Down's Syndrome and Alzheimer's disease: a review

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SYNOPSIS Neuropathological change found in nearly all individuals with Down's Syndrome over the age of 35 years closely resembles that of Alzheimer's disease. The extent to which dementia occurs as a result of this change is unclear, and the studies which have investigated presumed cognitive deficits are reviewed. The theories put forward to explain the association between these two disorders and their possible significance to the understanding of the aetiology of Alzheimer's disease are discussed.

INTRODUCTION

Alzheimer's disease is the single most common cause of dementia, accounting for more than 50% of the cases of dementia occurring in those over the age of 65 (Katzman, 1976). The cause is unknown and the diagnosis cannot be made conclusively during life as it depends ultimately on finding the characteristic neuropathological features of senile plaques, neurofibrillary tangles and granulovascular degeneration. Although these changes were first reported by Alzheimer in 1907, the cause of the observed clinical deterioration was thought to be arteriosclerotic, until Corsellis & Evans (1965) and Tomlinson et al. (1970) reported these changes to be consistently associated with the diagnosis of presenile dementia.

An association between Down's Syndrome and dementia was first noted over one hundred years ago by Fraser & Mitchell (1876) who, referring to those with Down's Syndrome, wrote: 'In not a few instances, however, death was attributed to nothing more than general decay—sort of precipitated senility'. Struwe (1929) was the first to describe the characteristic senile plaques of Alzheimer's disease in the brains of individuals with Down's Syndrome, and later Jervis (1948) and Verhaart & Jelgersma (1952) described clinical deterioration associated with Alzheimer-like changes at post mortem in a number of people with Down's Syndrome.

Following these reports, most relevant research focused on establishing similarities between the neuropathological changes in the brains of elderly Down's Syndrome persons and the senile plaques, neurofibrillary tangles and granulovascular degeneration characteristic of Alzheimer's disease. By the late 1960s the link between these two disorders was clearly established and, on the basis of post mortem data, it was argued that all people with Down's Syndrome, over the age of 35, have the neuropathological features of Alzheimer's disease (Heston, 1977).

Research into the association between these two disorders has increased because the average life expectancy of individuals with Down's Syndrome has lengthened dramatically from an estimated 9 years in 1929, to 12–15 years in 1947 and 18.3 years in 1961 (Penrose, 1963). Hase (1982) has shown that it is now greater than 30 years, with 25% of the Down's Syndrome population living to the age of 50. Similar studies have confirmed these findings (Forsman & Akesson, 1965; Richards & Sylvestor, 1969; Gallagher & Lowry, 1975; Richards & Siddiqui, 1980; Carter & Jancar, 1982). This increased longevity has given rise to a population of elderly people with Down's Syndrome not previously seen. Once the neuropathological changes that occurred in this elderly population were identified as Alzheimer-like, research concentrated on particular areas—for example, the hypothesized presence of cognitive deficits that should be manifest as a result of these changes, a possible genetic link between the two disorders (Heston et al. 1966, 1981; Heston & Mastri, 1977;
Whalley et al. 1982; Heyman et al. 1983), and on studies of the cause of the Alzheimer-like changes (Sinex & Merrill, 1982). These lines of research are clearly important because on the one hand if those with Down’s Syndrome are at high risk for dementia, there is a need to establish reliable diagnostic methods and to develop the appropriate services for this population; and, on the other hand, because an understanding of this association may give some insight into the cause of Alzheimer’s disease.

NEUROPATHOLOGICAL STUDIES

There have been many published reports of the similarity between age-related changes in Down’s Syndrome brains and the neuropathology of Alzheimer’s disease. The similarity has essentially been confirmed in all relevant studies, particularly in the large studies of Malamud (1966), Liss et al. (1980) and Ropper & Williams (1980). Sylvester (1984) reported that nearly 90% of the brains of individuals with Down’s Syndrome who had died aged 30 or over exhibited Alzheimer-like changes, and the most recent study by Wisniewski et al. (1985) found that 59 out of 100 Down’s Syndrome brains examined had Alzheimer-like changes, the extent of the change increasing with age. None of the brains of those who had died over the age of 30 years was free from plaques, and there was a correlation between the density of plaques and the degree of dementia and age. Only 15 out of the 100 studied had shown signs of deterioration prior to death. Table 1 lists those studies that have concentrated primarily on the neuropathological change and Table 2 lists those that include a description of clinical change.

O’Hara (1972), in a single case report of an electron-microscopical study of an affected Down’s Syndrome brain, found no difference from the Alzheimer changes in a non-Down’s Syndrome brain, a finding confirmed by two subsequent studies (Schochet, 1973; Ellis et al. 1974). Yates et al. (1980) reported a reduction of the enzymes choline acetyltransferase and acetyl cholinesterase in the affected brains of those with Down’s Syndrome, a characteristic of Alzheimer’s disease. Anderton et al. (1982) produced an antibody to neurofilaments, the precursors of the neurofibrillary tangles, and these have been shown to cross-react with those in the affected brains of Down’s Syndrome individuals. The neuropathological and neurochemical changes are therefore similar to those found in Alzheimer’s disease, and the neurofibrillary tangles are antigenically identical.

Generally, these changes are reported to occur more frequently with increasing age (Malamud, 1966; Solitaire & Lamarche, 1966; Burger & Vogel, 1973; Ropper & Williams, 1980; Sylvester, 1984; Wisniewski et al. 1985). However, Wisniewski et al. (1979) have described a 20-year-old man with Down’s Syndrome and advanced Alzheimer-like changes at post mortem, and Murdoch & Adams (1977), Maloney (cited by Whalley, 1982) and Janota (personal communication) have reported individuals aged 56 years, 49 years and 49 years respectively, without such change. The case reported by Maloney was a chromosome 21 mosaic.

The excessive occurrence of such neuropathological change appears to be specific to Down’s Syndrome and not to the mentally handicapped population in general (Neumann, 1966; Reid & Aungle, 1974). Therefore, it is not the result of a more general process causing mental handicap—for example, perinatal damage—but is specific to the inheritance of an extra chromosome 21.

These predominantly neuropathological studies can be criticized from several points of view. First, there is the question of selection. The majority of studies are from an institutional population and the post mortems may have been performed because of early or unexpected death. Secondly, some of the studies were conducted before chromosome studies were possible; however, even in later studies the diagnosis of Down’s Syndrome was rarely confirmed by chromosome analysis. Thirdly, the analysis of associated ‘clinical dementia’ is difficult because of poor pre-morbidity assessment and the reliance on retrospective data.

