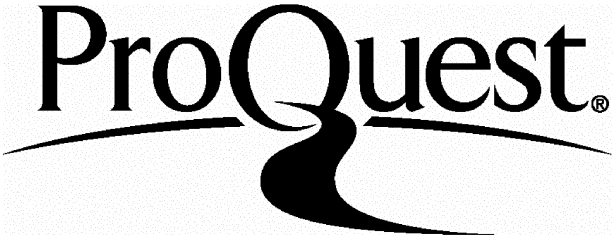
Epidemiological studies in the United Kingdom; incidence and lifetime prevalence rates of neurological disorders, and the prognosis of seizures

Bridget Kathryn MacDonald

Institute of Neurology

University of London

PhD thesis



Abstract

Two community-based neuroepidemiological studies in the United Kingdom constitute the basis of this thesis.

I *The National Hospital for Neurology and Neurosurgery General Practice Linkage Study*

The population of thirteen general practices was studied in order to describe the incidence and lifetime prevalence of neurological disorders.

Over an eighteen month period all incident cases of neurological conditions were ascertained prospectively in this defined urban population. Multiple case ascertainment methods were employed to address the difficulties inherent in neuroepidemiological case-finding. At the end of the period all the general practice notes were hand searched. In three practices lifetime prevalence was also surveyed.

Overall 0.6% of the population per year had an incident neurological condition and 6% had had a neurological diagnosis in their life. The annual incidence and lifetime prevalence rates for the individual neurological disorders are reported.

II *The National General Practice study of Epilepsy*

Patients who presented for the first time with an epileptic seizure were recruited between 1984 and 1987 forming a prospective community-based cohort. These patients have been followed subsequently in order to study the long-term prognosis for recurrence and remission of seizures.

a) The prognosis for febrile convulsions

Within this cohort were 220 children who had experienced febrile convulsions. The risk of subsequent development of epilepsy or neurological deficit using a Cox proportional hazards model with time-dependent co-variates was examined. In this cohort 6% had developed epilepsy by thirteen years.

b) The prognosis for epilepsy from first presentation

The baseline and remission data from the 792 patients recruited with seizures was analyzed using a Cox proportional hazards model to determine factors which are predictive of prognosis. A single dominant determinant was found - the higher the number of seizures occurring between first presentation and six months the lower were the chances for remission.

Table of contents

Table of tables and figures

Author's Contribution

I. The National Hospital for Neurology and Neurosurgery General Practice Linkage Study

The author was responsible for the design, planning and administration of the scheme and liaison with general practices. She worked in the linkage general neurology clinics and did outreach clinics in general practice. Case definitions and disease classifications were devised by her.

She participated in the notes searches and supervised the medical students. Likewise the quality control part of the study was arranged and supervised by her.

The author performed the data collection, entry, and statistical analysis for cases and for the population in the practices, together with Mrs Sana Zeidan of the Neuroepidemiology Unit at the National Hospital.

II. The National General Practice Study of Epilepsy

The author was the coordinator of this study during the period 1994–97. She was responsible for all aspects of the design, planning, administration and execution of the study in conjunction with the supervisors. She was responsible for data handling, and she carried out statistical work in conjunction with Dr A.L. Johnson.

Aims of the studies

I. The National Hospital for Neurology and Neurosurgery General Practice Linkage Study

The study was designed to ascertain the incidence and lifetime prevalence of all neurological conditions in an urban community.

a) The incidence of neurological conditions

The aim was to study prospectively the incidence of neurological conditions in an unselected population of 100,230 people. Case ascertainment was community based via participating general practitioners. The aim was also to calculate the age- and sex-adjusted incidence rate and the age-specific rates for stroke, Parkinson's disease and epilepsy.

b) The lifetime prevalence of neurological conditions

The aim was to survey the lifetime prevalence of neurological conditions by examining the general practice case notes of 27,658 patients.

II.The National General Practice Study of Epilepsy

The study was designed to identify an incident cohort and follow these individuals for a protracted period. A cohort of newly diagnosed patients with seizure disorders was identified between 1984 and 1987; these individuals formed the study population of the National General Practice Study of Epilepsy (NGPSE).

a) The prognosis of febrile convulsions

A cohort of children was identified from time of first febrile convulsion through the NGPSE. Outcome analysis was carried out by appropriate multivariate analysis using a Cox proportional hazards model with time-dependent co-variates. The study aimed to establish the long-term risk of epilepsy after a first febrile convulsion.

b) The prognosis for epilepsy from first presentation

To establish the remission rates for patients presenting with epilepsy in the NGPSE and to identify factors that allow the assessment of the prognosis from early in the course of the condition. This was examined using Cox multivariate analysis.

A critical review of the literature

"Epidemiology is concerned with the patterns of disease occurrence in human populations and the factors that influence these patterns" (Lilienfield *et al.*, 1994). Epidemiology is a key discipline, aiming to study disease with respect to time, place and pattern. Neuroepidemiology is the epidemiology of conditions falling within the remit of clinical neurology and neurosurgery.

The use of epidemiology in medicine to define and describe disease occurrence has been important in our understanding of many conditions. Initially, its use was confined to acute and usually severe infective conditions with rapidly changing patterns or epidemics, which typically run brief, stereotypical courses. Subsequently, it became apparent that adaptations of the techniques involved would allow exploration of chronic disorders and their underlying causes and prognoses.

Neurological conditions account for a significant amount of chronic morbidity and long-term dependence at a community level, although there is little information about the frequency and course of these conditions in the community. Neurological diagnosis and management require expertise, and it has been shown that both service and patient outcome are improved by the neurologist's care rather than by that of the general physician. Yet there are few neurologists per capita in the United Kingdom compared with other countries (Hopkins, 1997).

1.1 Current concerns in epidemiology

1.1.1 There are several areas in modern neuroepidemiology that need attention. Clinically relevant data are needed to allow management of individual patients and the allocation of resources. In neuroepidemiology, there are several outstanding gaps in the knowledge necessary to achieve this.

