SYNOPSIS  The introduction in 1985 of a genetic linkage test programme to identify asymptomatic heterozygotes among subjects at 50% initial risk for Huntington’s chorea\(^1\) required a review of all cases of Huntington’s chorea and their families referred to the Department of Medical Genetics of the Oxford Regional Health Area (population 2.5 million). From a representative sample of these subjects, psychiatric data were collected to estimate the frequency and time of onset of functional psychiatric illness and behaviour disorder. The rationale and method of the linkage test is described. The frequency of functional psychiatric disorder found was compared with that reported for the general population and for Alzheimer’s disease. The role in relation to the aetiology of functional psychiatric disorder (1) of the Huntington’s chorea gene and (2) of the family disturbance produced, was investigated by comparison between the frequency of functional psychiatric disorder in populations containing different proportions of heterozygotes as shown by (a) the manifestation of Huntington’s chorea, and (b) the result of the genetic linkage analysis. In order to investigate the influence of the onset of Huntington’s chorea on the production of functional psychiatric disorder the time of onset of the various functional psychiatric disorders was compared between asymptomatic subjects at 50% risk for Huntington’s chorea and their cohabiting spouses who were assumed to be at zero risk and who shared their environment. It is concluded that possessing the Huntington’s chorea gene: (1) has no influence on the production of functional psychiatric disorder in asymptomatic subjects at risk for Huntington’s chorea; and (2) increases the tendency to major depressive disorder in subjects already affected with physical signs of Huntington’s chorea.

\(^1\) Usually referred to as Huntington’s Disease in the USA since 1975.

Address for correspondence: Dr David C. Watt, 7 Churchway, Stone, Aylesbury, Bucks. HP17 8RG.
Chapter 1

Introduction

The opening paragraph of Caine & Shoulson’s (1983) study of psychiatric syndromes in Huntington's chorea states that ‘Huntington's disease presents a unique opportunity to investigate the development and evolution of psychopathological disorders. As a fully penetrant genetic disorder that can be diagnosed with great certainty, it provides an investigative setting seldom available to researchers studying “functional” psychiatric syndromes. The presence of an abnormal movement disorder and a positive family history provide “external” validating factors. Certain diagnosis is not in question.’ The cogency and relevance of this statement has been reinforced by the advent of a test for distinguishing the presence of the gene for Huntington's chorea in asymptomatic carriers (Gusella et al. 1983). The present study is an attempt to take this opportunity.

1.1 HUNTINGTON’S CHOREA

Sydenham in 1686 distinguished chorea from other movement disorders (Sydenham 1848–1850) and about two hundred years later, in 1872, Huntington separated a sub-group of chorea, now named after him, by distinguishing four definitive features. It is hereditary, progressive, has an onset in adult life and ‘shows a tendency to insanity’. Cerebral pathology, subsequently added to these features, was slowly delineated but not established as a diagnostic factor, by Dunlap, until 1927. It has the advantage of being diagnostically unequivocal, but was accessible only by post mortem examination until recent methods of imaging were introduced. As with most genetic diseases during this period there was little opportunity for therapeutic intervention and effort was directed towards assessing the scope of the problem and its public health implications, as indicated by the considerable number of epidemiological studies of Huntington’s chorea in which a population exceeding 1 million was surveyed (Panske, 1942; Bell, 1948; Pearson et al. 1955; Kishimoto, 1957; Parker, 1958; Read & Chandler, 1958; Wendt et al. 1959; Heathfield, 1968; Bolt, 1970; Wallace, 1972; Wallace & Parker, 1973; Myrianthropoulos, 1973; Mattsson, 1974a; Stevens, 1976; Harper, 1979; Hayden et al. 1980; Walker et al. 1981). These constantly give evidence of the ‘tendency to insanity’ which made such a strong impression on the young George Huntington whose father and grandfather had studied the same families.

1.2 PATHOLOGY

Huntington’s chorea is a dominant hereditary degeneration of the brain, prominently of the basal ganglia but also affecting the cortex and other parts. It manifests usually in middle-age with chorea, progressive cognitive impairment and emotional and behaviour disorder. There is no effective treatment and death occurs in about 15 years. Macroscopic examination of the brain shows marked atrophy of the caudate nucleus with dilatation of the lateral ventricles, particularly of their frontal horns. This appearance is characteristic and its presence provides the most reliable confirmation of the diagnosis of Huntington’s chorea in a family. It is reflected in the CAT and PET scans which, however, are not sufficiently specific for diagnosis (Neophytides et al. 1979; Hayden et al. 1987a) and cannot replace post mortem examination. Histology shows extensive loss of neurons in the striatum and in the cortex of the frontal and parietal lobes which results in massive abnormalities of brain and the neurotransmitter concentrations of receptors (Marsden, 1982).