A further finding in Down’s Syndrome, identified by computer tomographic (CAT) brain scanning (Wisniewski et al. 1982), and also reported in a recent neuropathological study (Takashima & Becker, 1985), has been that of basal ganglia calcification. This may be important because cell loss in the nucleus of Meynert is now recognized as a key feature in Alzheimer’s disease (Coyle et al. 1983). Takashima & Becker (1985) examined 33 Down’s Syndrome brains
### Table 1. Studies of Alzheimer-like (A-L) neuropathology (NP) in Down’s Syndrome (DS) and mentally handicapped (MH) controls

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Results</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Malamud (1966)</td>
<td>N = 251; 231 aged 20–37; 20 aged 37–66; all DS</td>
<td>All 20 &gt; 37 years had A-L changes; none &lt; 37 years showed significant changes</td>
<td>Evidence for the presence of A-L changes with increasing age</td>
</tr>
<tr>
<td>Sollsiaire &amp; Lamarche (1966)</td>
<td>N = 7; aged 45–65; all DS</td>
<td>All showed A-L changes, marked in the 4 oldest</td>
<td>Evidence for the presence of A-L changes, increased pathology with age</td>
</tr>
<tr>
<td>Neumann (1966)</td>
<td>N = 36; aged 29–36; all MH but not DS</td>
<td>Only 1 showed plaques and tangles</td>
<td>Evidence for A-L pathology being associated specifically with DS</td>
</tr>
<tr>
<td>Haberland (1969)</td>
<td>N = 7; aged 34–74; all DS</td>
<td>Subject aged 34 no A-L change; those aged 39 and 47 slight to moderate; others severe</td>
<td>Evidence of plaques preceding tangles and granulovascular degeneration; A-L changes increase with age</td>
</tr>
<tr>
<td>Olson &amp; Shaw (1969)</td>
<td>N = 30; 4 with DS aged 23–51; 26 MH controls</td>
<td>A-L changes noted in DS subjects aged 35, 47, 51; not in subject aged 23; control aged 61 mild A-L NP</td>
<td>Evidence of A-L change increasing with age, specific to DS; evidence of dementia reported in 1 case only</td>
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<tr>
<td>O’Hara (1972)</td>
<td>N = 1; aged 48; DS</td>
<td>Plaques and tangles present</td>
<td>Electron microscopical study</td>
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<tr>
<td>Burger &amp; Vogel (1973)</td>
<td>N = 13; aged 12–65; all DS</td>
<td>Significant plaques in all except subjects aged 12, 18; A-L changes marked in all &gt; 38</td>
<td>Evidence of senile plaques developing; granulovascular degeneration and tangles occurring after third decade</td>
</tr>
<tr>
<td>Schochet (1973)</td>
<td>N = 2; aged 38, 40; both DS</td>
<td>All A-L changes present</td>
<td>Some behaviour change, no dementia</td>
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<tr>
<td>Reid &amp; Aungle (1974)</td>
<td>N = 155; 8 DS, 147 other diagnoses</td>
<td>A-L changes in 2 with DS, and in 9 controls</td>
<td>Evidence for an increased propensity for A-L changes in DS, cf. other causes of MH</td>
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<tr>
<td>Murdoch &amp; Adams (1977)</td>
<td>N = 4; aged 40–60; all DS</td>
<td>A-L changes in 3 aged 40, 60, 66; not in one aged 56</td>
<td>Not all with DS affected in old age</td>
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<td>Wissniewski et al. (1979)</td>
<td>N = 7; aged 11–32; 1 DS, 6 others selected because of signs</td>
<td>DS subject aged 20 had all the A-L changes</td>
<td>Exemplifies wide variation in age of onset of changes in DS</td>
</tr>
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<td>Liss et al. (1980)</td>
<td>N = 32; all DS</td>
<td>Plaques, tangles in all &gt; 30 years</td>
<td>Plaques and tangles develop first</td>
</tr>
<tr>
<td>Ropper &amp; Williams (1980)</td>
<td>N = 24; aged &gt; 30; all DS</td>
<td>All but 2 showed plaques and tangles; 3 also had granulovascular changes</td>
<td>Increasing plaques and tangles with age; no evidence of increasing signs of dementia with more severe A-L changes; 14 with A-L change were not demening</td>
</tr>
<tr>
<td>Ball &amp; Nuttall (1980)</td>
<td>N = 5; aged 21–62; all DS</td>
<td>All A-L changes in some cases</td>
<td>Evidence of plaques preceding other A-L changes</td>
</tr>
<tr>
<td>Yates et al. (1980)</td>
<td>N = 3; aged 52–57; all DS</td>
<td>Reduction of choline acetyltransferase and acetylcholinesterase in all 3</td>
<td>Evidence of larger number of plaques in DS; in 2 subjects with equal A-L change one was the other was not demening</td>
</tr>
<tr>
<td>Yates et al. (1981)</td>
<td>N = 2; aged 52, 56; 1 mosaic DS</td>
<td>A-L change and reduced noradrenergic and cholinergic activity</td>
<td>Evidence of similar pathology in DS as in Alzheimer’s disease; one demening</td>
</tr>
<tr>
<td>Maloney (cited by Whalley, 1982)</td>
<td>N = 19; aged 13–58; all DS, one mosaic</td>
<td>Plaques and tangles absent in those aged 13, 18, 21, 32, 49 and 55 (mosaic); A-L changes in others aged 49–58</td>
<td>Evidence of variation in the degree of A-L change; 1 aged 49 and 1 aged 55 (mosaic) spared</td>
</tr>
<tr>
<td>Sylvester (1984)</td>
<td>N = 27; all DS</td>
<td>A-L changes in 88.9% aged &gt; 30, 93% ≥ 46, 100% &gt; 50 years</td>
<td>Increasing propensity for A-L changes with increasing age</td>
</tr>
<tr>
<td>Wissniewski et al. (1985)</td>
<td>N = 106; all DS</td>
<td>All 49 &gt; 30 years and 7 &lt; 30 years of age plaques or plaques and tangles</td>
<td>Increasing frequency with age, all over 30 years affected by A-L change</td>
</tr>
</tbody>
</table>
from individuals who had died between the ages of 1 and 60 years, and found that 45% of them had definite basal ganglia calcification. This was more obvious in the individuals who were older at the time of death. However, it was found predominantly in the medial side of the lateral medullary lamina of the globus pallidus, and was not reported as occurring in the nucleus of Meynert. They reported no association with the extent of Alzheimer-like change nor with the presence of congenital heart disease, and did not describe any associated clinical change prior to death. Although, initially, it might have been thought that this calcification would be a useful marker for impending dementia, this now appears less likely.

