British Journal of Psychiatry (1992), **160**, 24–35

Review Article

The Fragile-X Syndrome
On the Way to a Behavioural Phenotype

JEREMY TURK

The fragile-X syndrome accounts for up to 10% of individuals with mental handicap, and 50% of cases of X-linked mental retardation. Knowledge of the genetic basis of mental functioning, psychopathology, and neuropsychology is being furthered by this recently recognised condition. The disorder has considerable significance for psychiatrists, particularly, but by no means exclusively, those working in the field of mental handicap and with children. This review outlines the slow clarification of this complex and important behavioural phenotype and the implications of these advances for identification, diagnosis, genetic counselling and a wide range of management interventions.

The fragile-X syndrome consists of the association of learning difficulties of a variable degree with the cytogenetic abnormality known as the fragile-X chromosome. It accounts for approximately 10% of all boys with severe mental retardation of no obvious cause (Webb *et al*, 1986), and for 6–10% of unexplained mild mental retardation (Thake *et al*, 1987). It is recognised as the commonest genetic cause of mental retardation after Down's syndrome (Davies, 1989). The condition is transmitted in a sex-linked fashion, albeit atypically (see below). However, segregation studies confirm that only four-fifths of males who inherit the chromosomal mutation suffer learning difficulties (Nussbaum & Ledbetter, 1986), while one-third of carrier females are mentally retarded (Hagerman & Sobesky, 1989). There are no pathognomonic features, but a variety of commonly observed physical stigmata have been observed. These physical characteristics have also been observed in family pedigrees, in conjunction with learning difficulties but without the characteristic chromosomal anomaly – so-called Martin–Bell syndrome.

The recognition of the syndrome has been widely considered to be a major advance in explaining the common observations of familial aggregations of apparently idiopathic mental handicap, and the greater numbers of males than females who have learning difficulties. Claims have been made for various associated psychological dysfunctions, including autism, deficits in attention and concentration, speech and language anomalies, unique intellectual profiles indicative of certain underlying neuropsychological disturbances, and schizoaffective disorders. It is, therefore, important for psychiatrists to be fully aware of the fragile-X syndrome and its associated features, irrespective of their subspecialty and the mean age of their client group.

There are already good general reviews of the syndrome (Chudley & Hagerman, 1987; Hagerman, 1987). This article considers important genetic, epidemiological, and physical aspects, before addressing current understanding of psychological functioning in individuals with the fragile-X syndrome through a critical appraisal of research undertaken to date.

Genetics

The syndrome derives its name from the appearance of a hypochromic ragged-looking constriction site at the distal end of the long arm of the X chromosome – position Xq27.3. The appearance is due to failure of normal chromatid condensation during mitosis. Laboratory diagnosis is complicated by the need to culture lymphocytes in folate-deficient media in order to reveal the chromosomal abnormality (Sutherland, 1977). Cultures are stressed further by thymidine deprivation and the addition of cytotoxic agents such as methotrexate and 2′-deoxy-5-fluorouridine (Fudr) in order to enhance expressivity. Even then only a fraction of cells display the anomaly in positive individuals. The proportion of positive cells ranges from less than 5% to greater than 60%, but is mostly in the range 10–40% (Gardner & Sutherland, 1989).

The procedure's complexity provides scope for considerable variability in assay technique and consequent rates of expression of fragile sites. Recent moves towards standardisation of the test have improved inter-laboratory and test–retest reliability, although discrepancies in method persist. Clinically, it is essential to state clearly the desire for special culture and analysis to check for fragile X, and to support this request with sufficient detail. The test

will not usually be undertaken on samples sent for routine chromosomal analysis.

Using the best-known conditions for lymphocyte culture, the site at Xq27 is still not detectable in some females who are obligate carriers (Sutherland, 1982). Also, family pedigrees have documented apparently normal male carriers who transmit the fragile X to their daughters (Loesch *et al*, 1987), raising the possibility of a pre-mutation stage which does not express itself phenotypically (Pembrey *et al*, 1985). Currently, accepted practice is to examine at least 50 cells (sometimes up to 200 in female carriers) using a threshold of 4% expressivity as evidence of the syndrome (Pembrey *et al*, 1986). This is *not* to say that individuals expressing less than 4% Xq27.3 fragility do not have fragile X – they may. Subtle changes in culture conditions influence this expressivity and thus likelihood of detection (Tommerup, 1989). Furthermore, low frequencies of lesions resembling the fragile X have been found in cell cultures from unaffected subjects, as well as clinically irrelevant fragile sites close to Xq27.3 (Ledbetter *et al*, 1986). Explicit, consistent cytogenetic diagnostic criteria are therefore needed.

Age has been claimed to affect fragile-site expressivity. Chudley *et al* (1983) demonstrated a slight but significant inverse correlation of frequency of fragile-X cells with age in males using multiple-regression analysis. However, most reports are at variance with this finding. If there is a reduction it is indeed small – although given the possibility of very low percentage expressivity in affected individuals it may well be clinically significant in producing false-negative results (McGavran & Maxwell, 1983).

Unlike some other genetic conditions (e.g. Down's mosaicism), there is no relationship in fragile-X males between intellectual level and proportion of cells expressing the chromosomal anomaly on testing (Rogers & Simensen, 1987), and mean parental age is not elevated (Brondum Nielsen *et al*, 1982).

Antenatal diagnosis can now be undertaken by sampling chorionic villi or foetal blood. Molecular studies using recombinant DNA technology and restriction fragment length polymorphisms (RFLPs) are being evaluated for detection of carrier status (McKinley *et al*, 1988).

The pattern of inheritance is atypical for recessive or dominant X-linked inheritance. Theories have been developed to explain this, including the notion of X-chromosome inactivation (lyonisation), a pre-mutation phenomenon whereby initial insult to the X chromosome manifests clinically as fragile X only after transmission through an intermediate, asymptomatic, generation (Pembrey *et al*, 1985), and the concept of focal chromosomal imprinting during reactivation (Laird, 1987). The practical implication is not to be deterred from referring for testing for fragile X simply because the family pedigree does not fit snugly into a sex-linked pattern with asymptomatic female carriers and affected males.

The site and structure of the fragile-X mental retardation gene (FMR-1) has now been confirmed (Verkerk *et al*, 1991). It is located at the Xq27.3 'fragile' locus and consists of abnormal multiple CGG replications (coding for arginine) which grow transgenerationally, produce abnormal DNA hyper-methylation, and consequently disturb protein synthesis. The number of CGG repeats correlates with the degree of clinical involvement and the presence of methylation correlates with the lack of FMR-1 expression. In the general population, 3% may have a small CGG insert which represents carrier status.

Epidemiology

Fragile-X syndrome has been described in all races and ethnic groups studied (Turner & Jacobs, 1983). Total-population prevalence studies have been restricted by the practical and financial constraints of a relatively infrequent syndrome with a laborious and expensive diagnostic test. Researchers have, therefore, focused on institutional and school communities. Prevalence estimates based on calculations from these sources have ranged from 0.19 to 0.92 per 1000 (Herbst & Miller, 1980; Blomquist *et al*, 1983). The significance of these estimates is increased by findings that fragile X can be present in over 25% of families with so-called non-specific mental retardation, previously thought to be related to poor sociocultural environments and deprivation (Fryns & van den Berghe, 1983).