The onset of Huntington’s chorea is insidious and although suspected at an early stage may be too uncertain to allow diagnosis (Myers et al. 1984).

1.3 PSYCHIATRIC DISORDER IN HUNTINGTON’S CHOREA

An important constituent of psychiatric disorder in Huntington’s chorea is cognitive impairment, a component of the organic syndrome directly
attributable to cerebral pathology. The most striking psychiatric features, however, show characteristics indistinguishable from those of functional psychiatric disorders, the major psychoses, neuroses, personality and behaviour disorders. These contribute to the frequent picture of social catastrophe so striking to observers having direct contact with affected families. Thus, Oliver & Dewhurst (1969) illustrating from a pedigree of six generations ‘representative of many others studied in depth involving at least 425 families’, in which ‘children from at least four generations were subjected to both active cruelty and passive neglect’, cite an affected individual ‘...always in rages and tempers...vicious and cruel to all her children’; a man in his 40s who, before the clear onset of Huntington’s chorea, was ‘out of work, depressed, and under the impression that his wife was being persistently unfaithful to him... and had irrational aggressive outbursts against his wife and children, but otherwise showed little interest in his children, who were frequently farmed out to mentally-sick relatives’; a woman who followed ‘a feckless existence of casual prostitution starting a line of problem families, delinquents and jailbirds’; a man whose worklessness, physical violence, headaches and insomnia... drove his wife to leave him, abandoning their child to the care of unwilling grandparents who in turn farmed him out to a psychotic aunt’. Although the emphasis in this paper is on physical abuse of children, it also gives instances of children’s abuse of parents and aggression, suspicion and indifference towards spouses. The authors point out that mental instability also appears in spouses not at risk for Huntington’s chorea and in blood relatives showing no physical signs of Huntington’s chorea. For instance, in one generation of 20 individuals (all offspring of affected parents), in which three are affected with Huntington’s chorea, four of the unaffected showed mental illness and the wife of an affected man ‘had a bitter and sadistic temperament’ exemplified during visits to her son in gaol or in a special hospital, when ‘she discussed either his wife’s infidelities or details of his father’s perversions’.

1.4 SURVEYS OF FUNCTIONAL PSYCHIATRIC DISORDER IN HUNTINGTON’S CHOREA

Seven surveys of functional psychiatric disorder in Huntington’s chorea are summarized in Table 1. The figures shown have been derived from those supplied in the studies and where necessary converted to percentage frequencies to facilitate comparisons. Functional illness is shown separately from personality and behaviour disorder. The frequencies range from 21 to 56% for functional illness and from 24 to 70% for personality and behaviour disorder. This variation must be partly a product of the different diagnostic criteria employed and of the different arrangements and circumstances of the surveys. The authors obtaining low figures for illness (Hughes, Bolt, Mattson, Saugstad) deal only with psychosis while the remainder include neuroses and personality disorder (Dewhurst) or ‘psychiatric disturbance’ (Wallace). The explanation of the low figure of Saugstad & Ødegård (1986) for psychiatric illness is that it includes only the single diagnosis made during first psychiatric admission, before Huntington’s chorea was diagnosed.

Mattsson employs three diagnoses only: (1) depressive-anxious state; (2) schizophrenic-paranoiac state; and (3) personality disorders. Personality changes and behaviour disorders are described in a comprehensive list of 23 morbid behaviours, offences and attitudes by Hughes (1925), but Wallace (1972) limits himself to two: ‘anger outbursts’; and ‘sexual aberration’. The only survey using standardized diagnosis is Folstein et al. (1983a) who employ DSM-III, with the added condition that major depression must have lasted at least a month to be diagnosed.