CLINICAL SIGNS OF DEMENTIA IN THOSE WITH DOWN'S SYNDROME

Although the neuropathological studies are in general agreement about the relationship between these two disorders, the proportion of individuals with Down's Syndrome who can be said to be demented have the features of Alzheimer's disease has not been as well established.

The study of individuals in the general population with verified Alzheimer's disease has shown the clinical manifestations to follow three stages (Schneck et al. 1982). The first involves a subjective opinion of forgetfulness which may be accompanied by anxiety. The second is characterized by severe memory loss for recent events (Inglis, 1957, 1959; Miller, 1971, 1973), poor concentration, impaired orientation and minimal dysphasia (Barker & Lawson, 1968; Miller, 1981), with vocabulary and memory for past events remaining largely unaffected. The final stage is marked by severe disorientation, 'behaviour problems', pronounced anxiety and cognitive abulia. There may be some psychotic experiences but these are most likely to occur in the context of gross confusion and disorientation. Incontinence, helplessness and abnormal reflexes may occur at this stage. Paulson (1977) has summarized the signs and symptoms of dementia as being: memory impairment, affective disturbance, disorientation, diminished attention span, anomia, apraxia and released reflexes, themselves indicative of the loss of higher cortical function.

In some neuropathological studies of Down's Syndrome it has been suggested that the present diagnostic criteria and clinical signs of Alzheimer's disease are easily applicable (Reid & Aungle, 1974; Reid et al. 1978), while others argue that the signs of deterioration associated with ageing in Down's Syndrome need to be clarified before the diagnosis of Alzheimer's disease can be generally applied (Burger & Vogel, 1973; Ellis et al. 1974; Sylvester, 1984). The major difficulty in applying the criteria is the underlying mental handicap. There is great variation in the developmental histories (Levinson et al. 1955) and in the Intelligence Quotients (IQs) of people with Down's Syndrome, 30% scoring less than 20 points, 65% between 20 and 50, and 5% between 50 and 65 (Breg, 1977). This restricts the application and interpretation of normal test procedures, as failure on test items may be due either to the underlying mental handicap or to the acquired dementia. Many studies have either ignored this question or assumed a similar distribution of degree of handicap in all age groups. Others have matched age groups on the basis of IQ, to control for the level of handicap. However, matching by IQ alone does not eliminate the possibility that subjects may fail the dementia test items either because of mental handicap or because of dementia. Thus the problem of deficits being attributable to dementia or handicap is unresolved.

The restrictions on drawing conclusions from the testing of cognitive deficits would not be necessary if intelligence in the sample population was evenly distributed throughout age groups. There are a number of reasons why this is not so. One is the earlier age of death of the more severely handicapped, thus yielding a less handicapped older population. Secondly, there is a tendency for research workers to use institutional populations which usually include the more severely handicapped throughout all age groups. In addition, people with Down's Syndrome of higher intelligence were more commonly hospitalized in the past than is the case now, and the recent policy to move younger people into the community first, or not to hospitalize them at all, may leave older, more able Down's Syndrome people in institutions. All these factors and local policy variations produce an institutional population with unpre-
Table 2. Studies including description of clinical change in Down’s Syndrome (DS) and Alzheimer-like (A-L) neuropathology (NP)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Description of deterioration</th>
<th>Age at onset</th>
<th>Age at death</th>
<th>Post mortem findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jervis (1948)</td>
<td>1. Apathy, little emotional reaction, depressed, vocabulary more restricted, at 44 unable to feed himself, tremor; at 46 unsteady, doubly incontinent</td>
<td>42</td>
<td>47</td>
<td>SP and NF change</td>
</tr>
<tr>
<td></td>
<td>2. At 42 restless, moody, destructive, episodic noisy excitement, voracious appetite, pica, screaming</td>
<td>38</td>
<td>42</td>
<td>SP only</td>
</tr>
<tr>
<td></td>
<td>3. Moody, irritable, apathetic, wandering, destructive, reduced speech</td>
<td>31</td>
<td>35</td>
<td>SP and NF change</td>
</tr>
<tr>
<td>Verhaar &amp; Jalgersma (1952)</td>
<td>1. Apathy changing to irritability, less speech, stereotypic movements</td>
<td>36</td>
<td>37</td>
<td>SP present</td>
</tr>
<tr>
<td></td>
<td>2. No evidence of dementia</td>
<td>—</td>
<td>47</td>
<td>A-L change</td>
</tr>
<tr>
<td></td>
<td>3. No impairment at 29, moody, episodic depression</td>
<td>—</td>
<td>35</td>
<td>A-L change</td>
</tr>
<tr>
<td>Haberland (1969)</td>
<td>1. Became unmanageable, irritable, bouts of screaming, speech defect, mute, epilepsy and totally helpless</td>
<td>38</td>
<td>56</td>
<td>Severe A-L NP</td>
</tr>
<tr>
<td>Ellis et al. (1974)</td>
<td>1. Aged 18 stillness and apathy; aged 40 speech lost; aged 48 ‘premature ageing’, withdrawn, only follow simple commands; aged 52 seizures</td>
<td>18</td>
<td>54</td>
<td>Numerous SP, T</td>
</tr>
<tr>
<td>Crapper et al. (1975)</td>
<td>1. Lost interest, speech became limited, unable to find way round, seizures, slow, loss of self-help skills, rigidity, bedridden, limited response to people</td>
<td>51</td>
<td>54</td>
<td>A-L change</td>
</tr>
<tr>
<td>Reid et al. (1978)</td>
<td>1. Withdrawn, uncoordinated, became doubly incontinent, bedridden</td>
<td>50</td>
<td>53</td>
<td>Severe A-L change</td>
</tr>
<tr>
<td>Ropper &amp; Williams (1980)</td>
<td>1. Insidious onset; unkempt, apathy, incontinent, bedridden</td>
<td>33</td>
<td>49</td>
<td>SP, T present</td>
</tr>
<tr>
<td></td>
<td>2. No longer good assured, untidy, glutinous, aged 42</td>
<td>30/s</td>
<td>42</td>
<td>SP, T present</td>
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</tbody>
</table>

SP = senile plaques; T = tangles; NF = neurofibrillary.

sentative and certainly unpredictable age and handicap characteristics.

As well as the difficulties of testing for cognitive deterioration in people with a low IQ, there are behavioural and psychological differences between mentally handicapped people with and without Down’s Syndrome which complicate interpretation of test results. Johnston & Olley (1971) describe those with Down’s Syndrome as having lower verbal mental age, poorer tactile discrimination, slower conditioning and reaction times but more exploratory learning. If a pattern of cognitive ability and deficit is unique to Down’s Syndrome then this may affect the expression of dementia.

