with those quoted Smith & Berg (1976), the mean maternal age of the DS patients in Heston's series is the same as the average age of DS mothers in large international surveys and considerably higher than the average maternal age (28.2 years) reported in comparable general population series (Smith & Berg, 1976). If the genetic diathesis hypothesis is correct, the maternal age effect should be absent or less marked than is normally found among DS mothers. Furthermore, Heston's hypothesis should predict that the incidence of DS will be highest amongst the close relatives of Alzheimer probands and fall off with decreasing genetic relationship. This is not the case, as only one of the DS patients identified by Heston and co-workers (1981) was a first-degree relative of an Alzheimer proband, seven were born to second-degree relatives, and three born to third-degree relatives. Attempts to confirm these findings have met with varying success (Schmechel *et al*, 1981; Whalley *et al*, 1982). Less than half of the DS relative identified by Heston *et al* (1981) were shown to have free trisomy 21, so that the chance inclusion of subjects with translocation trisomy cannot be excluded. The association therefore, remains to be confirmed.

(iib) *Ageing, DNA repair and neuronal loss*

Several of the genetic syndromes found by Martin (1977) to have high ageing scores, including some of the classic progeroid syndromes, are associated with neuronal degeneration of varying degrees (Table V). About 40% of patients with zeroderma pigmentatosum (XP) have neurological involvement, which manifests at any time between infancy and the third decade. It varies in severity from mild intellectual and neurological deficits to a severe and progressive mental handicap (Andrews *et al*, 1978; Robbins, 1978). Neuropathological studies show widespread neuronal loss in the absence of specific histopathological features (Robbins *et al*, 1974). Deficiency of a UV-endonuclease that repairs defects in DNA inducible by ultra-violet (UV) irradiation has been shown to be the primary abnormality in most cases (Arlett & Lehmann, 1978). The severity of neurological features can be correlated with the extent of the DNA repair defects (Andrews *et al*, 1976). Robbins has proposed that while the skin abnormalities are related to UV damage, the neurological features may arise from failure to repair DNA damage produced by endogenous chemical substances(s) and that this represents a type of abnormal ageing of the CNS (Robbins, 1978). A different DNA repair defect has been identified in ataxia telangiectasia (AT), a condition associated with features of ageing and progressive degenerative changes in eye, skin, and brain (Table V). Neurological signs such as ataxia and dysarthria are most prominent, but mental handicap is present in about half of the cases and a progressive cognitive decline can occur in association with cortical cell loss (Reye & Mossman, 1960; Goldstein, 1978). A γ-endonuclease defect in DNA repair is known to be the primary abnormality in AT (Paterson & Smith, 1979). Most individuals with Cockayne's syndrome (Table V) develop normally in the first few years of life, but later show features of arrested physical and mental development leading to a progressive form of mental handicap indicative of degenerative changes. Calcification and hyalinization of cerebral blood vessels are found at autopsy, and although this is a characteristic of normal ageing, there is no other evidence of specific ageing-associated neuropathological changes in Cockayne's syndrome (Crome & Kanjilal, 1971). As with XP and AT, there is an increased sensitivity to irradiation-induced chromosome aberrations (Arlett & Lehmann, 1978), although as yet no specific DNA repair defect has been found. Robbins (1978) has suggested that DNA metabolism or repair defects may be important causal factors in a number of other primary neuronal degenerations. Primary neuronal degeneration signifies a progressive disease characterised by premature neuronal death and absence of pathological evidence of a specific cause (Oppenheimer, 1976)), and there is now evidence for this in some patients with Friedreich's ataxia, Huntington's disease, familial dysautonomia, Parkinson's disease, and olivopontocerebellar atrophy (Lewis *et al*, 1979; Scudiero *et al*, 1981, 1982; Robbins *et al*, 1983).