We must question whether estimates of prevalence have been taken from epidemiological samples, i.e. samples which include all subjects showing the disease within a specified area at a specified time. Samples including only hospital admissions leave out patients who have not been admitted. For those that include deceased subjects it must be decided whether these subjects were living and affected in the specified area at the specified time. To allow generalization, the diagnosis must arise from agreed descriptions, preferably using standardized diagnostic pro-
<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Population surveyed</th>
<th>Number of affected HC subjects (N)</th>
<th>Criteria for specifying functional psychiatric disorder</th>
<th>Circumstances of making diagnosis of functional psychiatric disorder</th>
<th>Stages of Huntington’s chorea included in N (%)</th>
<th>Functional psychiatric illness (%)</th>
<th>Personality and behaviour disorder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes (1925)</td>
<td>Michigan, USA</td>
<td>Institutionalized cases and their affected kin</td>
<td>218</td>
<td>Clinical diagnosis from hospital records and personal interview</td>
<td>Cases presenting behaviour problems after development of Huntington’s chorea</td>
<td>All stages; dead included</td>
<td>27 (of 175 cases with data available)</td>
<td>70 (after chorea)</td>
</tr>
<tr>
<td>Dewhurst et al. (1969)</td>
<td>Great Britain</td>
<td>Cases in 5 neighbouring counties</td>
<td>92</td>
<td>Author’s retrospective clinical diagnosis from records and survey history</td>
<td>Diagnosis during first admission to a psychiatric hospital</td>
<td>All stages</td>
<td>40†</td>
<td>Not ascertained</td>
</tr>
<tr>
<td>Bolt (1970)</td>
<td>W. Scotland</td>
<td>11 western counties Pop. 2,966 m</td>
<td>334</td>
<td>Summary of clinical features from hospital records. Clinical diagnosis</td>
<td>Functional psychosis noted as on admission</td>
<td>All stages; dead included</td>
<td>26†</td>
<td>59 (clinical features)</td>
</tr>
<tr>
<td>Wallace (1972)</td>
<td>Queensland, Australia</td>
<td>Survey of Queensland Pop. 1,75 m</td>
<td>182</td>
<td>Clinical diagnosis from author’s examination</td>
<td>Survey discovered history or presence of psychiatric disorder</td>
<td>All stages; all living</td>
<td>56‡</td>
<td>47 (anger and sexual aberration)</td>
</tr>
<tr>
<td>Mattisson (1974b)</td>
<td>Sweden</td>
<td>Survey of Swedish institutions admitting Huntington’s chorea</td>
<td>162</td>
<td>Choice of 3 diagnoses made from clinical records</td>
<td>Diagnosis on first admission to a psychiatric hospital</td>
<td>All stages from admission to psychiatric hospital; dead included</td>
<td>32‡</td>
<td>24 (initial diagnosis)</td>
</tr>
<tr>
<td>Saugstad &amp; Ødegård (1986)</td>
<td>Norway</td>
<td>National psychiatric register, 1st admissions for 60 years. Pop. 3,28 m</td>
<td>229</td>
<td>Clinical diagnosis recorded in national psychiatric register</td>
<td>Diagnosis during first admission to a psychiatric hospital</td>
<td>All stages from admission to psychiatric hospital or neurological unit; dead included</td>
<td>21‡</td>
<td>56 (personality disorder prior to admission)</td>
</tr>
<tr>
<td>Folsom et al. (1986)</td>
<td>Maryland, USA</td>
<td>Population survey. Pop. 4,2 m</td>
<td>186</td>
<td>DSM-III (1980) from interview and records (modified for major depression)</td>
<td>All living affected Maryland subjects examined by authors up to the date of survey</td>
<td>All stages; all living</td>
<td>47†</td>
<td>37 (explosive and personality disorder)</td>
</tr>
</tbody>
</table>

Alcoholism has not been included. This material is derived from the following in the publications: †Table 7; ‡p. 550; §p. 256(5); ¶p. 264; Appendix; ¶Table 10; ¶Table 3; ¶Table 6.
Psychiatric disorder in Huntington’s chorea

duced. Bolt (1970) makes an estimate of prevalence from a representative sample which is not, however, the sample on which her observations on functional psychiatric disorder are based. Of those appearing in Table 1, only the study of Wallace can be considered to have based the estimate of the prevalence of Huntington’s chorea on an epidemiological sample. The excellent study of Folstein is unfortunately marred by a curious error of ascertainment. Subjects ascertained after the day on which prevalence was estimated, but who were living in the specified area and affected on that day, were not included in the prevalence estimates (Folstein, 1989, p. 90). Overall, it is estimated that functional illness results in $\frac{1}{4}$ to $\frac{1}{2}$ of personality and behaviour disorder in $\frac{1}{2}$ of affected subjects.