In general, the possible clinical consequences of Alzheimer’s change in the brains of those with Down’s Syndrome has not been well documented. Table 2 lists those studies which have included some clinical description of the person prior to death together with the post mortem findings. A second line of research has been to examine age-related cognitive change in those with Down’s Syndrome (Table 3), as the neuropathological evidence suggests deterioration in later life is inevitable.

In the studies included in Table 2 the average age of onset of clinical signs was 37-7 years, with a range of 18-50 years, and an average duration of dementia of 11-3 years (appreciably longer than those without Down’s Syndrome and affected by Alzheimer’s disease).

The changes appear to be predominantly in the area of behaviour (‘unmanageable’, ‘withdrawn’), loss of self-care skills or deterioration in the use or understanding of language. Many of the neuropathological studies describe difficult behaviour (Jervis, 1948; Olsen & Shaw, 1969; Haberland, 1969; Ellis et al. 1974; Crapper et al. 1975; Ropper & Williams, 1980). The common
Table 3. Studies of psychological and clinical signs associated with ageing in Down’s Syndrome (DS)

<table>
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<tr>
<th>Authors</th>
<th>Design</th>
<th>Subjects</th>
<th>Measures employed</th>
<th>Findings and comments</th>
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</thead>
<tbody>
<tr>
<td>Nakenamura (1961)</td>
<td>Investigation of IQ distribution in DS</td>
<td>N = 64; aged 16-63</td>
<td>Griffiths-Binet (form L)</td>
<td>1. IQ range 12-39; mean = 23 2, s. o. = 6 9&lt;br&gt;2. No significant sex differences&lt;br&gt;3. Correlation between CA and IQ = 0&lt;br&gt;4. &gt; 34 age group; IQs lower than expected</td>
</tr>
<tr>
<td>Oweene et al. (1971)</td>
<td>Comparison of &gt; 35 age group and 20-25 age group</td>
<td>N = 19 &gt; 35, none &gt; 50; &lt;br&gt;N = 16 20-25 group; all IQ &gt; 25; DS groups matched</td>
<td>1. EEG&lt;br&gt;2. Orientation&lt;br&gt;3. Object identification, use, description, 4. Neurological signs</td>
<td>1. Younger group superior at object identification (P &lt; 0.021)&lt;br&gt;2. Increased frequency in older group of nose reflex (P &lt; 0.01), Babinski (P &lt; 0.022), Palmar mental sign (P &lt; 0.003)&lt;br&gt;3. No other significant differences</td>
</tr>
<tr>
<td>Dalton et al. (1974)</td>
<td>Comparison of 19-23, 39-43 and 44-58 age groups and 2 control groups 19-24, 42-61 matched for age and years in an institution</td>
<td>N = 32; aged 19-58; mean IQ = 27</td>
<td>1. Digit span&lt;br&gt;2. Visual matching to sample learning task&lt;br&gt;3. Delayed matching to sample learning task</td>
<td>1. Old MH control group superior on digit span to young and intermediate DS groups&lt;br&gt;2. MH control groups faster in learning matching to sample task compared with ‘old’ DS group (P &lt; 0.01)&lt;br&gt;3. No other significant differences in digit span or matching tasks between groups&lt;br&gt;4. IQ and performance positively correlated on matching to sample learning task (r = 0.59), age and performance not correlated (r = 0.03)&lt;br&gt;5. ‘Old’ DS group made more errors on retention tests (P &lt; 0.05)</td>
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<td>Dalton &amp; Cooper (1977)</td>
<td>5 and 3 year retest of the above study</td>
<td>As above</td>
<td>As above</td>
<td>1. 3 of ‘old’ DS group had deteriorated and could not return task at 1-5 years&lt;br&gt;2. 1 from ‘old’ DS group could not return at 3 years&lt;br&gt;3. Of remaining 7 ‘old’ DS subjects improved on memory test at 3 years (NS)&lt;br&gt;4. Remaining 2 subjects had scores similar to other 2 ‘younger’ groups&lt;br&gt;5. 2 of the 4 ‘deteriorated’ subjects showed cerebral atrophy on CT scan and abnormality on EEG&lt;br&gt;6. No EEG differences between 3 groups</td>
</tr>
<tr>
<td>Wintenweiler et al. (1978)</td>
<td>Comparison of &gt; 35 and &lt; 35 age groups</td>
<td>N = 50; aged 5-72</td>
<td>Orientation, vocabulary, performance, recent memory, short-term visual retention, neurological signs</td>
<td>1. Recent memory, orientation, colour identification, object use and memory: all lower in &gt; 35 age group&lt;br&gt;2. Ichthyosis, constriction and loosening: commoner in &gt; 35 group&lt;br&gt;3. Brain and muscle retraction, Palmar mental and Babinski signs, facial muscle hypertrophy: commoner in &gt; 35 group&lt;br&gt;4. (N.B. level of significance not given for any of the above results)</td>
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<tr>
<td>These et al. (1982)</td>
<td>Comparison of 25-34, 35-44, 45-54 with matched MH controls</td>
<td>N = 40 (10 for each group)</td>
<td>1. Neuropsychiatric interview; orientation, attention span, affect and praxis&lt;br&gt;2. Matching-to-sample visual memory, 5 and 30 s delay&lt;br&gt;3. Digit span&lt;br&gt;4. Object identification&lt;br&gt;5. Colour naming&lt;br&gt;6. General knowledge&lt;br&gt;7. CNS examination</td>
<td>1. On orientation, attention and digit span, object identification and both visual memory tasks scores for DS controls&lt;br&gt;2. DS subjects more apraxia (P &lt; 0.02), motor ‘release reflexes’ (P &lt; 0.05)&lt;br&gt;3. No significant differences (DS = controls) on ratings of affective lability, anxiety, colour identification, general knowledge, sensation, deep tendon reflexes, cranial nerve function, muscle tone&lt;br&gt;4. Scores of digit span recall, object identification and visual memory declined significantly with age in DS subjects&lt;br&gt;5. 75% DS subjects had 1 or more signs of dementia ≥ 30% controls (P &lt; 0.01)&lt;br&gt;6. 12 DS subjects with diagnosis of dementia all ≥ 45 years of age (P &lt; 0.05)</td>
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**Table 3. (cont.)**