1.1.2 Neurological conditions are generally rare, with the exception of stroke and epilepsy, and furthermore there are more different diagnoses than in any other specialty. The epidemiology of rare diseases is more difficult to study in a community than that of more frequently occurring conditions as a larger population must be studied.

1.1.3 A separate problem is that the incidence and prevalence of given diagnoses do

not reflect the workload of neurologists, because many new patients have to be seen to exclude neurological diagnoses.

1.1.4 A diagnosis does not in itself define a patient's disability or his or her capacity to benefit from intervention.

1.1.5 Figures help to define what specific service needs (e.g. wheelchairs, neurourological input, etc.) are required. However, even for the more common individual neurological conditions, such information is unavailable let alone the needs for the range of neurological conditions (Wade, 1997).

1.2 Descriptive neuroepidemiology

1.2.1 General considerations

To establish priorities for research support and service planning, it is necessary to know the impact of neurological disease on society. Knowledge of disease frequency is important when making diagnostic decisions – helping to judge the probability of a presentation being either an unusual presentation of a common condition or a rare disorder (Longstreth *et al.*, 1987).

The burden of neurological disorders is large, and accurate data are difficult to obtain. Population-based estimates from the USA (excluding headaches, trauma, back pain, psychosis, mental handicap, and non-neurological visual and hearing loss) give an incidence of 1 case per 100 people, with a point prevalence (excluding the above and disc disease, head injury and nervous system trauma) of 3.6 per 100 (Kurtzke, 1982). In the UK, disease of the nervous system accounted for 7.6% of all GP consultations between 1981 and 1982; the disparity between these figures and those from the USA may be accounted for in part by the inclusion of headache and diseases of the ears and eyes, but also by the expected difference between a point prevalence and the incidence of consultation over a period of time (Royal College of General Practitioners, 1986).

The Harris report looked at all disabilities in private households among those aged over 16 years in the UK. They were divided into groups; of those relevant to neurology (nerve VI: CNS disorders; XIII: muscular dystrophies; XIV: congenital malformations of spine and hydrocephalus; XV: cerebral birth injury; and XVI: senility as a cause of cognitive disability), 78 of 1,000 were disabled to some extent by these

disorders (Harris, 1971). The survey of disability by the Office for Population Census and Surveys (OPCS) 16 years later graded disability according to severity and overall frequency. The prevalence rate of complaints relevant to neurology was 13% for "CNS disorders", 2% each for dementia and mental handicap, and 6% for back complaints. "CNS complaints" accounted for 7% of all disabilities, but 16% of conditions scoring 9–10 out of 10 for severity (Martin *et al.*, 1988).

Difficulties encountered in neuroepidemiological studies are shown in Table 1.

Table 1. The problems encountered in neuroepidemiology

"Tip of the iceberg"
subclinical disease
illness that has not been brought to the attention of any medical agency
undiagnosed disease
Case definition variation
Case ascertainment
Population base
demographic variation between populations
geographic variation
Statistical methodology
correction for demographics
correction for migration
correction for case ascertainment methodology

The "tip of the iceberg" effect is important in epidemiology. That is to say that the number of people affected by a condition is higher than those known to have the condition. What proportion of cases are known depends on aspects of the disease, the medical system and the epidemiological research methodology. A patient with a neurological condition may be asymptomatic and therefore not seek a medical opinion. Such a patient would not be identified in surveys which are based on questionnaires about symptoms but might be found if the patient was examined by a doctor. Another source of under-reporting occurs if a patient has been seen by a doctor and the correct

diagnosis may not have been made - symptoms may be attributed to another condition. Alternatively a condition may be so frequent in a population that no medical agency is approached (e.g. essential tremor in certain parts of Papua New Guinea); only door-to-door surveys would identify cases not health record searches. Another reason for illnesses not presenting to medical agencies is when a symptom is not considered medical but is perceived as a magical or religious occurrence (e.g. epilepsy in certain cultures).

Surrogate markers for disease, such as the use of certain medications, may be incorporated into the study design; "drug tracer methodology". This is a good screening tool for diseases that are usually treated with a specific drug not used for other conditions e.g. co-careldopa in parkinsonism. Care must be taken to ensure that cases identified in such a fashion fulfil case-definitions for the study.

The diagnosis of the condition relies on case definitions which may vary with time and between different studies.

Hence it can be seen that attention to case ascertainment methodology is crucial and study design needs to be focused. This will ensure that means appropriate to the condition and population studied and are used.

1.2.2 The Carlisle study

Between 1955 and 1961, a study was carried out in Carlisle, England (Brewis *et al.*, 1966). It was designed to obtain a reliable population-based estimate of the incidence and prevalence of neurological disorders. Perhaps surprisingly, this is the only large-scale study of neurological disorders in Britain. The current study is the only other community-based study that has examined the frequency of neurological conditions.

Cases in the Carlisle study were established via hospital notes, GP records, Medical Officer of Health notes, private practice notes, death certificates and interviews with a sample of householders. The population base was all residents of the city of Carlisle – just over 71,000 people. The results were age and sex adjusted for the population of England and Wales.

Incidence and prevalence rates were reported for a wide range of neurological conditions; these are discussed with individual conditions below. They excluded

migraine, shingles, prolapsed intervertebral disc, cervical spondylosis and unspecified polyneuritis and neuralgia as there was "incomplete recording of minor neurological disease in general practice".

There were some methodological problems. Disease definitions are not given and reference to "standard clinical definitions" is made – this is obviously inadequate when trying to interpret figures for epilepsy, parkinsonism and dementia, for example. It predated modern investigations (for example, measurement of vitamin B_{12} levels was not possible locally; CT and MRI were not available). The demographic structure of Carlisle at that time does not reflect the age structure of the UK now which has many more elderly people as a result of increased survival and larger birth cohorts (Perkin, 1997).