Despite the variation in amount, all these surveys show a substantial frequency of psychiatric illness identified as such by psychiatrists, and a larger amount of seriously disordered behaviour which is often disruptive of family life and at times results in legal process and imprisonment. The study of Saugstad & Ødegård (1986) indicates the large number of affected persons admitted to a psychiatric hospital with psychosis before Huntington’s chorea manifested itself. (Table 1) by physical signs.

In accounting for the variety of results obtained from these studies, three elements in the method have become apparent. The first is the period in the course of Huntington’s chorea at which the subject is studied. The course can be divided into: (1) pre-choreic; (2) early; and (3) late stages, varying proportions of which may be represented in the populations studied. The second element arises from the frequent use of psychiatric hospital contact as a convenient method of collecting information about a population of Huntington’s choreics. Here the events recorded at the out-patient attendance or at first admission are most frequently used, but stages in the course of the hospital stay may be defined, such as cause of admission, and information taken from these as in Dewhurst et al. (1969). Finally, the criteria used for identifying the functional disorder may be chosen by the investigator as most appropriate for the material found (e.g. Mattsson, 1974a) or the diagnosis recorded in the hospital records may be adopted (Dewhurst et al. 1969) or a standardized diagnostic system may be used, such as the DSM-III, as in Folstein (1989).

### 1.5 TYPES OF FUNCTIONAL PSYCHIATRIC DISORDER IN HUNTINGTON’S CHOREA

The types and proportions of functional psychiatric disorder found in Huntington’s chorea are shown for two complete systematic studies in Table 2. Both studies are population surveys.

#### Table 2. The diagnoses of functional psychiatric disorder in two populations of subjects with Huntington’s chorea

<table>
<thead>
<tr>
<th>Symptom or syndrome</th>
<th>Bolt* (%)</th>
<th>Folstein† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Paranoid delusions</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>Irritability, rage</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Personality change</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>334</td>
<td>186</td>
</tr>
</tbody>
</table>

* Bolt (1970) – Table 4.
† Folstein et al. (1987) – Table 6.

in which living persons affected with Huntington’s chorea within a limited region were ascertained and examined by the authors. The majority of cases in both studies had previously been admitted to hospital or were resident. In Folstein’s study the diagnoses conform to DSM-III criteria (APA, 1980), but in Bolt’s study diagnoses are taken from hospital reports and the population is enlarged by the addition of the clinical records of deceased affected relatives of the index cases she contacted. In both studies, therefore, patients in all stages of the illness are included with, as Folstein (1989) points out, a possible under-representation of manifestations with onset in the course of late-onset Huntington’s chorea. Differences of method between the two studies will account for some of the difference in results, but nevertheless the proportion of depression and of irritability and rage is high in both studies. The lower proportion of irritability and rage in Folstein et al. (1987) is probably attributable to the criterion for this feature being the DSM-III category ‘Intermittent explosive disorder’ which requires that the episode results in ‘serious assault or destruction
of property’. Bolt applies the diagnosis schizophrenia (and paranoid psychosis) only to misdiagnoses attributed early in the course of Huntington’s chorea. Categories of illness resembling schizophrenia occurring throughout the course of Huntington’s chorea are contained within her category ‘paranoid delusions’, which shows a striking difference in frequency (33%) from Folstein et al.’s ‘Schizophrenia’ (6%), the low figure probably attributable to their adherence to DSM-III as criterion.

1.6 STAGES OF HUNTINGTON’S CHOREA AT WHICH FUNCTIONAL PSYCHIATRIC DISORDER OCCURS

The observation that functional psychiatric disorder is frequent in the early, even pre-choreic, period of Huntington’s chorea (Mattsson, 1974b; Folstein, 1989), often leading to misdiagnosis (Bolt, 1970; Mattsson, 1974b; Saugstad & Ødegård (1986) raises the question of the stages of the illness at which functional psychiatric disorder occurs. First admission to a psychiatric hospital is the most frequently quoted stage of illness for showing the extent and composition of functional psychiatric disorder. It is the most conspicuous event in professional recognition of the illness and is the first occasion on which the diagnosis is administratively recorded and dated. Mattsson (1974b) observes that initial symptoms are psychiatric in about half of the cases and that disorders of consciousness (confusional states) are never seen. Dewhurst et al. (1969) list ‘prodromal symptoms’, which they observe are non-specific and would not by themselves suggest Huntington’s chorea. Presenting symptoms at the onset of the disease were psychiatric in well over half of their 102 cases. They stress that ‘these syndromes are not separate entities, they merely reflect a preponderance of signs and symptoms rather than a distinct classification’, thus emphasizing the difficulty of assigning a formal psychiatric diagnosis over the whole range of the functional psychiatric disorders seen in Huntington’s chorea. Dewhurst et al. (1969) give the proportions of different types of functional disturbance that they found at four stages: in the prodromal period, among the earliest presenting symptoms, among the reasons for admission to a psychiatric hospital and among the diagnoses made at first admission. They draw attention to the many patients ‘wrongly regarded as having a psychiatric illness per se owing to the fact that several signs and symptoms would equally well substantiate a psychiatric or neurological diagnosis’.