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Subjects</th>
<th>Measures employed</th>
<th>Findings and comments</th>
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<tbody>
<tr>
<td>Sand et al. (1983)</td>
<td>Comparison of &gt; 35 and &lt; 35 age groups and MH controls</td>
<td>N = 30, aged 19-65</td>
<td>Testing of primitive reflexes</td>
<td>1. Palominosum and snout reflexes not correlated with degree of handicap</td>
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<td>2. Palominosum sign not correlated with age or reflex incidence</td>
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<td>3. Snout reflex in DS 0% &lt; 35 age group,</td>
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<td>25% &gt; 35 age group (P &lt; 0.05)</td>
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<td>4. Both reflexes significantly less prevalent in DS subjects than controls</td>
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<td>Par I compared with old controls except 'domestic activity' (results NS)</td>
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<td>2. 'Personal integrity' maintained in young vs. old DS subjects in the presence of</td>
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<td>cognitive failure</td>
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<td>3. Uniform pattern in regressed group, diverse pattern in non-regressed group</td>
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<td>4. Regressed/non-regressed differences greater in DS group than control group</td>
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<td></td>
<td>2. Orientation</td>
<td>(P &lt; 0.05), cooperation (P &lt; 0.05), digit span (P &lt; 0.05), visual memory 5 s delay</td>
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<td>3. Attention</td>
<td>(P &lt; 0.05), CNS signs including apraxia (P &lt; 0.05),  frontal lobe signs (P &lt; 0.05)</td>
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<td>4. Concentration</td>
<td>Palominosum reflexes (P &lt; 0.01)</td>
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<td>5. Digit span</td>
<td>2. Significant increase in age for DS r control group in: affective disturbance</td>
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<td>6. Short-term visual memory (5 and 30 s delay)</td>
<td>including: liability (P &lt; 0.001), apathy (P &lt; 0.05)</td>
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<td>7. Object and colour naming</td>
<td>(N.B. several measures showed significant deterioration in the over 30 DS age</td>
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<td>8. General knowledge</td>
<td>group)</td>
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<td>9. Vocabulary</td>
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<td>10. Affective apathy and liability</td>
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<td>11. CNS assessment</td>
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<td>2. Behavioural and skills schedule</td>
<td>2. All independent feeding, some required help in other self-care skills</td>
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<td>3. Behavioural deterioration in 3</td>
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<td>4. Deterioration associated with visual and hearing loss and macrocytosis</td>
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Feature in these descriptions is an initial change in mood, with apathy being particularly common. Following this, there may be a variety of behaviours progressing to complete helplessness. Comparing these descriptions with the pattern of progressive dementia in Alzheimer’s disease, it is apparent that the point of onset described for those with Down’s Syndrome coincides with the later stage of dementia in those without Down’s Syndrome.

In a study being conducted by one of the authors (A.J.H.), deterioration in self-care skills was a striking finding in 4 out of 11 individuals with Down’s Syndrome over the age of 40 years. In 3 of the 4 there was definite cerebral atrophy as demonstrated by a CT scan. Other findings of interest in some members of this group have been generalized motor slowing, unexplained weight loss and, in one case, a florid affective disorder.

These may be related to the onset of dementia, but long term follow-up is clearly needed to establish the significance of these observations.

It also seems likely that an increase in the prevalence of epilepsy with age is due to the Alzheimer changes. Saurander & Sjögren (1970) have reported that 50% of those with Down’s Syndrome develop generalized epilepsy in the last 6 months of life, and Veall (1974) found an increase to 12% in the prevalence of epilepsy after the age of 30 years. Tangye (1979), in a 6-year follow-up study of 128 individuals with Down’s Syndrome, reported a marked increase in encephalographic abnormalities (EEG) with increasing age. In another study with a verified case of Alzheimer’s change in Down’s Syndrome, the EEG showed increased disorganization of slow wave activity at 18 months and then 3 months prior to death (Crapfer et al. 1979).
STUDIES OF AGE-RELATED COGNITIVE DEFICITS IN DOWN’S SYNDROME

Despite the difficulties of sampling and testing discussed above, research workers have commonly examined differences in age groups to test the hypothesis that clinical dementia develops with increasing age in those with Down’s Syndrome. The studies which have considered the cognitive, psychological and clinical differences associated with ageing in Down’s Syndrome are summarized in Table 3. The previously mentioned problems give rise to some difficulty in the interpretation of results, but some tentative conclusions can be drawn.

These studies show that there are some age differences associated with Down’s Syndrome which may suggest the presence of dementia. The most consistent finding is that deficits indicative of dementia are more likely to be associated with increasing age in Down’s Syndrome than other forms of mental handicap (Dalton et al. 1974; Thase et al. 1982, 1984; Miniszek, 1983; Sand et al. 1983).

Orientation has been shown to deteriorate with increasing age by Wisniewski et al. (1978) and Thase et al. (1982, 1984), who also showed deterioration of attention; however, Owens et al. (1971) found no change in orientation. Measures of object identification have shown some age-related changes (Owens et al. 1971; Wisniewski et al. 1978; Thase et al. 1982, 1984), older groups being less able than younger.

Short-term memory deficits have consistently been associated with ageing in cross-sectional studies, apart from the study by Owens et al. (1971) (Dalton et al. 1974; Dalton & Crapper, 1977; Wisniewski et al. 1978; Thase et al. 1982, 1984). However, the longitudinal study by Dalton & Crapper (1977) showed that this deterioration was certainly not inevitable for older people with Down’s Syndrome and also that there were no learning differences between age groups.

While behavioural changes are often predominant in case descriptions, Thase et al. (1982) could not demonstrate any age differences in their first study, but later (1984) they reported significant increases in apathy and lability with increasing age. The study by Francis (1970), which has often been quoted as supporting a pattern of dementia in ageing people with Down’s Syndrome, reported behavioural differences which may, however, be attributable to institutionalization and not related to dementia. Miniszek (1983) has employed a behavioural measure in a cross-sectional, deteriorating versus non-deteriorating, comparison design, using the Adaptive Behaviour Scale (Fogelman, 1975). This scale is standardized on a mentally handicapped population and therefore the results may be more valid. Personal integrity in deteriorating Down’s Syndrome subjects was found to be maintained in spite of cognitive failure, suggesting a similar pattern of deterioration to that shown by individuals without Down’s Syndrome but who have Alzheimer’s disease.

Abnormal reflexes, commonly found in those with advanced Alzheimer’s disease, have also been reported to occur in older people with Down’s Syndrome (Owens et al. 1971; Wisniewski et al. 1978; Thase et al. 1982, 1984; Sand et al. 1983), the snout reflex being the most common to reappear after the age of 35 years.