1.2.3 Neuroepidemiology at the Mayo Clinic, Rochester

At the Mayo Clinic, Rochester, USA, a long-term prospective epidemiological study of illness including neurological disorders has been on-going for many years (Altman, 1994). It uses a system in which all the population (about 90,000) have their medical information recorded on a central database. It has produced over 100 publications on neuroepidemiology, and is a model for this type of epidemiological research. Nevertheless, the drawback to this system is the relevance of data to other populations; the unusually homogeneous rural Olmstead County population has an excess of younger, better-educated Caucasians (whites constitute 99% of the population) than the average for the USA (Glista *et al.*, 1977; Swanson *et al.*, 1994). Moreover, the denominator population is estimated from the latest area survey, which is less accurate than the list of patients registered at a general practice in the UK, where small changes in the population over time can be monitored easily on the practice database (Bamford *et al.*, 1988).

In addition, and perhaps most importantly, as the USA has no uniform health-care system, patients who leave the area of study are difficult to follow up with long-term follow-up rates in some studies being low (compare the study of febrile convulsions, which has 40% loss to follow-up as a result of migration out of the area – Annegers *et al.*, 1987).

1.2.4 Routine information in the UK

The general practice system provides a unique opportunity to monitor a given population in the UK. Over 98% of people are registered with a GP (Cartwright *et al.*, 1981). It is usual for the GP to be informed of any contacts between the patient and any other medical agency. The national morbidity surveys (Ebrahim, 1995) have attempted to address the frequency of complaints in general practice, but the difficulty with these data is that conditions having low incidence and relatively chronic courses appear to have falsely high "incidence" rates because patients in this system will count as "new" when they change practice and see the recording GP for the first time. This may, for example, lead to high incidence rates for epilepsy based on data from The Office for National Statistics' General Practice Research Database (GPRD)(Wallace *et al.*, 1998). What is useful is that 78% of all patients consult each year and 13% of all consultations are for conditions of the nervous system (a group that includes eye and ear complaints) (Ebrahim, 1995). There is a considerable amount of effort put into data collection at a general practice level, but unfortunately little has been thought through adequately and focused to answer specific questions (Newrick *et al.*, 1996).

Some studies have examined wide areas of health using questionnaires. For example, a postal survey of a sample of those aged over 65 in the UK suggested high rates of stroke, Parkinson's disease and seizures, but no assessment of false positives or negatives was attempted (Parker *et al.*, 1997) (Table 2).

Table 2. Rates of self-reported neurological diagnoses in the UK

Condition		65-74 years (%)	75+ years (%)
Stroke	**M**	6.4	10.5
	F	4.3	8.1
Parkinson's disease	**M**	0.7	1.8
	F	0.6	1.2
Seizures ever	**M**	1.7	1.1
	F	0.9	0.6

The statistics of small areas, which are generated from the UK census to describe populations within small geographical districts or wards, can be used to stratify for ethnicity and socioeconomic factors (Jarman, 1983; Majeed *et al.*, 1995). The "deprivation scores" all depend to some extent on census "small area statistics" data. Small area statistics are breakdowns of UK census data, based on questionnaires sent to a representative sample of the population; they are intended to apply small areas so that a more precise view of that district's profile may be obtained. One study that tried to look at the reliability of such measures, by comparing the percentage of those aged over 65 years, in the small area in which the percentage had actually been measured, with the practice registers in that area, found that they were relatively accurate; however, any divergence from the mean tended to be flattened out (Scrivener et al., 1995).

Table 3. Parameters used in the Jarman Index

Children <4 years
Unemployment
Poor housing
Ethnic minorities
Single parent households
Overcrowding
Lower social class
Changing house at less than yearly intervals
Familial instability (families with non-married couples)

(*Jarman,* 1983)

Deprivation scores may be used to assess socioeconomic factors. London has areas of deprivation side by side with more affluent areas. Patients who are "deprived" may experience more illness and require more medical and social help (Wilkinson, 1995). There are several ways of measuring this: the underprivileged area score or "Jarman score" (Jarman, 1983); alternatives are the Townsend and Carstairs scores (Jarman *et al.*, 1991). The Jarman score was developed in order to reimburse GPs for the extra work that was involved in working in areas with prevalent deprivation. GPs were consulted to identify those factors perceived to increase workload but which were not associated with old age (as these are already accounted for in reimbursement). The final score was based on social factors (Table 3 - see above). The Jarman score correlates well with infant mortality, whereas the Townsend and Carstairs scores are

better measures of material deprivation and correlate better with standardised mortality ratios.

1.2.5 Particular problems with prevalence

The measurement of incidence and prevalence rates has different problems and the rationale behind their measurement also differs. Often, early in a condition, the patient needs the full battery of investigations as either an inpatient or outpatient, with treatment as indicated. Conditions that present mainly to hospitals are relatively easy to check, and the services necessary for the management of acute conditions are relatively clearly defined; an example of such a condition is bacterial meningitis. The point prevalence of such conditions is useful knowledge for those managing the supply of "hospital services" to a large population. The frequency and range of disabilities that follow these conditions could be used, together with the lifetime prevalence, to explore the community prevalence of disabilities in these conditions.

Studies have often described the point prevalence of neurological disorders. The prevalence of active disease (in epilepsy studies) or prevalence (in cerebral palsy) can be of more or less use in different conditions. Although for some conditions, e.g. Bell's palsy, resolution of disease may be evident, for many conditions there is no such end-point: a patient who has had a stroke usually has underlying cerebrovascular disease; at what point can it be said that a patient who has had seizures no longer has epilepsy? Knowledge about the lifetime prevalence of those in the population with a given diagnosis is useful in avoiding the problems of point prevalence and end-points in neurology. In addition, lifetime prevalence is useful when one expects an increased mortality rate among affected individuals, but a life-table approach is inadequate in describing the affected population. The difficulty with lifetime prevalence is, however, that conditions in remission or having mild residual disability will be under-reported, giving a relative bias towards severe disease or deficit. No study of prevalence or lifetime prevalence should not be linked to disability benefits agencies, because this would introduce unacceptable bias.

The prevalence of disability does not correlate closely to disease frequency as traditionally measured. The point prevalence of disability might be a useful measure, but has not yet been thoroughly addressed using a current neurological assessment of

function at the time of study.