The retrospective observation from studies of affected subjects that functional psychiatric disorder sometimes has its onset before the onset of Huntington’s chorea makes it mandatory that those at risk and still asymptomatic should be examined, as well as affected subjects, to make a complete assessment of the stage of Huntington’s chorea at which functional psychiatric disorder occurs.

1.7 FUNCTIONAL PSYCHIATRIC DISORDER AS AN INDICATION OF LIABILITY TO HUNTINGTON’S CHOREA IN SUBJECTS AT AN INITIAL 50% RISK

In earlier studies of Huntington’s chorea (Davenport & Muncey, 1916; Hughes, 1925) the occurrence of functional psychiatric disorder in the pre-morbid period attracted investigators’ attention because it might indicate which relatives of an affected person at an initial 50% risk would themselves develop the disease. Hughes (1925) reports that during the pre-morbid period of 172 affected cases ‘temperamental irregularities’ stood out markedly in 42%. The author cites easily excited, shrewish, inconsistent, slyly, stubborn, and uninhibited display of eroticism, as examples. Hughes found, however, that 32% of the known cases had not displayed any such disturbance and that ‘all of the traits recorded in those who became choreic were found in their non-choreic relatives’. Her conclusion agrees with that of Davenport & Muncey (1916) that ‘there is no universal symptom indicating which member of a fraternity will develop chorea’.

1.8 CATEGORIZATION OF FUNCTIONAL PSYCHIATRIC DISORDER IN HUNTINGTON’S CHOREA

Considerable differences between authors are shown in the criteria of diagnosis used in categorizing the functional psychiatric disorders found in Huntington’s chorea. Many authors rely on the diagnosis found in medical records of
hospital admission which follows customary psychiatric hospital nosology (Hughes, 1925; Bolt, 1970; Wallace, 1972; Mattsson, 1974b). Dewhurst et al. (1969) searched records of 88 patients from a group of neighbouring mental hospitals for evidence of functional psychiatric disorder and differentiated their description according to stages of patients’ stay in hospital, for instance, prodromally and on admission, in terms of current psychiatric hospital nosology; the ‘reason for admission’ in terms of prominent features which are socially disabling or disturbing; the course in hospital in terms of symptoms classified as affective or psychotic features. Folstein et al. (1979), noted that most previous reports of psychiatric symptomatology in Huntington’s chorea were subjective and therefore used standardized and validated diagnostic methods to quantify more precise clinical categories in a group of 11 affected subjects. All 11 patients showed detectable functional psychiatric disorder, most of which was severe. Only five of the 11 subjects, however, were given formal diagnosis, while the remainder were categorized as hallucinatory state, anxious, demoralized, irritable or withdrawn. All 11 patients, only two of whom gave measurable evidence of dementia, therefore showed detectable functional psychiatric disorder, most of which was severe, but less than half could be categorized in a standardized diagnostic scheme. A considerable difference was shown from the same unit in the results of a survey of functional psychiatric disorder in Huntington’s chorea in the general population of Maryland (Folstein et al. 1987). DSM-III was again used and 90% of functional psychiatric disorders were diagnosed without recourse to the symptomatic description employed by Folstein et al. (1979) described above.

1.9 TYPES OF FUNCTIONAL PSYCHIATRIC DISORDER

1.9.1. Depression
Depression is frequently noted in practically all surveys of psychiatric disturbance in Huntington’s chorea (Davenport & Muncey, 1916; Dewhurst et al. 1969; McHugh & Folstein, 1975; Caine & Shoulson 1983; Folstein et al. 1983c, 1987). Folstein (1989) describes depressive illness as the most common psychiatric syndrome seen early in Huntington’s chorea. The features reported are those encountered in the general population as are the varied forms in which depression appears and its greater frequency among women (Tamir et al. 1969; Bolt, 1970).