Although few studies have been sufficiently extensive to produce incidence rates of deterioration in Down’s Syndrome, Thase et al. (1982) found that 45% of subjects (with Down’s Syndrome) over the age of 45 met the DSM-III criteria (APA, 1980) for a provisional diagnosis of dementia. Hewitt et al. (1985) found evidence of deterioration in cognitive performance (using the Stanford-Binet Intelligence Scale) in 9 39% of 23 hospital patients with Down’s Syndrome, but reported that none had the features of dementia and, in addition, that their cognitive deterioration was unrelated to length of hospitalization, chronological age or earlier mental age. It is clear, however, that a proportion of individuals with Down’s Syndrome deteriorate in their abilities in later life. This proportion falls short of that predicted by the neuropathological findings.

GENETIC ASSOCIATIONS

Ninety-five per cent of the cases of Down’s Syndrome are caused by non-dysjunction of chromosome 21 during gamete formation (meiosis), this type being associated with an increased maternal age at conception (Penrose, 1966).
Heston et al. (1966) were the first to suggest a possible familial link between this type of Down's Syndrome and Alzheimer's disease. In their family based study of Alzheimer's disease, they found an increased rate of Down's Syndrome births in the families of post mortem confirmed Alzheimer probands. When the data were analysed according to the age of the Alzheimer probands, the families of 'young probands' (<60 years) had the excess of Down's Syndrome births (Heston et al. 1981). This 'presenile' form of Alzheimer's disease appears to have a significant genetic component (Heston et al. 1981). Heston argued that whatever predisposes to non-dysjunction of chromosome 21 also predisposes to the defect of microtubular proteins that might lead to Alzheimer's disease. A later study by Whalley et al. (1982) found an excess of Alzheimer's disease in the families of Alzheimer probands, but did not find an increase of Down's Syndrome births. Their numbers were small and they relied on data obtained from the MRC Cytogenetics Unit, not interviewing the families directly. The study by Heyman et al. (1983) found a clear excess of Down's Syndrome births and also identified a family with a 15/21 'translocation', some family members therefore carrying an extra chromosome 21 and having Down's Syndrome. One member of this particular family with a balanced translocation (i.e. non-Down's Syndrome) and one with an unbalanced translocation (i.e. with Down's Syndrome) have been shown to have Alzheimer's disease (personal communication). Even if this familial form of Down's Syndrome is excluded from their study, the excess of Down's Syndrome in the 'Alzheimer' families remains.

Weinreb (1985), in a study of the dermatoglyphic patterns of 30 patients with presumed senile dementia of the Alzheimer type, reported an increased frequency of ulnar loops, a pattern commonly found in Down's Syndrome, when compared with the frequency of patterns found in a control, non-demented group and with population studies. His study was not performed blind to the diagnosis but, if this observation is shown to be correct, it further supports the possibility of a genetic link between these two disorders, as these patterns are established early in foetal life.

THE AETIOLOGY OF ALZHEIMER'S DISEASE IN DOWN'S SYNDROME

The effects of inheriting an extra chromosome 21 are severe. The major abnormalities of stature, the size and shape of the skull, facial appearance, dermatoglyphics and the likely presence of mental handicap are well known and form the basic Down's Syndrome phenotype. These people are at risk from a variety of other congenital abnormalities affecting the cardiovascular, gastro-intestinal and central nervous systems. This complex Down's Syndrome phenotype is most likely the result of a cumulative effect of the increased concentration of a large number of gene products, compounded by secondary reactions triggered by the imbalance of the genome (Epstein, 1983).

During life, they are at increased risk from infections, cataract formation, leukaemia and auto-immune disorders (Penrose & Smith, 1966). Furthermore, a variety of biochemical abnormalities have been described (Rosner et al. 1965) and, more recently, an abnormality of foetal and adult serum somatomedin levels have been reported (Sara et al. 1983). It is against this background of serious metabolic derangement and structural abnormalities that the risk for developing Alzheimer's disease has to be viewed. The Alzheimer-like changes may be the response of the nervous system to a variety of non-specific abnormalities. There are, however, a variety of aspects that deserve more detailed analysis.

DOWN'S SYNDROME AND AGEING

Down's Syndrome has been proposed as the best example of a premature or accelerated ageing syndrome. Pozsonyi et al. (1964) showed rapid ageing of the skeletal system; Rarick & Seefeldt (1974) demonstrated postural changes normally associated with the fifth or sixth decade of life but occurring in the third; and Domino & Newman (1965) found evidence of premature alopecia and wrinkling of the forehead, as well as other signs of early ageing. Martin (1978) reported increasing chromosomal aneuploidy, ageing pigment deposition, degenerative vascular disease, cataracts, and skin and adipose tissue changes. Other evidence supporting the idea of premature ageing has been the finding of early menopause,
testicular atrophy and the presence of cells normally seen post-menopausally (Gibson, 1978). St Clair & Blackwood (1985), in a study of P300 evoked potentials in individuals with Down's Syndrome and non-handicapped controls, reported that the pattern of change with increasing age was identical in the different groups; however, in cases of Down's Syndrome the pattern was brought forward by many years, supporting the hypothesis of premature, rather than accelerated ageing in Down's Syndrome, the ageing process being no more rapid but starting earlier. The decreased life span, and the observation that in Down's Syndrome there is a slowing and early cessation of development, has been taken as further evidence of a premature ageing process. For example, studies of young Down's Syndrome children have indicated a rapid deceleration in the developmental growth curves (Gessell & Amatruda, 1941; Benda, 1960; Carr, 1970), although it has been argued by Carr that this may be an artefact of the tests used. Loesch-Mdzewska (1968) has reported increasing neurological abnormality with age and has proposed that this may be due to neuropathology affecting the developmental process or to a progressive degenerative disorder. Gibson (1978) has argued that there is a plateau of mental development in Down's Syndrome around the age of 17 years; after that time, a decrease in 'mental age' occurs. Gibson suggests that this relates primarily to the timing of 'supressor events', rather than to an abnormality of 'growth or releaser events'.

The definition of premature ageing is itself disputed, and not all the evidence supports the idea that in the case of Down's Syndrome there is an abnormality of ageing. Murdoch & Evans (1978) found no evidence of abnormal ageing of the skin, although this was disputed by Edwards (1978) who argued that their findings were consistent with an advancement of 10 years in age. Murdoch et al. (1977) also reported that the blood pressure of Down's Syndrome subjects was lower than normal and that there was little evidence of atheromatous lesions, again arguing against premature ageing. However, the low blood pressure and the fact that few people with Down's Syndrome smoke may explain the reduced level of atheroma.