The prevalence of fragile X in an unselected series of severely mentally retarded boys has been found to be 6% (Blomquist *et al*, 1982). A subsequent study of children with mild mental retardation disclosed 5 out of 110 boys (4.5%) and none of 61 girls as having fragile X, giving a combined incidence of 5 out of 171 or 2.9%. Taken together these figures provide a combined prevalence of 1 in 3000 children having mental retardation and fragile-X syndrome (Blomquist *et al*, 1983).

A series of studies in the West Midlands found 8.9% of children with 'idiopathic' severe mental retardation to have fragile X (Bundey *et al*, 1985), with the prevalence of fragile X for all schoolchildren being calculated at 1 per 1000 – although children with normal intellectual functioning were not examined to corroborate this figure (Webb *et al*, 1986). A follow-up study in schools for children with mild learning difficulties (Thake *et al*, 1987) confirmed that even in this relatively able group, there were still almost 8% found to harbour the

fragile X chromosome; these children had previously been labelled as having idiopathic mental retardation. Furthermore, 14 out of 17 mothers of children with fragile X were found to have the fragile-X chromosome; this has considerable implications for genetic counselling. The three mothers who did not demonstrate X chromosome fragility were presumably 'non-expressing carriers', although there are the less likely possibilities that their offspring inherited the genetic defect from asymptomatic fathers, or that they were victims of fresh mutations.

Institutional studies confirm the syndrome's high frequency, with typical rates ranging from 2.5% to 5.9% for individuals with idiopathic mental retardation (Hagerman *et al*, 1988*a*; Neri *et al*, 1988). These figures indicate that the fragile-X syndrome is the most common inherited cause of mental handicap, and must be considered in any individual with unexplained developmental delay, irrespective of severity.

Physical features

Fragile-X syndrome is associated with a multitude of physical features, none of them pathognomonic. An underlying connective-tissue dysplasia has been demonstrated which explains many common associations, including joint laxity and soft, velvety skin (Opitz *et al*, 1984). Characteristically, the individual has a long face and a slightly increased head circumference (population mean on 60th centile) (Bundey *et al*, 1985), leading to possible diagnostic confusion with Sotos' syndrome (Cole & Hughes, 1990). Macrognathia may contribute to speech difficulties. Ears are large and protruding. The nasal bridge is often long and flattened, and the palate may be high-arched. Dermatoglyphics may be abnormal, for example, a curious deep vertical anterior plantar crease (Simko *et al*, 1989). Macro-orchidism has been reported in up to 96% of adult males studied (Turner *et al*, 1980). It is evident antenatally (Rudelli *et al*, 1983) but becomes useful diagnostically only after puberty. Above-average birth weight and infantile hypotonia have been observed (Brondum Nielsen, 1983). Cardiovascular complications include aortic dilatation with mitral-valve prolapse, and defects similar to those seen in other connective-tissue disorders such as Marfan's syndrome and Ehlers–Danlos syndrome (Sreeram *et al*, 1989; Redington & Bush, 1990).

Early hopes that it might be possible to make a clinical diagnosis of the fragile-X syndrome (Thake *et al*, 1985) have been superseded by awareness of just how extensive the variability in phenotypic expression actually is (Loesch *et al*, 1987). Recent work suggests body *shape* with the effect of body size removed may be a more useful indicator. Loesch & Wilson (1989) found individuals with fragile X to have shorter arms and upper face, with increased body width and jaw length in relation to overall body size. None the less, there is more agreement on the significance of the behavioural than the physical characteristics (Hock & Crowhurst, 1988).

Cognitive functioning

Developmental delay in the fragile-X syndrome varies considerably, from normal levels of intellectual ability through to severe/profound mental handicap, which affects approximately 30% (Curfs *et al*, 1989*a*; Hagerman & Sobesky, 1989). A significant proportion of males function in the average or borderline range initially, and early developmental milestones such as onset of walking may be normal (Lachiewicz *et al*, 1987). A few family studies suggest an uneven intellectual profile, with verbal intelligence substantially exceeding performance abilities (Veenema *et al*, 1987), raising the possibility of a motor organisational dysfunction. Testing on standardised psychometric tools such as the picture vocabulary and block design tests supports this claim (Theobald *et al*, 1987), although assessments of clinic populations have not always done so (Curfs *et al*, 1989*b*).

Non-retarded female carriers demonstrate the same verbal/performance discrepancy as the more severe affected males with fragile X, obtaining diminished scores in arithmetic, digit span, block design, and object assembly (Miezejeski *et al*, 1986), in the presence of relatively good performance in vocabulary and comprehension (Kemper *et al*, 1986).

Detailed assessment of 20 boys with fragile X and 20 comparison boys referred for testing but found to be negative has generated a distinctive cognitive phenotype which may relate to specific deficits in the central nervous system (CNS) (Kemper *et al*, 1988). Sequential scale scores were found to be diminished in relation to simultaneous scale scores, mental processing composite score poorer than achievement scale score, spatial memory subtest score worse than matrix analogies subtest score, and arithmetic subtest score poorer than the mean of achievement subtest scores.

Individuals with fragile X have greater difficulty processing novel information than with learning school-related, verbally based factual material (Reiss & Freund, 1990). Significant deficits in visual reasoning have been found relative to verbal reasoning abilities – problems being greatest in the processing of novel, sequential information, especially when short-term memory and flexibility in problem solving are required.

When institutionalised men with fragile X are compared with males with idiopathic retardation,

and with autistic individuals, there is little evidence for this specific cognitive profile, although there remains the suggestion of impaired visuomotor, performance and short-term memory skills in the males with fragile X (Dykens *et al*, 1988).

Intellectual level appears to diminish with age. Cross-sectional and longitudinal studies of the trajectory of cognitive development demonstrate steady cognitive growth until 10–15 years, at which point mental age plateaus and IQ declines, particularly in males with higher initial IQ scores (Dykens *et al*, 1989). Not all individuals suffer this fate, which may result from relatively greater weaknesses with abstract reasoning and symbolic language skills that are stressed in the cognitive testing of later childhood and adolescence (Hagerman *et al*, 1989).

Despite the wide variation in intellectual functioning, there remains good evidence for a characteristic profile of cognitive strengths and needs, with greater verbal than performance abilities and a tendency towards diminishing intellectual functioning, commencing in late childhood.

Speech and language

The development of speech and language is almost always retarded, from an entire absence of speech (Fryns *et al*, 1984) through to milder communication difficulties reflecting combined influences of social and behavioural dysfunctions on abnormally developing language skills. These often manifest as dysfluent conversation with incomplete sentences and palilalia (compulsive repetition of words and phrases reiterated with increasing rapidity and with decrescendo of voice volume) (Newell *et al*, 1983). A jocular quality has been reported (Hagerman, 1989*a*), as have narrative and compulsive utterances with swings of pitch, described as 'litany-like' (Turner *et al*, 1980). The term 'cluttering' ('tachyphemia') has been used to describe the fast and fluctuating rate of talking, with repetitions of sounds, words and phrases, and occasional garbled, slurred or disorganised speech in the presence of poor topic maintenance, frequent tangential comments, and revisions (Hanson *et al*, 1986).

Language form is superior to its content and use (Carpenter *et al*, 1982), and repetitive vocabulary skills excel over auditory memory and processing abilities (Hanson *et al*, 1986). This generalised language dysfunction is frequently combined with articulation errors (Howard-Peebles & Stoddard, 1979) and may reflect problems with higher-level motor encoding of linguistic information (Vilkman *et al*, 1988), developmental dyspraxia (McGlaughlin & Kriegsman, 1980), or difficulties due to associated macrognathia or high-arched palate.