1.3 Epidemiology of individual neurological conditions[1,2]

1.3.1 Brain tumours

1.3.1.1 Primary brain tumours

Definitions used

The case definitions for CNS tumours vary considerably, which is not surprising given their marked heterogeneity (Preston Martin, 1996). "Brain tumour" usually includes benign and malignant tumours in the cranial cavity, "brain cancer" only malignant tumours in the cranial cavity, "CNS tumours" includes spinal cord masses, and "nervous system tumours" also includes peripheral nerve tumours. Brain tumours may be primary (see below) or secondary (see page 22).

Problems

As study inclusion criteria are variable, it is important to know whether tumours are included that have been diagnosed on clinical grounds alone. If single tumours are identified on CT, the positive predictive value of this is 90% for gliomas and meningiomas and only 50% for metastases; these latter comprise the group of patients who do not have pathologically confirmed diagnoses in large series (Todd *et al.*, 1987). High rates of pathologically confirmed tumours in studies can mean that clinically diagnosed tumours have been overlooked or excluded, low rates can lead to problems of accuracy. As there are tumours of unknown behaviour, studies that ascribe a clear diagnosis to all tumours must be in doubt.

There is considerable heterogeneity among tumours, so it seems unlikely that they are affected by the same factors; as a consequence, the lumping together of disparate tumour types is likely to obscure important correlations (Schoenberg, 1978).

Epidemiological studies

The incidence of primary brain tumours in the USA in 1972–3 was 8.2/100,000

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[1] Throughout the discussion of epidemiology the terms used for ethnicity in the original paper are used to avoid the bias of reinterpretation. This means that they do not necessarily conform to current terminology.

[2] As a consequence of the variability in the number and quality of neuroepidemiological studies of different conditions, there is unavoidable unevenness in the lengths of sections devoted to each neurological disorder.

(Walker *et al.*, 1985); in Carlisle it was 7/100,000 (Brewis *et al.*, 1966). More recently, a retrospective study in Lothian reported an incidence rate of 15 (13–17)/100,000 p.a. This included sellar tumours, which accounted for 17% of tumours (Counsell et al., 1996). About 20% of tumours are meningiomas in men and 33% in women. After gliomas and meningiomas, nerve sheath tumours are the most frequent primary intracranial tumours, accounting for approximately 8%; 90% of these are on nerve VIII (Preston Martin, 1996).

Definitions of brain tumours vary; the National Institute of Neurological Disorders and Stroke (NINDS) (Walker *et al.*, 1985) looked at intracranial neoplasms and included benign and malignant, primary and secondary tumours within the cranial cavity, excluding spinal cord tumours and spinal meningiomas, but including pituitary masses, congenital cerebral tumours and dermoids. They separated primaries and secondaries as well as pathologically confirmed cases. It is not clear whether pituitary microadenomas are included. In the NINDS, women had more meningiomas and pituitary adenomas, and men aged over 40 years experienced more gliomas and neurinomas. The frequency of glioblastomas, neurinomas and meningiomas increased with age (Walker *et al.*, 1985). Women also showed better survival after meningiomas with 5-year survival rates of 94%, against 87% for men (Preston Martin, 1996). This may be related to the progesterone receptors on these tumours; oestrogen receptors are seen more rarely (Halper *et al.*, 1989).

Racially, there is also a variation, with higher rates in American whites and low rates of primary brain tumour (PBT) in American Asians (a group that is ethnically different to the UK Asian community, the former having more people of Pacific rim origin rather than the largely Indian, Pakistani and Bangladeshi population seen in the UK) (Preston Martin, 1996; Pfeffer, 1998). Geographically, there is some variation, with high incidence rates of acoustic neuromas reported in India (Eisenberg *et al.*, 1985) and of pineal tumours in Japan (Beghi *et al.*, 1984).

Social class also has an affect, with higher rates of PBT in higher socioeconomic groups (Counsell *et al.*, 1996); the effect is particularly marked in men.

Age is an important factor, with some tumour types being confined almost entirely to children at a peak age of under 10 years; in addition, the rates of PBT rise with

increasing age from 25 to 60 years. Over 60 years of age, studies with high postmortem rates show a continued upward trend whereas other studies do not (Schoenberg, 1978; Walker *et al.*, 1985; Preston Martin, 1996). The Lothian study showed a peak between 65 and 74 years for neuroepithelial tumours and 75 and 84 years for meningiomas (Counsell *et al.*, 1996).

Many risk factors have been investigated. The Israeli study of those exposed to cranial irradiation for scalp ringworm observed relative risks of 33 for nerve sheath tumours, 10 for meningiomas and 3 for gliomas (Ron *et al.*, 1988). Studies have repeatedly shown that fetal irradiation is associated with childhood brain tumours. Similarly, high-dose dental irradiation has been shown to increase nerve sheath tumours and meningiomas; the effect of low-dose dental irradiation is controversial (Preston Martin *et al.*, 1989). Other factors in the environment and diet have been studied, often in poorly designed studies or in animal toxicology studies, but they have not led to clear results. Notably, recent concern hypothesises that magnetic field exposure may lead to brain tumour growth, especially gliomas (Preston Martin *et al.*, 1989); this is supported by a historical cohort mortality study of men employed in electric power companies. However, despite the report discussing this increased risk, it was found to be present on subgroup analysis only after looking at over 40 variables (Savitz *et al.*, 1995). Likewise, an association between raised urinary lead and astrocytomas in children and PBT in experimental rats has been reported (Schreier *et al.*, 1976). Postmortem series suggest that the frequency of gliomas and cerebral metastases is lower than might be expected in people with diabetes; however, because of the bias in such a clinic-based investigation, this would need confirmation in a cohort study of people with diabetes (Aronson *et al.*, 1965).