In Huntington's chorea, there are reports of chromosomal or DNA instability (Arlett & Muriel, 1979; Scudiero *et al*, 1981) but this has not been confirmed in a more recent study (Evans *et al*, 1982). In Friedreich's ataxia (Table V), there are slowly progressive degenerative changes in the heart and nervous system associated with an increase in the frequency of irradiation-induced chromosomal aberrations (Lewis *et al*, 1979; Evans *et al*, 1983). Cerebellar and spinal cord degeneration are prominent, but cortical cell loss may be responsible for the mild but significant cognitive decline in this disorder (Lishman, 1978).

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TABLE V

Known and putative DNA repair defects in man

	Xeroderma Pigmentosum	Ataxia Telangiectasia	Cockayne syndrome	Down's syndrome	Friedreich's Ataxia	Alzheimer Dementia
Dementia or neurological degeneration	++(A,B,D)[1]	++	++	++++	+++	++++
Premature ageing	++	++	+++	++++	+	+
Spontaneous chromosome aberrations	−	++++	−	−	−	±
Radiation/mutagen sensivity	++++(UV)[2]	++++(γ,X)[3,4]	+++(UV)	+++(M,X,UV)[5]	++++(γ,X,M)	?
DNA repair defect	Incision (UV-endo-nuclease Post-replication (variant	Excision (endonuclease)	?	?	?	?

[1]Refers to genetic complementation groups A, B and D, which show neurological deficits.
[2]Induced by ultra-violet irradiation.
[3]Induced by X-irradiation.
[4]Induced by γ-irradiation.
[5]Induced by certain classes of mutagen.

Recently, Robbins and coworkers (Scudiero *et al*, 1982; Robbins *et al*, 1983) have reported that cell lines from patients with the sporadic type of ATD and from patients with PD both show significantly reduced survival after X-irradiation and mutagen treatment, compared with control cell lines. If these results can be confirmed and extended using more specific tests of DNA repair, they could have considerable significance to our understanding of these disorders.

Although the neuropathological features of the syndrome associated with known or putative DNA repair defects have only rarely been described, they appear to show non-specific patterns of neuronal loss, with the important exceptions of DS and ATD, which show more specific neuropathological features such as senile plaques and neurofibrillary tangles. The latter may be more indicative of the distribution of cell loss rather than of its causation. Robbins *et al* (1983) suggest that the plaques and tangles may be secondary to the death of cholinergic neurons that project to the cortex from Meynert's nucleus; they are not found in this nucleus itself in Alzheimer patients (Whitehouse *et al*, 1982). In the bacterium Escherichia coli, some 49 genetic loci have been identified that affect the metabolism of DNA (Clark & Ganesan, 1975): the number is likely to be considerably higher in man, given the increased complexity of genomic size and expression and of chromosomal structure. Other human disorders of ageing, perhaps including some types of dementia, may therefore be related to abnormalities of DNA repair or metabolism. The alternative possibility of increased production of endogenous DNA-damaging agents remains largely unexplored. Terminally differentiated cells, such as neurons, have a limited ability to repair DNA damage, compared with replicating cells (Modak & Price, 1971; McCombe *et al*, 1976). Accumulation of unrepaired DNA strand breaks occurs with ageing in the mouse brain (Chetsanga *et al*, 1979) so that an increase in unrepaired DNA damage (with actively transcribing sequences perhaps especially sensitive) might be responsible for the relatively widespread fall-out of neurons and the production of abnormal proteins in ATD. The increased sensitivity of specific neuronal pathways (eg iso-dendritic core) may be due to the high levels of transcriptional activity in their "housekeeping" genes (eg. concerned with energy metabolism), which are therefore susceptible to DNA damage and give rise to functional decline.