In the Maryland survey encompassing 217 cases of Huntington’s chorea, Folstein and colleagues (1983c) have given particular attention to affective disorder. From each of 186 persons with Huntington’s chorea a medical history was compiled and examination, which included a DSM-III (APA, 1980) psychiatric examination and showed that 38% had a history of major affective disorder or dysphoria (painful emotion), a larger proportion than for any other psychiatric category. Reactive depression was sharply distinguished and separated from major affective disorder. Chronic depression (under 5%) and mania were infrequent.

1.9.2 Schizophrenia
In the period during which functional psychiatric disorder has been observed in Huntington’s chorea, two important changes have occurred in making the diagnosis of schizophrenia. The first is that whereas paranoid disorders were formerly thought to be distinct from schizophrenia, with a small area of overlap, they are now combined under the term schizophrenia, with the exception of the rare condition true paranoia. The clear adoption of this view in the first edition of the textbook of Mayer-Gross et al. (1954) was an early indication of this change. Thus, Bickford (1953) gives 9/19 (47%) cases of Huntington’s chorea with ‘paranoid delusions’ from a population of 341,000; Bolt (1970) gives the prevalence of ‘schizophrenia’ in 334 cases derived from hospital records as 2% and paranoid psychosis as 15% whereas Folstein et al. (1982) found a total of 5-9% schizophrenia (p. 174, Table 6). Dewhurst et al. (1969), reporting different stages of the course of Huntington’s chorea, give 2% of all functional psychiatric disorders (68) as paranoid delusional states in the prodromal stage and, as initial diagnosis, schizophrenia (18%). Interestingly, the estimates of Folstein and her colleagues vary from 1979, no schizophreniza and 18% ‘hallucinatory states’ who did not meet all research criteria for schizophrenia, to 1987, 59% schizophrenia which the authors
point out may be an underestimate, and no other schizophrenia-like diagnosis.

The second change is the adoption of standardized criteria of diagnosis in psychiatric examination. The effect of this procedure on the diagnosis of schizophrenia has been to narrow the range of psychopathology included within the diagnosis of schizophrenia leaving an increased residue labelled as ‘schizophrenia symptoms’. These difficulties with schizophrenia are again illustrated by the Baltimore Huntington Disease Project where, in the course of the following five reports, subjects are labelled as (1) ‘delusional-hallucinatory’, indistinguishable from schizophrenia, but not identical with it (McHugh & Folstein, 1975); (2) ‘hallucinatory state’, which many psychiatrists would call schizophrenia but which did not meet all research criteria and did not respond to phenothiazines (Folstein et al. 1979); (3) ‘hallucinosis’, sometimes called schizophrenia, noticeably in mental hospital case records in the absence of clear delusions, which may have been suppressed by haloperidol prescribed for chorea (Folstein & Folstein, 1983); (4) ‘delusional and hallucinatory states’, particularly in young women where schizophrenia may have appeared before dementia and then been obscured by it (Folstein & McHugh, 1983); and finally, (5) schizophrenia was diagnosed in 10 Huntington’s disease patients in 8 years of observation (Folstein, 1989). The latter used standardized diagnosis (DSM-III-R, APA, 1987) of functional psychiatric disorder in Huntington’s chorea, but it is evident from them that standardized diagnostic procedures exclude a considerable amount of clinical material which, if it cannot be subsumed under schizophrenia, cannot be included in any other diagnostic category.

1.9.3 Prechoreic cases

A number of patients are admitted to psychiatric facilities and diagnosed as schizophrenia who are later diagnosed as Huntington’s chorea. Streiletski (1961) reviewed 1200 adequately recorded cases of Huntington’s chorea in a review of case records in Germany (quoted in Slater & Cowie, 1971). Among these were 32 (3%) cases of schizophrenia (including paranoid states) which occurred early in the illness. Markowe and colleagues (1967) reported a 10-year follow-up of 100 hospitalized schizophrenics. Nine died, of whom one was found on autopsy to have Huntington’s chorea. Two consultants had agreed the diagnosis of schizophrenia, on which they had no doubt. Saugstad & Ødegård (1986) had National Case Register information for Norway, from which they reported 199 psychiatric first admissions of subjects with Huntington’s chorea. Of these 39 left hospital with a discharge diagnosis of schizophrenia or paranoid psychosis only. Huntington’s chorea was diagnosed on a subsequent admission. Caro (1993) reports that in several members of a family he has known for 25 years schizophrenia preceded Huntington’s chorea. One member is now (in 1993) diagnosed as schizophrenic and is without signs of Huntington’s chorea.