Head trauma has been linked to meningiomas. There have been anecdotal reports of increases in frequency in various groups exposed to significant head trauma (Preston Martin *et al.*, 1989), although variation in national rates of head injury (see below) would be expected to cause variation in the incidence of meningiomas in different communities if head trauma were an important factor. Acoustic trauma has been linked to tumours of nerve VIII in a single case–control study; the biological plausibility is, however, low (Preston Martin, 1996). Meningiomas are the most common second primary tumours in women who develop breast cancer (Schoenberg *et al.*, 1975); this

may be linked to the expression of high-affinity progesterone receptors, as found in 69% of meningiomas in a prospective study (Halper *et al.*, 1989). Certain inherited conditions are associated with increased rates of CNS tumours; however, in population-based studies, only 4% of PBTs could be attributed to inheritance (Preston Martin, 1996).

It is not infrequently cited that atopic individuals have fewer PBTs and gliomas, although the confidence limits in a study examining this were too wide to reach such a conclusion (Ryan *et al.*, 1992). Some of the inconclusive findings are of interest: the demonstration of a link between noise damage and acoustic neuroma seems to be inexplicable based on current concepts of tumour genesis; the effect of diabetes on tumours is another effect that seems at odds with the current understanding of PBTs.

The 5-year survival rate varied according to tumour type and patient group: glioblastoma multiforme 5%; unspecified tumours 20%; tumours that were not pathologically confirmed 28%; for children under 14 years 59%; overall rates 25% (Preston Martin, 1996).

A prevalence of 45/100,000 was used to estimate the prevalence of brain tumour-related disability in the UK (Langton Hewer, 1993).

Interpretation and conclusion

A number of studies looking at risk factors have been carried out. This is an area of neurology that captures the imagination of the public, attracting funding from small groups (e.g. the electical workers union that funded the magnetic field exposure study), and it seems that some studies have pandered to this rather than addressing important methodological issues such as adequate sample size.

Spinal tumours are rare and have not been studied epidemiologically.

Future studies should be sufficiently large and of sufficient length for complete investigation of their aim rather than to leave suggestive but inconclusive findings.

1.3.1.2 Metastatic brain tumours

Definitions used

These tumours consist of intracranial tumours that are demonstrated to be metastases on histology, and/or where radiology and/or a personal history of systemic cancer gives

good reason to believe that the tumour is metastatic.

Problems

As with PBTs, reports differ in terms of which parts of the neuraxis have been included, and whether clinical, radiological and/or histological confirmation is included in the study.

Epidemiology

The incidence of secondary intracranial tumours in the NINDS was 8/100,000 p.a.; the diagnosis of metastatic brain tumour rather than PBT was far more likely to be from a clinical diagnosis with no histological confirmation. The recent study in Lothian identified an incidence of 14 (12–16)/100,000 p.a. for secondary tumours that were confirmed histologically or by CT (Counsell *et al.*, 1996). This high rate for non-clinically diagnosed secondary brain tumours may reflect the shorter scan times and the availability of CT scanners, both of which increase the likelihood of scans being used in modern studies. Men had higher rates for such tumours (10/100,000 p.a.) than women (7/100,000 p.a.). The finding in men that almost two-thirds of the metastases were from pulmonary primaries, with three times the incidence, could account for this.

Interpretation and conclusion

The occurrence of brain metastases is well documented, but there are no studies that aim to find risk factors for spread in certain tumour types or certain patients.

The recent Scottish study gives a rate that seems very high; there is no explanation for this and, until confirmation has been obtained, it must be assumed to be biased.

1.3.2 Cluster headache

Definitions used

The criteria of the International Headache Society for the diagnosis of cluster headache is at least five attacks of severe, strictly unilateral, orbital, supraorbital and/or temporal headache lasting 15–180 minutes, occurring from once every other day to eight times a day. These may be associated with one or more of the following: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, facial and forehead sweating, meiosis, ptosis or eyelid oedema. Attacks occur in series that last for weeks

or months (so-called cluster periods), and are separated by remission periods that usually last months or years. These attacks are not classified as cluster headache in the presence of the following conditions: trauma; cerebrovascular disease; intracranial disorders such as raised intracranial pressure, infection or neoplasia; substance abuse or withdrawal; non-cephalic infection, metabolic disturbance; or in relation to the bony structure of the face, skull or neck (Headache Classification Committee of the International Headache Society, 1988).

Problems

This condition is probably under-diagnosed in general practice because it does not appear in undergraduate medical textbooks. This affects community-based studies that rely on record linkage and general practitioners' diagnoses, but not "door-to-door"-type surveys.

Epidemiology

The only incidence reported is 10 (6–14)/100,000 person-years in Rochester, USA between 1979 and 1981. In this study, the International Headache Society's criteria were not adhered to, patients were included after a single attack rather than after five attacks, and the duration of 15–180 minutes was not adhered to rigidly. This may have altered some of the epidemiological features, for example it was found that the peak age of incidence was 40–49 years for men and 60–69 years for women (Swanson *et al.*, 1994), whereas cluster headache is generally thought to have a peak incidence between 20 and 40 years (Headache Classification Committee of the International Headache Society, 1988). Men are affected five to six times more commonly than women (Headache Classification Committee of the International Headache Society, 1988); the incidences in the Rochester study of 16 (9–22)/100,000 person-years for men and 4 (0.4–8)/100,000 person-years for women give a ratio with confidence limits that fall anywhere between 3 and 55 men to one woman (Swanson *et al.*, 1994).

Prevalence rates are shown in Table 4 (over page). Other studies are clinic based and hence uninterpretable.

Patients with cluster headache have been noted to be more likely to have peptic ulcers and to die from cancer; this may be influenced by the correlation between smoking and

cluster headache (cited in Swanson *et al.*, 1994).

Interpretation and conclusion

There are no good studies of the incidence of cluster headache; nor are there studies of risk factors and long-term prognosis. This would require at least some screening at a population level to avoid problems of under-reporting.

Table 4. Prevalence of cluster headache

Study	Population Base	Prevalence/ 100,000	
		M	F
D'Alessandro *et al.*, 1986	San Marino general population	109	28
Ekbom *et al.*, 1978	18-year-old male army recruits in Sweden	9	N/A

1.3.3 Congenital brain and spinal cord abnormalities: "major infantile neurological damage"

Definitions used

The term 'cerebral palsy' (CP) designates a group of disorders that have the following features in common: (1) aberrant control of movement or posture; (2) early onset; and (3) no recognised underlying or progressive disorder. It is not a single disease entity but a group of conditions differing in specific manifestations and associated handicaps (Nelson *et al.*, 1978b). Cerebral palsy poses a difficulty for epidemiologists because it is a diagnosis of exclusion.