There are two proposed links between Down's Syndrome, premature ageing and Alzheimer's disease. The first is the observation of increasing chromosome instability and inefficiency of cell division associated with increasing age (Whalley, 1982). These abnormalities have been reported to occur prematurely in those with Alzheimer's disease (Buckton et al. 1983) but not in all studies (Martin et al. 1981). Chromosome instability and failure of repair mechanisms have been observed in Down's Syndrome (Countryman et al. 1977). These abnormalities may lead to chromosome breakage and transcriptional errors which, in turn, may lead to abnormal proteins and miscoding for neurotubules and neurofilaments, giving rise to Alzheimer changes (Iqbal, 1979; Lancet, 1985).

Secondly, the basis for the abnormality of the ageing process may be related to the enzyme superoxide dismutase (SOD), the gene for which is located on the long arm of chromosome 21 (21q22). This enzyme is involved in a crucial oxidative process within the cell, resulting in the formation of hydrogen peroxide which, in turn, gives rise to the highly reactive hydroxyl radical. Sinet (1982) proposed that the resultant increase in this reaction, caused by the excess SOD activity, leads to oxidative damage within the cell and accounts for the increased 'ageing' process. Brookbank & Balazs (1983) have established that the activity of SOD is increased in the brains of those with Down's Syndrome but, unlike non-neural tissue, the brain has no compensatory mechanism and the effects of increased enzyme activity remain unchecked.

Using these models, Alzheimer's disease can be seen as the inevitable result of premature ageing. The counter argument is that, first, other premature ageing syndromes are not invariably associated with Alzheimer's change (DeBusk, 1972; Guzzetta, 1972); and, secondly, the inevitability of Alzheimer's disease occurring with increasing age in the general population is far from established (Katzman, 1976). It is clear that the risk increases with age (Nielsen, 1963), but it is far from clear whether those affected by Alzheimer's disease have 'aged' more rapidly or earlier than those not affected. It is not the ageing process per se which leads to Alzheimer's disease but a more specific abnormality, predominantly affecting neurons, that gives rise to the change in, and loss of, specific neurons over time. The question remains as to whether the aetiology of this change in those with Down's Syndrome has
any bearing on a similar change in the non-Down's population (Wright & Whalley, 1984).

**GENETIC MODELS LINKING DOWN'S SYNDROME AND ALZHEIMER'S DISEASE**

It has been argued that the potential double dose of a particular gene, or more correctly particular allele, carried on chromosome 21 may be the reason for the increased risk of developing Alzheimer's change in Down's Syndrome (Yates et al. 1980). However, the importance of any genetic predisposition to Alzheimer's disease is not clearly established.

There have been three large population-based family studies of Alzheimer's disease (Sjögren et al. 1952; Larsson et al. 1963; Heston et al. 1966). In addition, there have been over 50 reports of families with multiple cases of Alzheimer's disease, the largest being reported by Nee et al. (1983). The excess risk of developing Alzheimer's disease observed in relatives of affected probands and the pedigrees reported has, in general, led the various authors to conclude that Alzheimer's disease may be inherited in an autosomal dominant or polygenic manner, such factors as age of onset affecting the apparent degree of expression. Monozygotic twins discordant for the disorder have, however, been reported (Davidson & Robertson, 1955; Hunter et al. 1972), suggesting that the disorder cannot be solely genetic. Cook et al. (1981), reporting a concordant monozygotic twin pair, pointed out that in the case of this pair there was a 10-year difference in the age of onset, raising doubts about whether reported discordant pairs would remain discordant if followed up for longer periods.

The observation of excess Down's Syndrome births within these families (Heston et al. 1981; Heyman et al. 1983) has raised the possibility that the cause of non-dysjunction of chromosome 21 and a genetic predisposition to Alzheimer's disease may be linked. Whether that is specific to chromosome 21 or not remains uncertain, and the presence of such a 'genetic' association is still speculative; however, the use of chromosome 21 probes to identify particular DNA polymorphisms (inherited normal variations in the DNA, which can be used as linkage markers), either in cases of Alzheimer's disease or in Down's Syndrome, is in progress. Antonarakis et al. (1985) reported a particular DNA haplotype on chromosome 21 that is found more commonly in parents and their Down's Syndrome children, compared with a control population with a haemoglobinopathy (P < 0·02). This is important evidence that a site on chromosome 21 may predispose to non-dysjunction of that chromosome. Evidence that non-dysjunction is not only related to advanced maternal age but also to a genetic predisposition is supported by the fact that the risk of having a child with non-dysjunction type of Down's Syndrome is increased if there has been a previously affected child. Furthermore, families with more than one affected member have been described (Soltan et al. 1964; Mikkelsen, 1966). A genetic hypothesis is that an allele at a particular locus on chromosome 21 increases the risk of non-dysjunction of that chromosome (Antonarakis et al. 1985). This, in turn, is also related to the cause of Alzheimer's disease. A single dose of this allele may not significantly increase the risk of developing Alzheimer's disease during life, but if non-dysjunction occurs, giving rise to Down's Syndrome, the double dose of this allele further increases the risk of Alzheimer's disease. Although the gene for SOD has been the most studied, the genes for the α interferon receptor (Epstein et al. 1982), phosphoribosylglycinamidase synthetase (Bartley & Epstein, 1980), and phosphofructokinase–liver isoenzyme (Vora & Francke, 1981) have all been assigned to chromosome 21; and there are clearly many other, as yet unidentified, genes on that chromosome which may be significant. Replication of the Antonarakis study is clearly needed, as is a family study of dementia in the families of those with Down's Syndrome to see whether these two disorders cluster together.

**IMMUNOLOGICAL ABNORMALITIES**

It is unlikely that a transmissible agent is the cause of the occasional familial clustering of Alzheimer's disease (Goudsmit et al. 1980), but the observation that those with Down's Syndrome are at high risk for Alzheimer-like changes has again suggested that an abnormality of the immune system may be significant. Subjects with Down's Syndrome carry an increased risk for developing infections (Collman & Stoller, 1963),
leukaemia (Stowens, 1973) and auto-immune disorders such as thyroid disease (Aarskog, 1969). The immune response has been shown to deteriorate rapidly in response to phytohaemaglutamine (PHA) (Seger et al. 1971) but, as Walford (1982) pointed out in his review, the evidence concerning susceptibility to infection and auto-immune disorders is conflicting.

A recent paper by Pouplard et al. (1983) reported the presence of prolactin cell antibodies in the sera of 26 out of 27 cases of Alzheimer’s disease and in 10 out of 11 cases of people with Down’s Syndrome suffering from dementia. Philpot et al. (1985) have been unable to replicate these findings, but there were methodological differences between the two studies. Heyman et al. (1984) reported an increased history of thyroid disease in the female members of a cohort of individuals with Alzheimer’s disease, compared with a control group. They proposed that this may be an additional environmental factor, not directly causative but in some way involved in the aetiology of Alzheimer’s disease.