Other common language and communication abnormalities include echolalia, verbal perseveration, and idiosyncratic responses (Bregman *et al*, 1988). Significantly affected heterozygous females may have characteristic high-pitched speech, with repetitions, poor topic maintenance, and occasional cluttering (Hagerman, 1987).

This characteristic jocular, litany-like phraseology may well be the feature most reliably associated with fragile X. The underlying neuropathology responsible for such a specific language style remains a mystery.

Autism and other social impairments

Associations between fragile-X syndrome and a variety of behavioural disturbances have been suggested. The frequent coexistence of autistic features and fragile X has been commented on for almost a decade (e.g. Brown *et al*, 1982*a*). However, studies have yielded contradictory findings, with the incidence of autism ranging from 0% (Chudley, 1984) to over 60% (Levitas *et al*, 1983). These wide discrepancies are partly explained by differing diagnostic criteria, with considerable persisting controversy as to the nature of autism as a syndrome. Many studies have relied on anecdotal reports, or have failed to utilise reliable standardised behavioural inventories. There has often been no attempt to control for intellectual level – a crucial aspect given that the prevalence of autism increases with the degree of mental retardation (Wing & Gould, 1979). Hence, many conclusions drawn could relate to all individuals with intellectual impairment – not just those with fragile X.

Early case reports hinted at a direct association between autism and fragile X on the basis of their simultaneous occurrence in individuals (Meryash *et al*, 1982), and concordant findings in siblings (August & Lockhart, 1984), twins (Gillberg *et al*, 1988), triplets (Gillberg, 1983), and family pedigrees (Reiss *et al*, 1986). Ensuing efforts to clarify this possible association can be separated into those which have searched for fragile X in individuals with autism, those which look for autism in individuals with fragile X, and studies comparing cohorts with fragile X with matched controls.

Testing individuals with autism for fragile X

Studies which have tested individuals with autism for fragile X have found rates ranging from 0–20%. A major intrinsic weakness in these 13 investigations, reviewed in Table 1, is the absence of comparison groups. Also, conclusions have been shown to be significantly affected by sample size as well as by behavioural and cytogenetic protocols (Fisch *et al*, 1988*a*). The widely discrepant results doubtless reflect these shortcomings.

Table 1
Testing of individuals with autism for fragile X

Authors	Subjects	Selection process	Prevalence of fragile X
Brown *et al* (1982*b*)	22 males from 16 families	Individuals with autism referred for diagnostic evaluation; 16 families with fragile X discovered; other members of these families subsequently tested for fragile X	5 out of 22 males (22.7%)
Venter *et al* (1984)	40 boys, 17 girls	Survey of 2 autism schools; no selection for positive family history or mental handicap	0%
Watson *et al* (1984)	76 individuals with infantile autism	-	8 out of 76 (10.5%)
Blomquist *et al* (1985)	102 individuals with autism (multicentre study)	77 individuals ascertained through total-population screens for autism; additional 25 individuals diagnosed as autistic	13 out of 83 males (15.7%); 0 out of 19 females (0%); 13 out of 102 individuals (13%)
Gillberg & Wahlstrom (1985)	46 individuals with DSM-III infantile autism; 21 with other psychoses, i.e. similar symptoms but for whom onset before 30 months of age could not be documented	DSM-III autism: 25 individuals ascertained through total-population screen, 21 consecutive out-patient attenders with diagnosis. Other psychoses: 13 individuals ascertained through total-population screen + 8 consecutive out-patient attenders with diagnosis	DSM-III autism: total population 5/25 (20%); clinic attenders 3/21 (14%). Other psychoses: total population 0/13 (0%); clinic attenders 0/8 (0%)
Goldfine *et al* (1985)	34 males, 3 females with DSM-III autism: out-patients living at home	-	0%
Pueschel *et al* (1985)	350 males with autism and family history of mental retardation	18 individuals selected for testing due to dysmorphic features	0%
Brown *et al* (1986)	179 males with autism (multicentre study)	-	24 out of 179 (13.4%), range for different centres 0–23%, mean prevalence 9.8%
Fisch *et al* (1986)	398 males referred as autistic or with family history of mental retardation or autism	144 met DSM-III criteria for infantile autism	18 out of 144 (12.5%); of the 254 remaining individuals (many of whom had autistic-like features), 52 (20.6%) had fragile X
McGillivray *et al* (1986)	32 males, 8 females with autism from mental retardation institution	-	3 out of 32 males (9.3%); 0 out of 8 females (0%); 3 out of 40 individuals (13%)
Wahlstrom *et al* (1986)	122 consecutive children with DSM-III autism referred to cytogenetic laboratory	-	16 out of 101 males (15.8%); 0 out of 21 females (0%); 16 out of 121 individuals (13%)
Wright *et al* (1986)	31 males, 9 females (mean IQ 43.5) most living at home and attending day-treatment programmes	-	1 out of 40 (one male) (2.5%)
Payton *et al* (1989)	85 males with DSM-III autism referred to in-patient programme for handicapped children	-	2 out of 85 (2.4%)

It could also be argued that too narrow a definition of autism is responsible for some of the low prevalence rates found. Only two studies included subjects obtained from total-population surveys for autism (Blomquist *et al*, 1985; Gillberg & Wahlstrom, 1985) – displaying rates of 13% and 20% respectively for fragile X in the autistic groups. These findings are particularly important because of their avoidance of referral bias. Indeed, Gillberg & Wahlstrom (1985) demonstrated an even higher rate of fragile X in the total-population group than in clinic-referred cases.

https://doi.org/10.1192/bjp.160.1.24 Published online by Cambridge University Press

Table 2
Assessing individuals with fragile X for autistic features

Authors	Subjects	Selection process	Findings
Fryns *et al* (1984)	21 males aged 2–21	Unselected	Echolalia with perseveration (10); absent eye contact (3); self-injurious behaviour (13)
Largo & Schinzel (1985)	13 boys from 3 families	Unselected	Profound delays in imitative and symbolic play; diminished eye contact and stereotyped or repetitive behaviour common (9/13)
Hagerman *et al* (1986*b*)	50 males	Unselected	Hand flapping, hand biting and poor eye contact each in at least two-thirds; DSM–III autism in 16% (8)
Bregman *et al* (1988)	14 males aged 3–27	Diagnosed after testing due to developmental delay with family history of mental retardation or as part of a thorough mental retardation 'work-up'	DSM–III infantile autism in 1 (7%); gaze aversion in 50%; frequent stereotypies, occasional perseverative preoccupations

Findings to date therefore suggest that a substantial minority of individuals with autism have fragile X, and enough findings are sufficiently striking to support the current consensus that any individual with autism of unknown aetiology should be tested for fragile-X syndrome.

Assessing individuals with fragile X for autism

Four studies have addressed the possibility of a direct association between autism and fragile X by observing individuals with fragile X for autistic features (Table 2). Despite a lack of comparison groups, these studies have the advantage of being able to isolate those dimensions of social impairment that have predisposed fragile-X individuals to being labelled autistic.