Spina bifida aperta and anencephaly are apparent as major structural abnormalities at birth.

Problems

There is a wide range of metabolic, genetic, syndromic and secondary causes of congenital and neonatal disorders resulting in major neurological handicap. The presentation of CP is often late and diagnosis can take years. The development of a tool to subdivide these disorders has proved difficult.

Epidemiology

The lifetime prevalence of CP seems to fall around 2.7/1,000 live children aged 7–10 years, serious learning difficulties (IQ < 50) occurring in 20–30% (Freeman J.M., cited in Rosen *et al.*, 1992). The American community-based National Collaborative Perinatal Project (NCPP) found a lifetime prevalence of 4.6/1,000 infants at age 7 years. A later review of studies of incidence reported an average (excluding the NCPP) lifetime prevalence rate of 2.7/1,000 children aged 7 years (Rosen *et al.*, 1992).

The rates for CP have not fallen with improvements in prenatal and obstetric care, and its cause is unknown. With advances in technology, more pre-term and small-for-date infants survive and their outcome is suboptimal (Rosen *et al.*, 1992). The NCPP carried out a multivariate analysis of potential risk factors for CP on their community-based cohort of 189 affected children: 41% of these children had an IQ of less than 70; 22% had non-cerebral malformations; and 23% had febrile convulsions (FCs). On multivariate analysis, maternal mental handicap (in the absence of an identified heritable cause of this) was the strongest predictor of CP. Other factors are shown in Table 5.

Table 5. Factors associated with cerebral palsy

Maternal or genetic factors	The baby	Around birth
Severe proteinuria	Delayed first cry	Short gestation
Oestrogen or thyroid hormone	Low birth weight	Breech presentation
Third trimester maternal bleeding	Congenital abnormalities	Placental complications
Motor deficit in a sibling	Neonatal seizures	Chorionitis
Maternal mental retardation		

Although these analyses could be used to show that the 5% at highest risk experienced 37% of all the CP, the specificity was low because 97% at high risk were normal, and 63% of those with CP had not been at particularly high risk (Nelson *et al.*, 1986).

Spina bifida has been subject to public health intervention, which limits the

comparability of current and old studies. First, there was prenatal monitoring with abortion of affected fetuses, and more recently (following a randomised controlled trial that demonstrated that folic acid reduced the IR of spina bifida) a public awareness campaign encouraging women to take folic acid as a preventive measure. The incidence in England and Wales in 1966 for all CNS malformations, the majority being spina bifida and anencephaly, was 4.8/1,000 live births (Kurtzke, 1980).

Perinatal and childhood stroke were studied in Rochester, USA and an incidence of 1 (0–4)/100,000 p.a. in children up to the age of 15 years was found for ischaemic stroke and 2 (0–6)/100,000 p.a. for haemorrhagic stroke (unassociated with birth); for the perinatal period the incidence was 1 (1–2)/100,000 live births p.a. for intracranial haemorrhage (Schoenberg *et al.*, 1980).

The average lifespan for patients with CP was found to be 30 years, with the highest mortality being in the group with spastic diplegia or quadriplegia (cited in Nelson *et al.*, 1978b).

Other disabilities affect these individuals. Intellectual impairment is severe in about half of the children with CP. Seizure disorders occur in one-third, and are particularly associated with severe learning difficulties and postnatally acquired hemiplegia. Half have visual difficulties, including squint, high myopia, nystagmus and blindness (cited in Nelson *et al.*, 1978b).

Interpretation and conclusion

The epidemiological study of CP has failed to produce a good theory of causality. This contrasts markedly with spina bifida, where studies of long duration have produced not just a cause but a preventive measure.

The changes in survival of low-birth-weight and very pre-term babies affect the epidemiology of CP.

There is scope for continued well-designed studies of causality in CP, which has already been the subject of many studies. Neonatal stroke is less well researched.

1.3.4 Dystonia

Definitions used

There has been considerable controversy about the aetiology and classification of the

dystonic syndromes. Primary dystonia is the presence of sustained involuntary muscle contractions, often causing twisting and repetitive movements or abnormal posture, in the absence of a neurological diagnosis such as stroke, cerebral palsy or basal ganglia disease, with which it may be associated; if associated with a structural lesion, it is termed secondary. Dystonia may be focal (affecting, for example, the neck or hand) or generalised (Warner *et al.*, 1998).

Problems

It is difficult to separate primary from secondary dystonia. Secondary dystonia is a rare diagnosis so large populations must be studied in order to examine community-based neuroepidemiology.

Generalised dystonia is a primary dystonia with an important genetic contribution, and most cases can be traced to a founder mutation that occurred around 1650 in the Jewish Pale settlement of Lithuania and Byelorussia; hence its distribution is likely to be non-uniform but to follow emigration patterns.

Epidemiology

The prevalence of focal dystonia in Rochester was reported as 30 (CL = 17–48)/100,000, nine times the rate of generalised dystonia measured in the same study (Nutt *et al.*, 1988). The frequency of generalised dystonia has been studied in Jews living in New York City and in Israelis of European origin (Warner *et al.*, 1998). These figures cannot necessarily be extrapolated to other geographical locations because the gene frequency varies.

Interpretation and conclusion

The epidemiological study of these conditions is limited. Their underlying cause is unknown and it seems that further investigations could be of use.

1.3.5 Epilepsy

Epidemiological factors relevant to the prognosis of epilepsy are discussed below (page 84).

Definitions used

Epilepsy is defined as two or more unprovoked seizures. Classification of seizure type has been modified over the years, because of the accrual of information on aetiology

and prognosis. The International League Against Epilepsy (ILAE) has produced a classification of seizures. Single and acute symptomatic seizures are not considered to be epilepsy. Febrile convulsions in children are a separate disorder (see "a) The prognosis of febrile convulsions", page 73) (ILAE Commission Report, 1997).