1.9.4 Neurosis

Bolt (1970) noted that among 334 subjects with Huntington’s chorea 96 were misdiagnosed at first psychiatric admission. Of these 15% (5% of the whole sample) were included in the category ‘neurosis and personality disorder’. In 11 Huntington’s patients not referred for psychiatric symptoms but who were subjected to extensive psychiatric assessment, Falston et al. (1979) found four with reactive depression among eight who were identified as psychiatrically abnormal by the General Health Questionnaire (Goldberg, 1972) and among 186 choreics Falston et al. (1987) reported 48% as dystymic disorder. Bolt et al. (1971) used the Minnesota Multiphasic Personality Inventory (MMPI) to screen out emotional disorders in comparing 9 pairs of matched subjects from each of whom one was Huntington’s chorea and the other cerebral damage. In both groups the more impaired in motor skills and problem-solving showed most psychopathology. Mean scores and profiles were not different between the two groups.

1.9.5 Alcoholism

Evidence of the prevalence of alcoholism in Huntington’s chorea has been reviewed by King (1985), who found in the literature that both excess of alcohol abuse and a prevalence no greater than that of the general population have each been reported by several authors. To resolve the question he ascertained the prevalence of alcoholism in 45 randomly selected subjects with Huntington’s chorea from the pedigrees of the
representative sample of the Maryland Survey of Huntington’s chorea (Folstein et al. 1987). The overall prevalence was 17% (males 24%, females 6%). This prevalence is similar to the lifetime alcohol abuse/dependence found in the general population by Robins et al. (1984) to be 25% for males, 4% for females and 14% overall for Baltimore. He concluded that Huntington’s chorea does not increase the risk of alcoholism. In this most thorough study of alcoholism in Huntington’s chorea to date this result seems conclusive and we have not included alcoholism in our investigation.

1.9.6 Behaviour disorder
In a paper entitled ‘Personality Disorder in Huntington’s Disease’ (1970) Dewhurst reports that among 69 cases of Huntington’s chorea from a single kindred of six generations, 20% were categorized as personality disorder at the onset of Huntington’s chorea. Ten were admitted to a psychiatric hospital before development of chorea and there diagnosed as personality disorder and several others had been repeatedly convicted. In many cases on follow-up the disordered behaviour continued until it was obscured or submerged by dementia, or the patient died. Two subjects from the same kindred, however, unaffected with chorea but with severe behaviour disorder were followed up long enough to show that they achieved a settled life, married and showed no disturbed behaviour thereafter. Furthermore, three half-siblings from the same mother unaffected with Huntington’s chorea and a different unaffected father also developed severe personality disorders. Dewhurst points out that earlier accounts (Hughes, 1925; Rosenbaum, 1941; Chandler et al. 1960; Brothers, 1964) reported a high incidence of disturbance of temperament and behaviour, particularly in the prodromal phase of Huntington’s chorea. Arguing from his own cases, Dewhurst suggested ‘that adverse environmental factors rather than a deleterious gene are likely to cause a behaviour disorder’. The weights to be assigned to each of these factors in the cases at 50% initial risk for Huntington’s chorea cannot be determined from the clinical findings however, and it seems equally possible that behaviour disorders can be attributed either to environmental (exogenous) or genetic (endogenous) influences or to their combined influence. In a historical outline of this dilemma in psychiatry, Lewis (1971) has traced its extensive roots. The difficulty, as he points out, is that ‘the external causes which justified the term “exogenous” [are] manifest, identifiable, and even measurable; the internal causes of “endogenous” disorders [are] hypothetical, intangible, elusive predispositions, constitutional or hereditary forces which could be conjectured but not demonstrated’. In the case in point, the relative influence of the Huntington gene in the production of behaviour disorders cannot be determined although in the future it is conceivable that the pathology of gene action may give this information. Personality disorders must be classified by the type of behaviour or change of temperament displayed.

1.9.7 Personality disorder
In the course of Huntington’s chorea change of temperament and attitude may occur in the absence of disorder classifiable as psychotic or neurotic. These are alterations in the pre-morbidly stable characteristics of an affected subject manifesting as morbid jealousy, suspicion, irritability, aggression, stubbornness, egocentricity, apathy, negligence, indifference to responsibility and social obligations, self-neglect or lack of control and restraint, or the like. They are excessive individually in that they are more easily provoked, more frequent, and more disproportionate to the precipitating stimulus than had previously been characteristic. These changes vary in prominence according to the circumstances in which they are reported or ascertained. Irritability and aggression, for instance, are more likely in our experience to come to notice and to be disclosed by a relative in a domestic than in an out-patient setting.

