differences did not result in a discrepancy of more than a week in any patient scanned between eight and 14 weeks. When real-time equipment is used the fetal movements are readily appreciated, and with electronic callipers several measurements can quickly be made, thus minimising errors.

In practice, however, most patients do not attend this early, so that other schemes are needed. At King's College Hospital⁷ a plan of routine scanning between 16 and 18 weeks has been adopted for the following reasons. Measurements of the biparietal diameter are easy at this time and, though less precise than early crown-rump length (by ± 4 days), are considered clinically acceptable; the abdominal circumference measurement is a check on the biparietal diameter; early diagnosis of multiple pregnancy is facilitated; patients with low placental implantation are identified for further study; and gross abnormalities such as anencephaly are readily diagnosed.

Though spina bifida cannot reliably be detected with real-time equipment, recent advances in imaging hold out much promise. Enlargement of the lateral ventricles may point to hydrocephalus, and exomphalos has been described at this time. At King's blood is also taken for estimation of alpha-fetoprotein at this visit.

Nevertheless, even if the accuracy of scanning in the average district general hospital is generally as good as in the centres of excellence, there remains the problem of a systematic error of about a week either way in gestational estimation for most of the 75% of patients who present before 18 weeks, and at present this cannot be improved. To cope with this difficulty the Cardiff group⁸ has devised a "fail-safe" procedure. Women with serum alpha-fetoprotein concentrations above the 90th centile are carefully scanned for obvious abnormalities and multiple pregnancies and to reassess gestational age. Amniocentesis is offered where doubt remains or if the serum alpha-fetoprotein concentration is higher than the 95th centile.

Elsewhere early attendance remains disappointing. For instance, in Mid-Glamorgan in 1978 only 40% of women had attended by 16 weeks, and 30% had not attended by 20 weeks. As in Aberdeen, many late attenders (42%) were primigravidae who had delayed reporting the pregnancy to the general practitioner. On the other hand, most women at particularly high risk during pregnancy and who have medical disorders such as diabetes refer themselves promptly for care, as do those patients with an unhappy obstetric history. These highly motivated mothers are those most in need of the benefits conferred by early attendance and in the main take full advantage of this facility.

It might be argued that delaying most screening procedures to between 16 and 18 weeks, as is the practice at King's, might further encourage late booking. Furthermore, some patients, thinking themselves to be earlier in pregnancy than they really are, might miss out altogether. In practice, however, 16-18 weeks is currently the most popular time to book anyway, and errors in estimation of gestational age from the menstrual history are mostly overestimates.⁹

In a perfect world such considerations would be unnecessary, but until we can educate our prospective patients in what we consider to be prudent behaviour we must take the world as it is and compromise as best we can.

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Genetics of Alzheimer's disease

Waning intellectual power may be accepted as part of old age, but dementia in the prime of life causes appalling social and personal problems. For patients with Alzheimer's disease the misery may be worse since they are often aware of their plight: insight is often retained while memory and intelligence are destroyed. With little sound data based on biopsy evidence the prevalence of Alzheimer's disease is not known with certainty¹; perhaps one in every 20 in the British population suffers from dementia by the age of 70.² When no treatable underlying cause is found for dementia the clinician may easily succumb to diagnostic nihilism, discouraged by the need for a brain biopsy to delineate the precise form of presenile dementia. Certainly the immediate need is to cope with the distress of the patient and family, but accurate diagnosis is essential both to determine the prognosis and to advise close relatives who are worried about their risk of becoming demented in the future.

Animals can be infected experimentally with virus-like agents transmitted from the brains of patients with Creutzfeldt-Jakob disease or with Alzheimer's disease.³⁻⁵ Gajdusek⁶ has suggested that a single agent may be responsible not only for Alzheimer's disease, Creutzfeldt-Jakob disease, and kuru in man but also for scrapie in sheep and transmissible encephalopathy in the mink. The transmission of kuru in New Guinea, which mimics dominant inheritance, depends on the local custom of honouring deceased relatives by eating their brains,⁷ while Creutzfeldt-Jakob disease has been transmitted on one occasion after the transplantation of the cornea of a patient.⁸ Just how a slow virus might be transmitted naturally in man to cause presenile dementia is not known, but Harper⁹ has suggested that disease attributable to slow virus infection may often mimic the pattern of autosomal dominant inheritance. Yet even in striking, but fortunately rare, "dominant" Alzheimer pedigrees well over half of the close relatives remain healthy. Perhaps this is due to chance lack of exposure to the causative agent, but most observers would accept that resistance genes also operate. The major histocompatibility complex in animals and in man includes immune response genes,¹⁰ and these are influential in resistance to viral infection.