Problems

Case definition

The case definition of epilepsy is deceptively clear-cut: "two or more unprovoked epileptic seizures". A key difficulty is the diagnosis of the seizure. Seizures are brief, pleomorphic – albeit often stereotypical in an individual – and unpredictable. The diagnosis is based on the history of the episodes, with some support from investigations. The witnessed account, even when available, may be difficult to interpret for many reasons, among which are poor observation or capacity to describe the seizure, and the inaccuracy of second-hand accounts – both are common sources of difficulty. In addition, there is variability in how clinicians interpret the information, which leads to diagnostic variation, for example, in some reports 20% of patients referred to specialist epilepsy clinics are diagnosed as not having epilepsy (Betts, 1983; Lesser, 1985).

Adding to the difficulty of diagnosis are other paroxysmal conditions, the presentation of which may be confounded with epileptic seizures; examples are syncope, vertigo, panic disorders, hyperventilation syndrome and disorders of sleep (Appleton, 1993; Lempert, 1996; Roberts, 1998). Numerous conditions may underlie seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), and no investigation is definitive or highly reliable in the diagnosis of seizure disorders.

Seizures that occur during a metabolic disturbance or acute illness are not considered as epilepsy because they are deemed to be caused by a pathological process; this process, because it is transient, cannot be assumed to provoke further seizures, so, as a consequence, there is no continuing tendency to seizures. The distinction is, however, a convention and not the result of a clear-cut physiological difference.

There is difficulty in diagnosis throughout the course of epilepsy; thus, non-epileptic seizures inflate the figures for chronic epilepsy, although it can be difficult to estimate how much they contribute to the 20–30% of patients who suffer chronically (Shorvon, 1991). Difficulties in diagnosis need to be treated seriously in epidemiological studies.

A major difficulty is comprehensive case ascertainment. As seizures are symptomatic of many conditions, they may be dealt with in different specialist departments – accident and emergency, general medicine, neurology, neurosurgery, primary care, psychiatry, among others. In addition, they affect all age groups, so care is spread between paediatric, adult and care of the elderly services. Many patients will never see a hospital consultant (The Research Committee of the Royal College of General Practitioners, 1960). They may take some time to diagnose and the degree to which the diagnosis is sought is related to the severity of the seizures.

There are diverse methods of calculating recurrence; actuarial survival analysis and crude recurrence rates are the ones used most frequently. The former may slightly inflate recurrence rates through loss of more mobile seizure-free patients, but crude rates are likely to be inaccurate because they do not take account of incomplete follow-up.

Classification

By convention, the diagnosis of epilepsy is made only after a second unprovoked seizure. Seizures are the expression of a wide range of conditions and the use of the term "the epilepsies" is to be encouraged (Sander, 1993). A comprehensive syndromic classification was commissioned by the ILAE (Commission on Classification and Terminology of the ILAE, 1989).

The prognosis of epilepsy is confounded by the diversity of the underlying diagnoses. In addition to the different risks for the underlying conditions, there are the risks of the seizures themselves.

In an attempt to classify epilepsy, some syndromes are clear-cut, e.g. childhood absence epilepsy. Despite extensive investigation and prolonged follow-up, however, many patients remain difficult to classify; in addition, different aetiologies may underlie an apparently identical epileptic syndrome. Moreover, the early remission of most

epilepsies allows little time for observation and investigation of the active disorder. In most reliable studies not all the cases are classified.

Epidemiology

The incidence has been reported as between 24 and 71/100,000 p.a. (Pond *et al.*, 1960; Brewis *et al.*, 1966; de Graaf, 1973; Granieri *et al.*, 1983; Li *et al.*, 1985; Loiseau *et al.*, 1990; Hauser *et al.*, 1993). The prevalence is between 4 and 8/1,000 (Pond *et al.*, 1960; The Research Committee of the Royal College of General Practitioners, 1960; de Graaf, 1973; Granieri *et al.*, 1983; Li *et al.*, 1985). There are a large number of epidemiological studies of epilepsy which, where relevant, are discussed below.

There is one study of the incidence of epileptic syndromes (Loiseau *et al.*, 1990). Individuals with a first seizure were included unless the seizure was neonatal or a febrile convulsion. The overall incidence was 71/100,000 p.a. of which 29/100,000 p.a. were acute symptomatic seizures (Table 6).

Table 6. Incidence of seizure syndromes in south-west France

Seizure syndrome	Incidence/100,000p.a.
1.1 Idiopathic localisation related epilepsies	1.7
1.2 Symptomatic localisation related epilepsies	13.6
2.1 Idiopathic generalised epilepsies	5.6
2.2 Symptomatic generalised epilepsies	1.1
2.3 Isolated unprovoked seizures	18.3
2.4 Undetermined epilepsies	1.9

An incidence of 20–70/100,000 p.a. should generate a prevalence rate of 2–5%, and not the observed prevalence rate of active epilepsy of around 0.5% (Pond *et al.*, 1960; The Research Committee of the Royal College of General Practitioners, 1960; Gudmundsson, 1966; Hauser *et al.*, 1975). The discrepancy between incidence and lifetime prevalence rates in a condition with low case fatality implies that there is remission.

The lifetime risk of having at least one afebrile epileptic seizure is between 2% and 6%, assuming an average life expectancy of 70 years (Hauser *et al.*, 1975; Goodridge *et al.*,

1983a, 1983b). There are a number of hospital-based descriptive studies of newly diagnosed seizures, but far fewer community-based studies. There are even fewer community-based studies that are prospectively designed and that continue follow-up for lengths of time that are suitable for a condition that may reflect a lifelong tendency.

Chronic epilepsy

After a first seizure, most patients experience at least one more seizure. It is usual for treatment to be started at this point and most patients go into remission. However, the minority who do not remit form the 20–30% whose epilepsy becomes chronic and for whom antiepileptic agents (AEDs) fail to achieve seizure control (The Research Committee of the Royal College of General Practitioners, 1960). All hospital-based studies have such a group and such groups are those on whom all former gloomy prognoses for epilepsy were made.