Using DSM-III categories, 5-9% of the 186 cases on the Maryland survey showed antisocial personality (Folstein et al. 1987). A problem arises here in categorizing psychiatric disorder associated with Huntington’s chorea. Both ICD-9 (WHO, 1978) and DSM-III (APA, 1980) in defining the criteria emphasize that manifestation of personality disorder occur by adolescence or earlier. To qualify as being associated with Huntington’s chorea, however, it is necessary that, except for the rare juvenile onset, a change in attitudes, reactions and conduct should have occurred after the time at which
personality can be assumed to have developed fully and stabilized. In the study of Folstein (1987) quoted above there is an implication that this is the case, but it is not explicitly stated, and the DSM-III category ‘intermittent explosive disorder’ is exclusively employed.

It can be seen that behaviour disorder provides the evidence on which temperamental or personality disorder is based. In the present study both aspects are included in the term ‘Personality and Behaviour Disorder’.

1.9.8 Irritability
Irritability is among the most frequently found of psychiatric symptoms. Among 150 cases found in an Australian survey, the most frequent psychiatric disturbance was irritability and quick temper found in 70% of cases where mental symptoms preceded chorea (Brothers & Meadows, 1955). In a Scottish population survey of 3 million, which yielded 334 records of Huntington's chorea at all stages, Bolt (1970) noted irritability and violence (50%) as the most frequently recorded clinical feature. Among 30 cases of Huntington's chorea intensively examined by Caine & Shoulson (1983) and categorized by DSM-III (1980) criteria, two cases (7%) showed intermittent explosive disorder. Thirty-one per cent in this category were found at some time during the course of their illness in the 186 cases of the Huntington disease survey of Maryland (Folstein et al. 1987).

Ratings on scales of irritability, aggression and apathy were made by Burns and colleagues (1990) from interviews with relatives on 26 subjects with Huntington's chorea and 31 with Alzheimer's disease randomly selected from outpatients and a comparison group of unaffected relatives. The two affected groups showed the same proportion (58%) who were irritable, but aggression was significantly more marked in Huntington's than in Alzheimer's subjects. It was also more frequently rated (P < 0.01), more severe (NS) and lasted longer (P < 0.005). In both groups aggressive outbursts were precipitated by a preceding event such as an argument between spouses about money. In both Huntington's and Alzheimer's subjects ratings of aggression were greatly in excess of those of the controls. Irritability was correlated with the premorbid trait ‘bad tempered’ (P < 0.01) but was not associated with pre-morbid aggression.

From an examination of 32 hospital case records, Tamir et al. (1969) found significantly more male than female patients with Huntington's chorea were aggressive.

1.10 THE RELATION BETWEEN HUNTINGTON'S CHOREA AND FUNCTIONAL PSYCHIATRIC DISORDER
The diagnosis of Huntington's chorea can be made correctly by experienced psychiatrists with thorough investigation in practically all cases, except for the 3% with onset at 60 years or over, where a proportion are handicapped by concurrent illness and failure to yield family history (Folstein et al. 1986) is more frequent. The duration from onset to death has been found by Conneally (1984) to be independent of age of onset and remarkably constant, with a mean of 17 years and a range of 14 to 18 years (except for the 2% with onset below 10 or exceeding 69 years, where the mean is 9). A likely influence on the frequency of onset of functional psychiatric disorder is therefore the period during the course of Huntington's chorea at which this occurs. This can conveniently be measured by the time between the onset of functional psychiatric disorder and the onset of chorea.

We may note from the survey of previous studies that in the diagnosis of functional psychiatric disorder in Huntington's chorea problems over diagnosis remain. This relates especially to schizophrenia and to behaviour and personality disorder. Standardized psychiatric methods do not satisfactorily match symptomatology relating to these two disorders as it is encountered in Huntington's chorea.

1.11 AIMS OF THE STUDY
1. Our first purpose was to obtain a representative sample of subjects affected with Huntington's chorea with demographic features measured and to estimate the adult frequency of first onset of functional psychiatric disorder. (N.B. ‘Psychiatric disorder’ comprises psychiatric illness and personality and behaviour disorder. In this study the term ‘psychiatric illness’ does not include personality and behaviour disorder.)
2. To examine the distribution of the first onset of functional psychiatric disorder in time over the course of Huntington's chorea.