Fryns *et al* (1984) evaluated 21 unselected males with fragile X aged 2–21 years. Ten were found to have echolalia with perseverative speech, 13 had self-injurious behaviour, most notably hand-biting and scratching provoked by frustration and excitement, and three had poor eye contact. Assessment of 13 boys with fragile X from three families (Largo & Schinzel, 1985) uncovered profound delays in imitative and symbolic play. Nine of the 13 had difficulties with eye contact and stereotyped, repetitive behaviour. In a study of 50 unselected males with fragile X, hand-flapping, hand-biting and poor eye contact were each seen in at least two-thirds of the sample (Hagerman *et al*, 1986*b*); 18% demonstrated a pervasive lack of ability to relate to others, with 16% fulfilling DSM–III criteria for autism. The report by Bregman *et al* (1988) of 14 males with fragile X aged 3–27 showed one individual to have DSM–III infantile autism, and two more to have once fulfilled criteria for DSM–III pervasive developmental disorder. However, 50% of the sample had gaze aversion, including those individuals described as socially responsive and affectionate. Over 50% displayed stereotypies or self-injurious behaviour, and nearly 25% had perseverative preoccupations and interests. In general these symptoms were distributed randomly.

It seems that a substantial minority of males with fragile X have autism. Many more display certain autistic features.

Comparing fragile-X populations with matched comparison groups

Only three projects have utilised a case-control design – the only experimentally sound approach (Table 3). Matching has been by both chronological age and developmental level. Results are relatively consistent in showing greater impairment on certain dimensions of social behaviour in fragile-X cohorts. Most notable of these are increased relational disturbance, with more social avoidance behaviour and enhanced wariness of strangers, aversion to eye contact with less social gaze, and sometimes more hand-flapping.

Current research pursues these findings in moving away from explorations of possible direct associations between narrowly defined autism and fragile X, in favour of examining the nature and severity of specific social impairments to which those with fragile X are prone. Comparison of children who have fragile X with a matched non-fragile-X autistic cohort demonstrates that although both groups have significantly impaired eye contact, the mechanisms

Table 3
Comparisons of fragile-X populations with matched control groups

Authors	Subjects	Control group	Findings
Borghgraef *et al* (1987)	23 pre-pubertal males	17 similarly aged males with non-specific mental retardation	Greater prevalence of autistic features in fragile-X group, in particular increased relational disturbance, aversion to gaze, and fugitive eye contact
Cohen *et al* (1988)	12 males	7 individuals with Down's syndrome; 8 non-handicapped individuals; cases matched on level of language development	No subject met DSM-III criteria for infantile autism or childhood-onset pervasive developmental disorder; fragile-X group displayed less social gaze, increased social avoidance behaviour, and enhanced wariness of strangers
Einfeld *et al* (1989)	45 individuals obtained from clinical genetics unit register of patients with fragile X	Individuals selected randomly from the register of a clinic assessing all developmentally delayed individuals in a geographical area; matched on age, sex and IQ	No significant differences between groups; hand flapping and eye/hand turning characteristic of fragile X group

are qualitatively different. Children with fragile X find eye contact distinctly aversive and will actively avoid meeting another person's gaze. In contrast, children with autism simply lack any preference for what or who they look at (Cohen *et al*, 1989*b*). This idiosyncratic gaze avoidance has been observed in a magnified form during contrived greeting ceremonies (Wolff *et al*, 1989). In this setting the whole upper body, as well as the eyes, is turned and deviated away from the greeter.

Conclusion

Controversy persists regarding the nature of the association between fragile X and autism, with authors expressing widely divergent views (Hagerman, 1989*b*; Rutter *et al*, 1990). However, there appears to be a characteristic profile of autistic-like social impairments experienced by individuals with fragile X which may yet prove to be diagnostically useful. Social anxiety is more characteristic than social indifference, abnormalities in speech and language are frequent, and stereotyped behaviour and self-injury are also common.

Disorders of attention and concentration

Possible associations of attentional problems, concentration difficulties, and overactivity with fragile X have attracted considerably less research interest than autistic disturbances. None the less, they have been observed frequently in association (e.g. Mattei *et al*, 1981), and have been considered by some to be the most striking and universal of the behavioural impairments experienced by this group (Fryns *et al*, 1984). Hyperactivity has been reported as the presenting feature in non-retarded boys with fragile X (Hagerman *et al*, 1985). Hagerman (1987) described 73% of a sample of 37 pre-pubertal boys with fragile X as fulfilling DSM-III criteria for attention deficit disorder and having a score on the Conners' rating scale (Conners, 1973) in the hyperactive range. Of the 14 individuals in Bregman *et al*'s sample (1988), 13 had significant degrees of impulsivity and met DSM-III criteria for attention deficit disorder. Borghraef *et al* (1987) showed attention deficit disorder to be twice as common in pre-pubertal boys with fragile X than in similarly aged boys with non-specific mental retardation. This hyperkinetic behaviour was unrelated to intellectual level, and was worst in early childhood, diminishing with age although persisting sufficiently to disturb social contacts and occupational abilities. Consistently high scores have been found on externalising dimensions of the Childhood Behavior Checklist, Parent Version in boys (McConaughy & Achenbach, 1988), supporting the association (Turk, 1989), although more recent research suggests that this finding may be largely due to the degree of mental retardation in the group studied (Turk, unpublished data).

The above evidence suggests there may be a central attentional deficit in fragile X which can not be fully explained by the level of intellectual functioning or family/social factors alone. However, findings remain equivocal and further research is required to clarify the exact nature and implications of this possible association.

Psychiatric disturbance in female carriers

A growing number of projects examine females heterozygous for fragile X. As well as the advantage

of being able to study psychological functioning in individuals with usually average intellectual ability, there is a widespread belief that fragile-X heterozygosity in females might have important repercussions on phenotype and mental status (Fryns, 1986). Physical stigmata may be similar to those in male sufferers and become more marked with increasing degrees of intellectual impairment. Cognitive profiles demonstrate the same uneven profile, and fragile X has been found to be as common in autistic females as in similarly affected males (Cohen *et al*, 1989*a*).

More worrying are suggestions of increased prevalence rates of psychotic disturbance in female carriers. Fryns (1986) diagnosed psychosis in 5.5% of a sample of fragile-X obligate female carriers (8 out of 144 individuals). Comprehensive psychiatric evaluation of 35 obligate carriers disclosed a 40% incidence of chronic affective disorders, with nearly a third of the total cohort meeting diagnostic criteria for schizotypal features, including odd communication patterns, inappropriate affect, emotional withdrawal, unusual thought content, conceptual disorganisation, and increased emotional lability (Reiss *et al*, 1988*a*). Parental origin of the fragile X chromosome, and the presence or absence of expressivity, may be important determinants of psychopathology (Reiss *et al*, 1989). As a group, women who inherited the fragile X chromosome from their mother and who demonstrated positive fragility in the karyotype manifested significantly more impairment of social, educational, and psychological functioning when compared with women who inherited a fragile X chromosome from their fathers or with well women.

It may well be that the fragile-X genetic defect in female heterozygotes confers increased vulnerability to particular forms of adult psychopathology, and that the risk is increased if the fragile X chromosome derives from the mother and demonstrates positive karyotype fragility.