(iii) *Ageing-pigment deposition*

In Table II, two of the criteria of ageing relate to the deposition of ageing-associated pigments. In the case of amyloid, increased deposition in the nervous system occurs both in ageing and in ATD. Amyloid fibrils consist of a number of different glycoproteins of both immunoglobulin and non-immunoglobulin origin (Kohn, 1977). With advancing age, amyloid can accumulate in a variety of tissues including cerebral blood vessels and the brain (Wright *et al*, 1969). Both

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in the ageing brain and in ATD, amyloid deposits occur either independently or as part of a senile (neuritic) plaque (Wisniewski *et al*, 1982) and in both circumstances, the causes of amyloid deposition remain largely obscure. The term lipofuscin denotes a second group of pigments deposited in ageing tissues. Its accumulation in neurons and other post-mitotic cells is so well established as an age-correlated phenonenon that is has been proposed as a basic law of cellular ageing (Strehler & Barrows, 1970; Brody & Vijayashankar, 1977b). Lipofuscin and the related pigment ceroid are heterogenous substances that are thought to represent different degrees of polyunsaturated lipid peroxidation, although their functional significance is uncertain (Nishioka *et al*, 1968). Neuronal ceroid-lipofuscinosis (Batten's disease) is a lipidosis presenting in juveniles with progressive dementia, epilepsy, blindness, and motor disorders (Zeman, 1971). On histological examination, generalised brain atrophy is seen to be due to widespread neuronal loss with gliosis, but there is an absence of most of the specific features usually found in the ageing brain (Crome & Stern, 1976). The major feature that is specific to Batten's disease is the presence of large inclusions of ceroid and lipofuscin in affected neurons and certain peripheral cells. In ATD, an excess of lipofuscin has been observed in central neurons by several authors (Malamud, 1972; Yamanda, 1978) but not by others (Mann & Sinclair, 1978; Torack, 1978). Recently, a detailed comparsion of histological sections from 10 Alzheimer brains and 13 detailed non-demented brains showed a significant excess of lipofuscin in one of the two brain areas examined (Dowson, 1982). In Huntington's chorea, marked lipofuscin deposition has been reported in cortical biopsies and some post-mortem samples (Tellez-Nagel *et al*, 1974; Brizzee, 1975) but so far no adequately controlled study has been reported.

(iv) *Ageing, malignancy and dementia*

The marked increase in certain types of neoplasm associated with ageing is widely recognised and was cited by Martin as another criterion of ageing (Table II). Many studies have shown that the occurrence of cancers in man and animals increases logarithmically with age (see Ponten, 1977). Heston and co-workers (Heston and Mastri, 1977; Heston *et al*, 1981) reported a significantly increased incidence of lymphomas among the 866 relatives of 125 probands with ATD. Lymphomas show a peak incidence in early adult life but also increase steeply again in older age-groups (Burnet, 1974). Whalley *et al* (1982) were unable to confirm this association in a study limited to the first-class relatives of 74 Alzheimer probands. There is no evidence of an increased incidence of lymphomas or other malignancies in ATD patients themselves, which is hard to reconcile with the reported increase in relatives. Patients with DS have a high incidence of malignant disease, but the increase is most marked (about fifty-fold) for chronic myeloid leukaemia rather than for the lymphoma group (Smith & Berg, 1976). Several of the other disorders shown in Table V have greatly increased rates of malignancy including XP, AT and Cockayne Syndrome (Goldstein, 1978). The criterion of malignancy as an argument for ageing-associated changes in ATD remains to be established.

(v) *Dementia and autoimmunity*

Autoimmune disorders (Table II) increase markedly with age in humans (MacKay, 1972) and ageing itself is associated with increased blood titres of autoantibodies (Goidl *et al*, 1981). Nandy (1978; 1982) has observed an age-related increase in brain-reactive antibodies (BRA) in man, other primates, and mice. These antibodies bind and are cytotoxic to brain cells (Nandy, 1978) sugggesting that they may be involved in the neuronal degeneration of ageing. Patients with ATD and other cerebral disorders have higher levels of BRA (Nandy, 1977; 1982), possibly as a result of an autoimmune reaction associated with ageing. There is no direct evidence that BRA is involved in the pathogenesis of ATD or of other dementias.