Pogo & Elizan (1985) have looked for viral DNA sequences in the brains of histologically confirmed cases of Alzheimer’s disease using Southern blot hybridization techniques. No viral sequences were found in Alzheimer or control brains. This supported previous work which reported that antibodies to well-known viruses are not found in excess in those affected by Alzheimer’s disease (Whalley et al. 1980). However, Epstein & Epstein (1980) reported that trisomic 21 cells had an enhanced sensitivity to interferon and that this might paradoxically adversely affect immune function and therefore increase susceptibility to extrinsic or intrinsic infectious agents.

Whether or not immune dysfunction, autoimmunity and/or infectious agents are central to the causation of the Alzheimer’s change in Down’s Syndrome or in the aetiology of Alzheimer’s disease is unknown.

DISCUSSION

From the neuropathological literature the assumption arises that all elderly people with Down’s Syndrome have the neuropathological signs of Alzheimer’s disease and would therefore be expected to have the clinical signs of dementia. However, the psychological studies reviewed here, and other evidence from neuropathological studies, show a number of inconsistencies with this premise.

First, although the neuropathological studies suggest that all those with Down’s Syndrome over the age of 35 can be expected to exhibit the changes of Alzheimer’s disease, none of the studies of cognitive functioning show deficits in all members of this age group, as compared with a younger group. For example, Thase et al. (1982) reported one subject aged 59 who showed no evidence of dementia, and Dalton & Crapper (1977) described 5 Down’s Syndrome subjects over the age of 44 as showing slight improvement in memory over a 3-year time span. Apart from psychological tests, it is clear from anecdotal evidence that many people with Down’s Syndrome show no evidence of deterioration in their fourth or fifth decade. Secondly, some people with Down’s Syndrome show Alzheimer-like changes at post mortem but have shown no signs of clinical deterioration prior to death (Olson & Shaw, 1969; Schochet, 1973; Ropper & Williams, 1980; Yates et al. 1980, 1981); from an alternative point of view, if there is evidence of dementia its degree is not indicative of the extent of the neuropathology (Ropper & Williams, 1980). Neuropathological changes do not therefore necessarily lead to clinical dementia, and the presence of clinical dementia does not necessarily indicate marked neuropathological change.

There are a number of alternative explanations of these findings. In elderly individuals with Down’s Syndrome who have no sign of dementia the neuropathology may simply not be present. As Dalton & Crapper (1977) have suggested, the incidence of neuropathological change of the Alzheimer-type may be considerably lower than the 100% post mortem based findings, perhaps because Alzheimer’s disease is a contributory factor in the death of older subjects, and this group of dementing subjects is more likely to be hospitalized and thus to receive a post mortem than those living in the community. Furthermore, in the case of Down’s Syndrome, death from other age-related causes may occur at an earlier stage at the neuropathological change before clinical signs develop.

However, if the neuropathology is present it may be that there is a degree of neuronal redundancy (Crapper et al. 1975) and, therefore, the degeneration does not initially affect certain
basic functions, although 'higher' functions in those with Down's Syndrome may be prevented from developing. It may also be that cognitive tests used to detect deterioration are not sufficiently sensitive to the changes which occur. Miniszek (1983) has argued that it is the nature of the institution that masks the cognitive deficits by sheltering the individuals from such tasks that might expose the deficits. It may also be that as the label 'handicap' is dominant, as opposed to 'aged' or other labels, difficulties may therefore be attributed to the underlying handicap, as opposed to a developing dementia, thus underestimating the prevalence of dementia in this population. Sylvester (1984) has reported changes in the neuronal structures, not present in the Down's Syndrome foetus, but developing early in life. He has suggested that these changes have 'primed the gun' for later Alzheimer's pathology and clearly may themselves contribute to the handicap, supporting the concept that what is labelled as due to 'handicap' is in fact due to 'dementia'. The lack of previous information on cognitive performance, combined with the great variability on cognitive testing of people with Down's Syndrome (Breg, 1977), makes it difficult to infer a previous performance level and therefore to recognize the signs of deterioration.

CONCLUSIONS

Neuropathological and clinical evidence clearly points to a link between Down's Syndrome and Alzheimer's disease. Whereas a high proportion of those with Down's Syndrome develop the neuropathological changes of Alzheimer's disease, only a proportion develop definite signs of deterioration and have the clinical features characteristic of the later stages of Alzheimer's disease. The studies discussed here have implications for future research. While cross-sectional designs comparing cognitive deficits in age groups would seem to be the most practical approach, it is important to examine a large range of age groups, bearing in mind the variation in age of those with Down's Syndrome who show neuropathological change at post mortem. With this reservation, it may be beneficial to develop more sensitive tests of cognitive dysfunction (e.g. abstract memory tests with varying recall times and degrees of distraction) in order to establish early signs and patterns of deterioration. Combining these cognitive tests with other measures of Alzheimer's pathology (e.g. CAT scans demonstrating atrophy and density changes, delayed evoked potentials) may reveal more distinctive early clinical indicators of deterioration. In the light of St Clair & Blackwood's (1985) finding that evoked potential latency in those with Down's Syndrome increased significantly earlier in life than normal controls, correlating cognitive test results with evoked potential latency may provide early indicators of deterioration in those with Down's Syndrome. One of the authors (C.O.) is currently comparing evoked potential latencies with cognitive and behavioral measures in people with Down's Syndrome and also in those with the Fragile-X Syndrome. This may then, in turn, assist in the identification of early signs and predisposing factors in Alzheimer's disease in those people with and without Down's Syndrome.

The reasons for the association between these two disorders are unknown, but several hypotheses have been suggested, including an abnormality of ageing, a failure of chromosome repair mechanisms, an inherited predisposition to both non-dysjunction of chromosome 21 and Alzheimer's disease, and a disorder of the immunological system. Down's Syndrome, however, is associated with many congenital and acquired abnormalities which may predispose to Alzheimer's type change. There is also evidence from a variety of sources that Down's Syndrome may be a progressive disorder and that the 'handicap' and the 'dementia' may, at least partially, have a common aetiology in the form of the Alzheimer-like pathology (Corbett, 1985).

Further study is needed into the risk to those with Down's Syndrome of developing the clinical features of Alzheimer's disease, what determines the age of onset and its relationship to Alzheimer's disease in the non-Down's population. The risk of dementia in those with Down's Syndrome has clear implications for the establishment of appropriate services and, in addition, any treatment delaying the development of the Alzheimer neuropathology is potentially very significant for those with Down's Syndrome.

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