Neuroscience research

The wealth of literature characterising the psychological features of fragile X has prompted a hunt for underlying neurophysiological and neuroanatomical factors mediating between the fragile chromosomal site and the intellectual/behavioural phenotype. Widespread CNS dysfunction is suggested by findings of multiple neurological signs on clinical examination (Finelli *et al*, 1985), and a common association with epilepsy – usually generalised tonic–clonic epilepsy (Musumeci *et al*, 1988). Other findings on electroencephalography have been reported, including high-voltage, low-frequency activity with diffuse spikes and sharp waves (Gillberg *et al*, 1986), and temporal spike activities on sleep recordings (Musumeci *et al*, 1988).

Studies using brain-stem auditory evoked potentials (Arinami *et al*, 1988; Ferri, 1989) demonstrate selective prolongation of interpeak latencies III–V and I–V, indicative of central, as opposed to peripheral, nervous system dysfunction. Prolonged transmission times suggest brain-stem white matter may also be involved. Global latency delay may also be producing high-frequency hearing loss, which could explain some of the speech defects.

In-depth neuropsychological evaluation confirms perceptual/motor problems (Goldfine *et al*, 1987). Also, impaired visuospatial processing, with poorer sequential than simultaneous processing abilities, has been demonstrated in males with fragile X when compared with males with Down's syndrome matched on mental and chronological age, indicative of a generalised deficit in a number of functions of the non-dominant hemisphere (Crowe & Hay, 1990).

Focal neurological dysfunction is also supported by studies by Grigsby *et al* (1987, 1990) of female carriers. However, the frequent findings of dyscalculia, constructional dyspraxia, dysgraphia, finger agnosia and left–right confusion were interpreted as arising from a discrete developmental lesion, akin to Gerstmann's syndrome, and probably indicating local damage in the angular gyrus of the dominant hemisphere.

A preliminary report of results from magnetic resonance imaging suggests significantly decreased area of the cerebellar vermis, particularly posteriorly, on planimetric analysis in the midsagittal plane in men with fragile X. The pons and fourth ventricular areas were decreased and increased respectively as well (Reiss *et al*, 1988*b*). Small neocerebellar vermal lobules have also been observed on magnetic resonance scans in 18 non-fragile-X autistic individuals with a wide range of intellectual functioning, when compared with 12 non-autistic controls (Courchesne *et al*, 1988). However, these imaging studies do not necessarily support the argument of an association of autism with fragile X. There were only four men with fragile X and four controls. Furthermore, the fragile-X men were all mentally handicapped (IQ 36–68) while the control men all had intellectual levels within the normal range. Also, two of the fragile-X subjects were described as demonstrating at least moderate autistic symptoms, with one of the four meeting DSM–III–R diagnostic criteria for pervasive developmental disorder, while the four comparison men showed no evidence of developmental disability. Thus, there are several possible explanations for the findings, including the small group sizes, the nature and degree

of mental retardation in the fragile-X group, the greater prevalence of autistic features, and the possession of a fragile X chromosome.

The most plausible explanation for these strands of evidence would be a widespread disturbance of CNS functioning with specific vulnerabilities arising within the non-dominant hemisphere, parietal areas, and posterior fossa. Further studies are needed to clarify the somewhat confusing picture.

Treatment

Both psychological and pharmacological treatments are being developed with specific reference to fragile X. Hagerman & Sobesky (1989) report a cognitive–behavioural package for emotional and social difficulties experienced by female carriers. Phase one comprises biofeedback and relaxation techniques to enhance the individual's sense of control over her internal world and affective life, and to decrease social anxiety. The second phase includes the building of social and practical skills through self-monitoring techniques to slow thinking, using anxiety as a trigger, in order to evaluate cognitions better and thus modify them in the light of objective experience. Finally, grief counselling is required to work through loss of the idealised perfect self, and the associated guilt and anger at harbouring a genetic defect.

Interest in the potential usefulness of folic acid in treating difficulties experienced by individuals with the fragile-X syndrome developed following the recognition of folic acid's central role in chromosomal culture techniques designed to elicit the fragile site in the X chromosome. Anecdotal reports of its benefits followed the original observations by Lejeune (1982). Bregman *et al* (1987), in reviewing the literature, described four double-blind cross-over studies involving a total of 14 pre-pubertal subjects and contrasted these with four double-blind cross-over studies involving 14 post-pubertal subjects. The authors concluded that, despite differences in methods between the studies on pre-pubertal subjects, similar findings were reported, including a significant attenuation of hyperactive behaviour and a concomitant increase in attentional ability. No changes were noted in either intellectual functioning or language ability. In contrast, results from the studies on post-pubertal individuals failed to demonstrate consistent improvement in intellectual functioning, linguistic functioning, activity level, and attention span. The suggestion is that folic acid may decrease symptoms associated with attention deficit disorder among pre-pubertal children with the fragile-X syndrome.

Subsequent studies have yielded contradictory results (e.g. Fisch *et al*, 1988*b*). None the less, Hagerman *et al* (1986*a*) were left with the clear impression that folate sometimes reduced hyperactivity. Why it should do so remains uncertain. Its mode of action may be more akin to the concentration- and attention-enhancing effects of stimulant medication. In support of this view is the finding of improvements in hyperactivity problems experienced by individuals with fragile X when given methylphenidate (Hagerman *et al*, 1988*b*). Thus, the efficacy of folic acid may have little to do with fragile X *per se*, but a lot to do with a mild stimulant action of folic acid on a central attentional deficit.

Conclusion

Fragile-X syndrome manifests as a behavioural phenotype, which accounts for up to 10% of individuals with mental handicap, and 50% of cases of X-linked mental retardation. The disorder has considerable significance for all psychiatrists, but especially those working in the field of mental handicap and with children. Advances in its identification and diagnosis now allow for genetic counselling. The effects of the syndrome may be alleviated by a wide range of interventions.

Acknowledgements

The author acknowledges gratefully financial support from the Wellcome Trust in the form of a research training fellowship in mental disorders. Grateful thanks also go to Professors P. Graham, B. Neville, and A. Gath, and Drs R. Hagerman and E. Taylor for invaluable comments on early drafts.

References

AUGUST, G. J. & LOCKHART, L. H. (1984) Familial autism and the fragile-X chromosome. *Journal of Autism and Developmental Disorders*, **14**, 197–204.

ARINAMI, T., SATO, M., NAKAJIMA, S., *et al* (1988) Auditory brainstem responses in the fragile X syndrome. *American Journal of Human Genetics*, **43**, 46–51.

BLOMQUIST, H. K., GUSTAVSON, K. H., HOLMGREN, G., *et al* (1982) Fragile site X chromosomes and X-linked mental retardation in severely retarded boys in a northern Swedish county. A prevalence study. *Clinical Genetics*, **21**, 209–214.

———, ———, ———, *et al* (1983) Fragile X syndrome in mildly mentally retarded children in a northern Swedish county. A prevalence study. *Clinical Genetics*, **24**, 393–398.

———, BOHMAN, M., EDVINSSON, S. O., *et al* (1985) Frequency of the fragile X syndrome in infantile autism. *Clinical Genetics*, **27**, 113–117.

BORGHGRAEF, M., FRYNS, J. P., DIELKENS, A., *et al* (1987) Fragile (X) syndrome: a study of the psychological profile in 23 prepubertal patients. *Clinical Genetics*, **32**, 179–186.

BREGMAN, J. D., DYKENS, E., WATSON, M., *et al* (1987) Fragile X syndrome: variability of phenotypic expression. *Journal of the American Academy of Child and Adolescent Psychiatry*, **26**, 463–471.