(vi) *Increased mortality in the dementias*

Premature death is a likely consequence of any disorder associated with accelerated or pathological ageing. Numerous reports have established that mortality in ATD is substantially increased when compared with the general population (Wang, 1978), in spite of the fact that ATD is rarely given as a certified cause of death (Katzman, 1976). Senile dementia of Alzheimer type may be one of the most common causes of death in persons over 65 (Katzman & Karasu, 1975). Studies in Sweden and the United States have demonstrated that the mean expectation of life at the onset of ATD is about half of that for a person of the same age in the population (Wang, & Whanger, 1971). Heston *et al* (1981) found evidence of increased mortality in the relatives of ATD patients, compared with the general population and a control group. Similarly, it is well established that mortality is increased and life expectancy diminished in MID (Wang, 1978).

However, the causes of death in dementia are usually considered non-specific, so that bronchopneumonia or myocardial degeneration are frequently cited (Kay, 1972). Patients with organic brain syndrome have been found to die of such non-specific causes considerably more often than older patients with functional psychiatric illnesses (Kay, 1972). Although these observations are at least consistent with an

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hypothesis of accelerated ageing, this argument can only be advanced with considerable caution. There is evidence that the life expectancy of patients with senile dementia may be more closely related to environmental factors such as the quality of medical care than to biological factors intrinsic to the disorder. Before 1949, the life expectancy of a patient at the onset of senile dementia was less than 3 years, but by 1957 this had increased to about five years (Gruenberg, 1978). Peck *et al* (1978) have emphasised the importance of the general physical condition rather than the degree of dementia in determining mortality in patients with chronic brain syndrome. The effects of dementia (regardless of cause) on other body systems, the effects of ageing on brain and other tissues, or personal and medical neglect, may such contribute importantly to the excess mortality observed in ATD and MID. The nature and extent of these factors in determining the cause of death in dementia remain unknown.

Conclusion

The two major organic mental illnesses of old age, ATD and MID, have features indicative of abnormal ageing processes. In ATD, the brain shows neuropathological, ultrastructural and neurochemical similarities to changes that occur commonly in senescence. Within the broad spectrum of patients who show Alzheimer neuropathological changes, there is evidence of heterogeneity. Since there is an exponential increase in the prevalence of ATD after the age of 65 years (Nielsen, 1963; Kay *et al,* 1970), comparable to age-specific incidence curves for cancer and other ageing processes, it can be argued that a major group of ATD patients are primarily manifesting the inevitable consequences of cerebral ageing, albeit at a somewhat early age. The distribution of ageing changes found at autopsy in ATD is likely to be biased towards the involvement of structures important for memory because of the way in which patients are selected for study. In contrast, if patients are ascertained because of extra-pyramidal disturbance, as in PD, then the basal ganglia are most affected, although there may be considerable overlap with ATD. The ageing hypothesis of ATD is supported by neurochemical evidence of diffuse degenerative changes, with significant reductions in both neuronal and glial cell populations and more than one neurotransmitter deficit. The genetic evidence in older patients with ATD is consistent with this view, and suggests a relatively small but significant heritable component, compatible with a multifactorial process such as ageing. An alternative hypothesis is that ATD is a relatively specific cholinergic deficit in which non-cholinergic involvement reflects trophic or other influences on associated structures. This is supported by the neurochemical evidence showing more severe cholinergic, compared with other deficits. This might imply more specific genetic factors, such as the major gene hypothesis of Larsson *et al* (1963). While there is undoubtedly a rare sub-group showing autosomal dominant inheritance, the mode of inheritance in the majority of patients is complex. Within this framework, family studies show that early onset is associated with a greater genetic risk to relatives than late onset. This suggests that early onset can be equated with increased severity and a more extreme genetic liability due to the combined effects of many genes. Clinical, neuropathological, and neurochemical evidence supports this view that early onset is associated with increased severity. Late onset ATD on the other hand appears to merge more easily into the elderly population. Neuronal losses are less extensive than in younger patients; cholinergic and noradrenergic deficits are also less severe (Rossor, 1982). This is not to deny specific ageing-associated pathogenetic mechanisms in early-onset cases but, as with the progeroid syndromes, the more specific the mechanism the more the disorder becomes a caricature of normal ageing, which is by definition a very heterogeneous process. In PD, the limited evidence available suggests that genetic factors are again most marked with early-onset disease, while ageing-associated clinical and neuropathological changes are most evident with late onset.