Henschke *et al*¹¹ and others (reviewed by Walford and Fortoul¹²) have studied HLA antigens and some, but not all, have found that HLA-B7 and HLA-CW3 occur more fre-

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quently in patients with Alzheimer's disease than in normal controls. These antigens also segregated in the same haplotype in a large family studied in Manchester by Harris, Klouda, and Neary and reported to the International Histocompatibility Workshop.¹³ In this family most members with presenile dementia had the B7, CW3 haplotype which also carried DR2. Finding this rare combination of HLA antigens in population studies of unrelated patients¹² and independently in Manchester in a large kinship should encourage the search for major histocompatibility complex-linked genes controlling susceptibility to the putative slow virus of Alzheimer's disease.

A quite separate unresolved problem is the part played by chromosome abnormalities in Alzheimer's disease. Most, perhaps all, people aged over 40 with Down's syndrome develop an Alzheimer-like disease,^{14 15} and Heston *et al*¹⁶ found a fivefold increase in the prevalence of people with Down's syndrome in families of patients with early-onset Alzheimer's disease. Though more than half of the patients with Down's syndrome in the report of Heston *et al* were born to mothers of 35 years and over, higher maternal age was not thought to be important in this fivefold increase. These findings are disturbing and suggest that amniocentesis should be offered to women in families with early-onset or familial Alzheimer's disease. Ward *et al*¹⁷ believe that chromosome abnormalities are so typical of Alzheimer's disease that aneuploidy might be diagnostic even before the development of symptoms, but White *et al*¹⁸ failed to find any consistent cytogenetic abnormalities in seven patients with familial and five with sporadic Alzheimer's disease. Perhaps different forms of Alzheimer's disease were represented in these studies.

In the mean time, what information can be given to anxious relatives of patients with dementia about the genetic risk to themselves and to their children? The first step must be to establish the precise diagnosis, excluding secondary and potentially treatable dementia. The distinction between the various forms of "idiopathic" presenile dementia is based both on clinical findings and on neuropathological examination. A rapid course with pyramidal and extrapyramidal signs and death within a year suggests Creutzfeldt-Jakob disease, which can be confirmed neuropathologically. Pick's disease, while also distinguishable neuropathologically, may be confused clinically with Alzheimer's disease. Finding neurofibrillary tangles and senile plaques in a brain biopsy specimen or at necropsy is characteristic both of Alzheimer's disease and of senile dementia, with which Alzheimer's disease overlaps clinically. In common with all genetic counselling problems a detailed family history is essential with confirmation of the diagnosis in relatives, usually by reference to hospital records. Dramatic pedigrees with multiple cases of presenile dementia do occur and should alert the counsellor to the higher risk in these families than in those with an isolated case.¹⁹⁻²¹ The genetic risk is also much higher when the index patient's symptoms begin below the age of 65. Heston *et al*¹⁶ studied 125 patients with histologically proved Alzheimer's disease in the United States. In 60% of cases the index patients were isolated with no other cases in the family. Patients were younger and the disease had a more rapid course in families in which secondary cases did occur. The findings of Heston *et al* seem to clinch the argument that symptoms of dementia first occurring after the age of 70 carry little genetic risk for close relatives. In contrast, when the disease occurs in

patients below the age of 65 and when another relative has had the disease the risk is considerable. When the proband and a parent are affected nearly half the siblings eventually become demented, the pattern closely resembling autosomal dominant inheritance in these unusual families.

Current epidemiological and clinical studies promise to help identify the subtypes of Alzheimer's disease. The patterns of familial occurrence resembling autosomal dominant inheritance may be mimicked by a transmissible agent, but the effect of genes in controlling the response to slow viruses may explain why only some relatives develop the disease. Alzheimer's disease may prove a classic example of the relation between genes and viral disease.

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