——, LECKMAN, J. F. & ORT, S. I. (1988) Fragile X syndrome: genetic predisposition to psychopathology. *Journal of Autism and Developmental Disorders*, **18**, 343–354.

BRONDUM NIELSEN, K. (1983) Diagnosis of the fragile X syndrome (Martin–Bell syndrome). Clinical findings in 27 males with the fragile site at Xq28. *Journal of Mental Deficiency Research*, **27**, 211–226.

——, TOMMERUP, N., DYGGVE, H. V., *et al* (1982) Macroorchidism and fragile X in mentally retarded males. *Human Genetics*, **61**, 113–117.

BROWN, W. T., FRIEDMAN, E., JENKINS, E. C., *et al* (1982*a*) Association of fragile X syndrome with autism. *Lancet*, *i*, 100.

——, JENKINS, E. C., FRIEDMAN, E., *et al* (1982*b*) Autism is associated with the fragile-X syndrome. *Journal of Autism and Developmental Disorders*, **12**, 303–308.

——, ——, COHEN, I. L., *et al* (1986) Fragile-X and autism: a multicenter survey. *American Journal of Medical Genetics*, **23**, 341–352.

BUNDEY, S., WEBB, T. P., THAKE, A., *et al* (1985) A community study of severe mental retardation in the West Midlands and the importance of the fragile X chromosome in its aetiology. *Journal of Medical Genetics*, **22**, 258–266.

CARPENTER, N. J., LEICHTMAN, L. G. & SAY, B. (1982) Fragile X-linked mental retardation. *American Journal of Diseases of Children*, **136**, 392–398.

CHUDLEY, A. (1984) Behavior phenotype. In *Conference Report: International Workshop on the Fragile X Syndrome and X-linked Mental Retardation* (eds A. Chudley & G. Sutherland). *American Journal of Medical Genetics*, **17**, 45–53.

—— & HAGERMAN, R. J. (1987) Fragile X syndrome. *Journal of Pediatrics*, **110**, 821–831.

CHUDLEY, A. T., KNOLL, J., GERRARD, J. W., *et al* (1983) Fragile (X) X-linked mental retardation 1: Relationship between age and intelligence and the frequency of expression of fragile (X) (q28). *American Journal of Medical Genetics*, **14**, 699–712.

COHEN, I. L., FISCH, G. S., SUDHALTER, V., *et al* (1988) Social gaze, social avoidance, and repetitive behavior in fragile X males: a controlled study. *American Journal of Mental Retardation*, **92**, 436–446.

——, BROWN, W. T., JENKINS, E. C., *et al* (1989*a*) Fragile X syndrome in females with autism. *American Journal of Medical Genetics*, **34**, 302–303.

——, VIETZE, P. M., SUDHALTER, V., *et al* (1989*b*) Parent–child dyadic gaze patterns in fragile X males and in non-fragile X males with autistic disorder. *Journal of Child Psychology and Psychiatry*, **30**, 845–856.

COLE, T. R. P. & HUGHES, H. E. (1990) Sotos syndrome. *Journal of Medical Genetics*, **27**, 571–576.

CONNERS, C. K. (1973) Rating scales for use in drug studies with children. *Psychopharmacology Bulletin* (Special Issue, Pharmacotherapy of Children), 24–84.

COURCHESNE, E., YEUNG-COURCHESNE, R., PRESS, G. A., *et al* (1988) Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine*, **318**, 1349–1354.

CROWE, S. F. & HAY, D. A. (1990) Neuropsychological dimensions of the fragile X syndrome: support for a non-dominant hemisphere dysfunction hypothesis. *Neuropsychologia*, **28**, 9–16.

CURFS, L. M. G., BORGHGRAEF, M., WIEGERS, A., *et al* (1989*a*) Strengths and weaknesses in the cognitive profile of Fra(X) patients. *Clinical Genetics*, **36**, 405–410.

——, SCHREPPERS-TIJDINK, G., WIEGERS, A., *et al* (1989*b*) Intelligence and cognitive profile in the fra(X) syndrome: a longitudinal study in 18 fra(X) boys. *Journal of Medical Genetics*, **26**, 443–446.

DAVIES, K. E. (1989) *The Fragile X Syndrome*. Oxford: Oxford University Press.

DYKENS, E., LECKMAN, J., PAUL, R., *et al* (1988) Cognitive, behavioral, and adaptive functioning in fragile X and non-fragile X retarded men. *Journal of Autism and Developmental Disorders*, **18**, 41–52.

——, HODAPP, R. M., ORT, S., *et al* (1989) The trajectory of cognitive development in males with fragile X syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, **28**, 422–426.

EINFELD, S., MOLONY, H. & HALL, W. (1989) Autism is not associated with the fragile X syndrome. *American Journal of Medical Genetics*, **34**, 187–193.

FERRI, R. (1989) Brain-stem auditory evoked poten-tials in the fragile X syndrome. *American Journal of Human Genetics*, **45**, 977–978.

FINELLI, P. F., PUESCHEL, S. M., PADRE-MENDOZA, T., *et al* (1985) Neurological findings in patients with the fragile-X syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 150–153.

FISCH, G. S., COHEN, I. L., WOLF, E. G., *et al* (1986) Autism and the fragile X syndrome. *American Journal of Psychiatry*, **143**, 71–73.

——, ——, JENKINS, E. C., *et al* (1988*a*) Screening developmentally disabled male populations for fragile X: the effect of sample size. *American Journal of Medical Genetics*, **30**, 655–663.

——, ——, GROSS, A. C., *et al* (1988*b*) Folic acid treatment of fragile X males: a further study. *American Journal of Medical Genetics*, **30**, 393–399.

FRYNS, J. P. (1986) The female and the fragile X. A study of 144 obligate female carriers. *American Journal of Medical Genetics*, **23**, 157–169.

—— & VAN DEN BERGHE, H. (1983) X-linked mental retardation and fragile (Xq27) site. *Clinical Genetics*, **23**, 203–206.

——, JACOBS, J., KLECZKOWSKA, A., *et al* (1984) The psychological profile of the fragile X syndrome. *Clinical Genetics*, **25**, 131–134.

GARDNER, R. J. M. & SUTHERLAND, G. R. (1989) The fragile X syndrome. In *Chromosome Abnormalities and Genetic Counselling*. Oxford: Oxford University Press.

GILLBERG, C. (1983) Identical triplets with infantile autism and the fragile X syndrome. *British Journal of Psychiatry*, **143**, 256–260.

—— & WAHLSTROM, J. (1985) Chromosome abnormalities in infantile autism and other childhood psychoses: a population study of 66 cases. *Developmental Medicine and Child Neurology*, **27**, 293–304.

——, PERSSON, E. & WAHLSTROM, J. (1986) The autism-fragile-X syndrome (AFRAX): a population-based study of ten boys. *Journal of Mental Deficiency Research*, **30**, 27–39.

——, OHLSON, V. A., WAHLSTROM, J., *et al* (1988) Monozygotic female twins with autism and the fragile-X syndrome (AFRAX). *Journal of Child Psychology and Psychiatry*, **29**, 447–451.

GOLDFINE, P. E., MCPHERSON, P. M., HEATH, A., *et al* (1985) Association of fragile X syndrome with autism. *American Journal of Psychiatry*, **142**, 108–110.

——, ——, HARDESTY, V. A., *et al* (1987) Fragile-X chromosome associated with primary learning disability. *Journal of the American Academy of Child and Adolescent Psychiatry*, **26**, 589–592.