In MID there is again neuropathological overlap with the changes of normal senescence. Other features that are commonly associated with MID include hypertension and degenerative vascular disease, which are themselves features of normal ageing. Genetic studies in MID have been much less satisfactory than in ATD but what few data are available are consistent with a significant non-Mendelian heritable component. Mixed MID-ATD neuropathology has been reported to be as common as MID alone in a survey of institutionalised demented patients (Tomlinson *et al,* 1970). Genetic evidence suggests that the two are to be a large extent transmitted independently (Constantinidis *et al,* 1962; Larsson *et al,* 1963), but since they are both common, their chance co-existence in the same patient will not be unusual.

Other sources of evidence suport this thesis that a significant proportion of ATD patients show features of accelerated or pathological ageing. Firstly, the association between features of premature ageing and Alzheimer-type neuropathology in DS indicate that in at least one instance the two may be inter-related, since the neuropathological changes can not be accounted for on the basis of other abnormalities in DS. It remains to be seen whether any important distinctions can be made between the neuropathological or clinical features of DS and ATD. At present, these observa-

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tions suggest that when ATD occurs in individuals without trisomy 21, it may also be associated with premature ageing. Further evidence comes from the studies of somatic cell aneuploidy in ATD patients. These studies show a small and still doubtful increase in aneuploidy compared with age- and sex-matched controls. The deposition of ageing pigments may also be increased in ATD, although this has been hard to quantify and in the case of amyloid, may occur secondarily to neuronal degeneration arising from a variety of causes.

The increasing evidence for an association between premature ageing, unrepaired damage to DNA, and neuronal degeneration suggests that these factors may be important in ATD and other primary dementias. Several primary neuronal degenerations, including XP, AT and certain inherited cerebellar ataxias, show increased sensitivity to ionizing radiation or other DNA-damaging agents and specific DNA repair defects have been described (Arlett & Lehmann, 1978). Reports of such hypersensitivity have also appeared in relation to Huntington's Chorea, PD, and ATD, although these reports have either been contradicted (eg. Evans *et al*, 1982), or have yet to be confirmed. In the case of DS there is a well-recognised increase in susceptibility to DNA-damaging agents, although the mechanism remains obscure. Future studies of chromosome breakage, ageing, and Alzheimer-type neuropathology in DS patients with partial trisomies may help to clarify these interrelationships.

There is some evidence for increased auto-reactive antibodies in ATD patients, which is consistent with abnormal ageing processes, but their pathogenic significance has yet to be established. The striking increase in mortality shown by patients with ATD and MID might also be consistent with accelerated ageing processes. However, the available evidence does not distinguish between increased mortality as a primary consequence of the disease process and as a secondary consequence of dementia per se.

Genetic factors have been shown to account for some of the variation in ageing processes seen in man. This applies to longevity and to the features of ageing that are found prematurely in the progerias and other rare genetic syndromes. On the basis of these findings, a large number of genes appear capable of exerting small effects on ageing and a small number of specific genes may have very marked effects on ageing (Martin, 1977). There is no genetic syndrome that prematurely reproduces all the features of normal ageing. ATD, MID, and some types of PD are among the many disorders that show features of ageing to a greater extent than can be accounted for by the age of the patients. Although there is evidence for multifactorial inheritance in each of these disorders, specific genetic factors contributing to their causes remain unknown. Further molecular cytogenetic studies in the rare familial type of Alzheimer's disease and in DS will help to identify some of these.

At present, much useful information might be obtained by careful clinical or laboratory assessment of biological features of ageing in patients with dementia, their close relatives, and non-demented elderly controls. A wide variety of parameters might be suitable for such a study, ranging from glomerular filtration rate to the structure of skin collagen (see Finch and Hayflick, 1977). The adopted measures must change predictably with chronological age and could be taken singly or as a group to provide an index of biological age. Further studies of biological ageing in carefully defined groups of demented patients may help to clarify the relationships discussed in this article and assist in the identification of specific genetic factors contributing to the aetiology of dementia.

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