GRIGSBY, J. P., KEMPER, M. B. & HAGERMAN, R. J. (1987) Developmental Gerstmann syndrome without aphasia in fragile X syndrome. *Neuropsychologia*, **25**, 881–891.

——, ——, ——, *et al* (1990) Neuropsychological dysfunction among affected heterozygous fragile X females. *American Journal of Medical Genetics*, **35**, 28–35.

HAGERMAN, R. J. (1987) Fragile X syndrome. *Current Problems in Pediatrics*, **17**, 627–674.

—— (1989*a*) Behaviour and treatment of the fragile X syndrome. In *The Fragile X Syndrome* (ed. K. E. Davies). Oxford: Oxford University Press.

—— (1989*b*) Genes and chromosomes in autism. In *Diagnosis and Treatment of Autism* (ed. C. Gillberg). New York: Plenum.

——, KEMPER, M. & HUDSON, M. (1985) Learning disabilities and attentional problems in boys with the fragile X syndrome. *American Journal of Diseases of Children*, **139**, 674–678.

——, JACKSON, A. W., LEVITAS, A., *et al* (1988*a*) Oral folic acid versus placebo in the treatment of males with the fragile X syndrome. *American Journal of Medical Genetics*, **23**, 241–262.

——, ——, ——, *et al* (1986*b*) An analysis of autism in 50 males with the fragile X syndrome. *American Journal of Medical Genetics*, **23**, 359–374.

——, BERRY, R., JACKSON, A. W., *et al* (1988*a*) Institutional screening for the fragile X syndrome. *American Journal of Diseases in Children*, **142**, 1216–1221.

——, MURPHY, M. A. & WITTENBERGER, M. D. (1988*b*) A controlled trial of stimulant medication in children with the fragile X syndrome. *American Journal of Medical Genetics*, **30**, 377–392.

—— & SOBESKY, W. E. (1989) Psychopathology in fragile X syndrome. *American Journal of Orthopsychiatry*, **59**, 142–152.

——, SCHREINER, R. A., KEMPER, M. B., *et al* (1989) Longitudinal IQ changes in fragile X males. *American Journal of Medical Genetics*, **33**, 513–518.

HANSON, D. M., JACKSON, A. W. & HAGERMAN, R. J. (1986) Speech disturbances (cluttering) in mildly impaired males with the Martin–Bell/fragile X syndrome. *American Journal of Medical Genetics*, **23**, 195–206.

HERBST, D. S. & MILLER, J. R. (1980) Nonspecific X-linked mental retardation II: The frequency in British Columbia. *American Journal of Medical Genetics*, **7**, 461–469.

HOCKEY, A. & CROWHURST, J. (1988) Early manifestations of the Martin–Bell syndrome based on a series of both sexes from infancy. *American Journal of Medical Genetics*, **30**, 61–71.

HOWARD-PEEBLES, P. N. & STODDARD, G. R. (1979) X-linked mental retardation with macroorchidism and marker X chromosomes. *Human Genetics*, **50**, 247–251.

KEMPER, M. B., HAGERMAN, R. J., AHMAD, R. S., *et al* (1986) Cognitive profiles and the spectrum of clinical manifestations in heterozygous fra(X) females. *American Journal of Medical Genetics*, **23**, 139–156.

——, —— & ALTSHUL-STARK, D. (1988) Cognitive profiles of boys with the fragile X syndrome. *American Journal of Medical Genetics*, **30**, 191–200.

LACHIEWICZ, A. M., GULLION, C. M., SPIRIDIGLIOZZI, G. A., *et al* (1987) Declining IQs of young males with the fragile X syndrome. *American Journal of Mental Retardation*, **92**, 272–278.

LAIRD, C. D. (1987) Proposed mechanism of inheritance and expression of the human fragile-X syndrome of mental retardation. *Genetics*, **117**, 587–599.

LARGO, R. H. & SCHINZEL, A. (1985) Developmental and behavioural disturbances in 13 boys with fragile X syndrome. *European Journal of Pediatrics*, **143**, 269–275.

LEDBETTER, D. H., LEDBETTER, S. A. & NUSSBAUM, R. L. (1986) Implications of fragile X expression in normal males for the nature of the mutation. *Nature*, **324**, 161–163.

LEJEUNE, J. (1982) Is the fragile X syndrome amenable to treatment? *Lancet*, *i*, 273–274.

LEVITAS, A., MCBOGG, P. & HAGERMAN, R. (1983) Behavioral dysfunction in the fragile X syndrome. In *The Fragile X Syndrome – Diagnosis, Biochemistry, and Intervention* (eds R. J. Hagerman & P. M. McBogg). Dillon, Colorado: Spectra.

LOESCH, D. Z., HAY, D. A., SUTHERLAND, G. R., *et al* (1987) Phenotypic variation in male-transmitted fragile X: genetic inferences. *American Journal of Medical Genetics*, **27**, 401–417.

—— & WILSON, S. R. (1989) Multivariate analysis of body shape in fragile X (Martin–Bell) syndrome. *American Journal of Medical Genetics*, **33**, 200–208.

MATTEI, J. F., MATTEI, M. G., AUMERAS, C., *et al* (1981) X-linked mental retardation with the fragile X. A study of 15 families. *Human Genetics*, **59**, 281–289.

MCCONAUGHY, S. H. & ACHENBACH, T. M. (1988) *Practical Guide for the Child Behavior Checklist and Related Materials*. Burlington: University of Vermont Department of Psychiatry.

MCGAVRAN, L. & MAXWELL, F. (1983) Cytogenetic aspects of the fragile X syndrome. In *The Fragile X Syndrome – Diagnosis, Biochemistry, and Intervention* (eds R. J. Hagerman & P. M. McBogg). Dillon, Colorado: Spectra.

MCGILLIVRAY, B. C., HERBST, D. S., DILL, F. J., *et al* (1986) Infantile autism: an occasional manifestation of fragile (X) mental retardation. *American Journal of Medical Genetics*, **23**, 353–358.

MCGLAUGHLIN, J. F. & KRIEGSMAN, E. (1980) Developmental dyspraxia in a family with X-linked mental retardation (Renpenning syndrome). *Developmental Medicine and Child Neurology*, **22**, 84–92.

MCKINLEY, M. J., KEARNEY, L. U., NICOLAIDES, K. H., *et al* (1988) Prenatal diagnosis of fragile X syndrome by placental (chorionic villi) biopsy culture. *American Journal of Medical Genetics*, **30**, 355–368.

MERYASH, D. L., SZYMANSKI, L. S. & GERLAD, P. S. (1982) Infantile autism associated with the fragile-X syndrome. *Journal of Autism and Developmental Disorders*, **12**, 295–301.

MIEZEJESKI, C. M., JENKINS, E. C., HILL, A. L., *et al* (1986) A profile of cognitive deficit in females from fragile X families. *Neuropsychologia*, **24**, 405–409.

MUSUMECI, S. A., COLOGNOLA, R. M., GIGLI, G. L., *et al* (1988) Fragile-X syndrome: a particular epileptogenic EEG pattern. *Epilepsia*, **29**, 41–47.

NERI, G., SANFILIPPO, S., PAVONE, L., *et al* (1988) The fragile X in Sicily: an epidemiological survey. *American Journal of Medical Genetics*, **30**, 665–672.

NEWELL, K., SANBORN, B. & HAGERMAN, R. (1983) Speech and language dysfunction in the fragile X syndrome. In *The Fragile X Syndrome – Diagnosis, Biochemistry, and Intervention* (eds R. J. Hagerman & P. M. McBogg). Dillon, Colorado: Spectra.

NUSSBAUM, R. L. & LEDBETTER, D. H. (1986) Fragile X syndrome: a unique mutation in man. *Annual Review of Genetics*, **20**, 109–145.

OPITZ, J. M., WESTPHAL, J. M. & DANIEL, A. (1984) Discovery of a connective tissue dysplasia in the Martin–Bell syndrome. *American Journal of Medical Genetics*, **17**, 101–109.

PAYTON, J. B., STEELE, M. W., WENGER, S. L., *et al* (1989) The fragile X marker and autism in perspective. *Journal of the American Academy of Child and Adolescent Psychiatry*, **28**, 417–421.

PEMBREY, M. E., WINTER, R. M. & DAVIES, K. A. (1985) A premutation that generates a defect at crossing over explains the inheritance of fragile X mental retardation. *American Journal of Medical Genetics*, **21**, 709–717.

——, —— & —— (1986) Fragile X mental retardation: current controversies. *Trends in Neurosciences*, **9**, 58–62.

PUESCHEL, S. M., HERMAN, R. & GRODEN, G. (1985) Screening children with autism for fragile-X syndrome and phenylketonuria. *Journal of Autism and Developmental Disorders*, **15**, 335–338.

REDINGTON, A. & BUSH, A. (1990) Fragile X mental retardation. *Archives of Disease in Childhood*, **65**, 335.

REISS, A. L., FEINSTEIN, C., TOOMEY, K. E., *et al* (1986) Psychiatric disability associated with the fragile X syndrome. *American Journal of Medical Genetics*, **23**, 393–401.

——, HAGERMAN, R. J., VINOGRADOV, S., *et al* (1988*a*) Psychiatric disability in female carriers of the fragile X chromosome. *Archives of General Psychiatry*, **45**, 25–30.

——, PATEL, S., KUMAR, A. J., *et al* (1988*b*) Preliminary communication: neuroanatomical variations of the posterior fossa in men with the fragile X (Martin–Bell) syndrome. *American Journal of Medical Genetics*, **31**, 407–414.

——, FREUND, L., VINOGRADOV, S., *et al* (1989) Parental inheritance and psychological disability in fragile X females. *American Journal of Human Genetics*, **45**, 697–705.

—— & —— (1990) Fragile X syndrome. *Biological Psychiatry*, **27**, 223–240.

ROGERS, R. C. & SIMENSEN, R. J. (1987) Fragile X syndrome: a common etiology of mental retardation. *American Journal of Mental Deficiency*, **91**, 445–449.

RUDELLI, R. D., JENKINS, E. C., WISNIEWSKI, K., *et al* (1983) Testicular size in fetal fragile X syndrome. *Lancet*, *i*, 1221–1222.

RUTTER, M., MACDONALD, H., LE COUTEUR, A., *et al* (1990) Genetic factors in child psychiatric disorders – II. Empirical findings. *Journal of Child Psychology and Psychiatry*, **31**, 39–83.

SIMKO, A., HORNSTEIN, L., SOUKUP, S., *et al* (1989) Fragile X syndrome: recognition in young children. *Pediatrics*, **83**, 547–552.

SREERAM, N., WREN, C., BHATE, M., *et al* (1989) Cardiac abnormalities in the fragile X syndrome. *British Heart Journal*, **61**, 289–291.

SUTHERLAND, G. R. (1977) Fragile sites on human chromosomes: demonstration of their dependence on the type of tissue culture medium. *Science*, **197**, 265–266.

—— (1982) Heritable fragile sites on human chromosomes. VIII. Preliminary population cytogenetic data on the folic-acid-sensitive fragile sites. *American Journal of Human Genetics*, **34**, 452–458.

THAKE, A., TODD, J., BUNDEY, S., *et al* (1985) Is it possible to make a clinical diagnosis of the fragile X syndrome in a boy? *Archives of Disease in Childhood*, **60**, 1001–1007.

——, ——, WEBB, T., *et al* (1987) Children with the fragile X chromosome at schools for the mildly mentally retarded. *Developmental Medicine and Child Neurology*, **29**, 711–719.

THEOBALD, T. M., HAY, D. A. & JUDGE, C. (1987) Individual variation and specific cognitive deficits in the fragile X syndrome. *American Journal of Medical Genetics*, **28**, 1–11.

TOMMERUP, N. (1989) Cytogenetics of the fragile site at Xq27. In *The Fragile X Syndrome* (ed. K. E. Davies). Oxford: Oxford University Press.

TURK, J. (1989) Hyperactivity, conduct disturbances and the fragile X syndrome. *First World Congress of Psychiatric Genetics; Abstracts*. Southampton: Duphar.

TURNER, G., DANIEL, A. & FROST, M. (1980) X-linked mental retardation, macro-orchidism, and the Xq27 fragile site. *Journal of Pediatrics*, **96**, 837–841.

—— & JACOBS, P. (1983) Marker (X)-linked mental retardation. In *Advances in Human Genetics*, vol. 13 (eds H. Harris & K. Hirschorn). New York: Plenum.

VEENEMA, H., VEENEMA, T. & GERAEDTS, J. P. M. (1987) The fragile X syndrome in a large family. II Psychological investigations. *Journal of Medical Genetics*, **24**, 32–38.

VENTER, P. A., OPT HOF, J., COETZEE, D. J., *et al* (1984) No marker (X) syndrome in autistic children. *Human Genetics*, **67**, 107.

VERKERK, A. J. M. H., PIERETTI, M., SUTCLIFFE, J. S., *et al* (1991) Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, **65**, 905–914.

VILKMAN, E., NIEMI, J. & IKONEN, U. (1988) Fragile X speech phonology in Finnish. *Brain Language*, **34**, 203–221.

WAHLSTROM, J., GILLBERG, C., GUSTAVSON, K., *et al* (1986) Infantile autism and the fragile X. A Swedish multicenter study. *American Journal of Medical Genetics*, **23**, 403–408.

WATSON, M. S., LECKMAN, J. F., ANNEX, B., *et al* (1984) Fragile X in a survey of 75 autistic males (letter). *New England Journal of Medicine*, **310**, 1462.

WEBB, T. P., BUNDEY, S., THAKE, A., *et al* (1986) The frequency of the fragile X chromosome among schoolchildren in Coventry. *Journal of Medical Genetics*, **23**, 396–399.

WING, L. & GOULD, J. (1979) Severe impairments of social interactions and associated abnormalities in children: epidemiology and classification. *Journal of Autism and Developmental Disorders*, **9**, 11–29.

WOLFF, P. H., GARDNER, J., PACCIA, J., *et al* (1989) The greeting behaviour of fragile X males. *American Journal of Mental Retardation*, **93**, 406–411.

WRIGHT, H. H., YOUNG, S. R., EDWARDS, J. G., *et al* (1986) Fragile-X syndrome in a population of autistic children. *Journal of the American Academy of Child Psychiatry*, **25**, 641–644.

Jeremy Turk, MB, BS, BSc, DCH, MRCPsych, *Wellcome Research Training Fellow and Honorary Senior Registrar, Academic Department of Child Psychiatry, Institute of Child Health, 30 Guilford Street, London WC1N 1EH*