Interpretation and conclusion

There appears to be a shift in the overall incidence of epilepsy, with higher rates in the older age groups, which would merit further exploration. Little is known about the incidence of the different epileptic syndromes. The risk factors for excess mortality have not been fully studied (Sander *et al.*, 1996).

1.3.6 Essential tremor

Definitions used

Essential tremor is an autosomal, dominantly inherited condition with variable penetrance. It causes tremor at 4–9 Hz, predominantly in the upper half of the body, which worsens with action (in contrast to Parkinson's disease) (Findley *et al.*, 1987). The definition of essential tremor is a patient who gives a history of often recurring or continuous tremor in the extremities and/or head, and someone in whom a postural or action tremor can be demonstrated on clinical examination, in the absence of any systemic or neurological disorder associated with tremor. The patient must not be taking a drug known to cause tremor. A positive family history is supportive of but not essential to the diagnosis (Larsson *et al.*, 1960).

Problems

This is a common condition, so probably the best method of finding cases is use of the door-to-door survey. In addition, as this is a familial condition that is rarely disabling,

patients may never see a doctor for the diagnosis. It can be confused, clinically, with exaggerated physiological tremor and parkinsonian tremor; it can be distinguished best by objective measurement of tremor frequency.

Epidemiology

In Rochester, USA, an incidence of 18/100,000 p.a. for 1935–79 has been reported. However, in the 1965–79 cohort, the incidence was 24/100,000 p.a.; previous years' rates had been considerably lower. Age was positively associated with diagnosis and, in this cohort, the mean age of diagnosis was 58 years. Sex had no influence on incidence. There was a positive family history in 39% of cases (Rajput *et al.*, 1984a). There are a number of prevalence studies, as shown in Table 7.

Table 7. Prevalence of essential tremor in different studies

Study	Prevalence rate	Comments
Rajput *et al.*, 1984a; Rochester	3/1,000	
Haerer *et al.*, 1982; Copiah County	4/1,000	Study in those aged over 40 years - higher rates in those classified as "white" and in women
Larsson *et al.*, 1960; Sweden	17/1,000	In an isolated population affected 56% of those aged over 40 years
Hornabrook *et al.*, 1976; Papua New Guinea	210/1,000	96% identified by door-to-door enquiry
Rautakorpi *et al.*, 1982; Finland	55/1,000	

Interpretation and conclusion

There is wide geographical variation in frequency of this genetic disorder. Often populations with a known high frequency of the condition have been chosen for epidemiological investigation, so the results may have little bearing on other populations.

Rigorous adherence to diagnostic criteria is especially important. If further investigation of this condition were needed, objective criteria would be important for

case definition.

1.3.7 Head and other serious neurological injury

Definitions used

Head injury may cover a wide range of injury from "bumps" on the head for which medical attention has never been sought to life-threatening injuries. Often, the definitions used in studies have been operational, e.g. "all patients seen in casualty departments", or use presumptive measures of severity such as length of amnesia or period of unconsciousness. Studies have also examined the epidemiology of head injury by outcome, e.g. "with objective new neurological signs after head injury"(Jennett, 1996).

Problems

There are two key issues upon which studies of head injury concentrate: first, the prediction at outset of those patients who will do poorly; second, the prevalence of those with significant deficits from head injuries and their health and service needs. Classification in many studies is based on outcome rather than earlier features, and comparison between studies is limited through the use of different classifications.

One problem in the study of major head injury is that it may occur together with multiple trauma; hence the study of data generated in hospitals may under-estimate head injuries, when other trauma or complications of trauma have been listed as either the main problem or the cause of death.

Epidemiology

There have been numerous investigations into frequencies of head injury and its outcome.

Many studies report the incidence of all those with head injuries attending accident and emergency services, and many of these include trivial head injury. However, there is a dearth of information about the community-based effect of these injuries. The overall evidence points to an incidence of 4–6 cases/100,000 p.a. of permanent major disability from head injury; many more (around 24/100,000 p.a.) will have significant rehabilitation needs. The prevalence estimated in a review of neurological disability in the UK was 120/100,000 (Langton Hewer, 1993).

There has been a decline in the reported numbers of deaths from head injury every year from 1967 to 1978. The WHO demographic year book reports that the UK has a low rate of deaths attributable to accidents compared with other countries: 4,191 deaths in 1990 from skull fracture and serious head injury (cited in Jennett et al., 1981). In 1981 in Scotland, an incidence of deaths from head injury of 9/100,000 p.a. was reported; it caused 15% of deaths in the 15- to 24-year-old age group, 46% of these deaths occurring before reaching hospital (Jennett et al., 1981). The National Institutes of Health of the USA (NIH) reported 22 deaths from head injury per 100,000 p.a. in San Diego and 25/100,000 p.a. in Virginia; this difference is not accounted for by differences in demography between the UK and the USA. The relative incidences of patients admitted in coma after head injury are 16/100,000 p.a. in Scotland, 25/100,000 p.a. in San Diego and 43/100,000 p.a. in Virginia (cited in (Jennett et al., 1981)). The relative contribution of road traffic accidents, falls, assaults and sports or other recreational activities varies geographically; outcome is affected by this (Jennett, 1996). The prognosis of head injury is therefore difficult to establish. There is good evidence that severe, focal and penetrating injuries to the brain, as described in cohorts of war wounded, are associated with high rates of subsequent epilepsy (Caveness et al., 1961). The more severe a head injury, the more likely is the occurrence of post-traumatic epilepsy arising from an incidence ratio of 1.5 (CL = 1.0, 2.2) for mild head injury to 17 (CL = 12.3, 23.6) for severe head injury; the incidence ratio remained significantly raised in the severely head-injured group for over 10 years (Annegers et al., 1998). In this last study, multivariate analysis identified the following as risk factors for epilepsy: brain contusion with subdural haematoma, skull fracture, loss of consciousness or memory of more than one day, and age over 65 years.

Interpretation and conclusion

Head and spinal cord injury are a source of low incidence of severe neurological handicap in all age groups. The studies of the incidence of neurological injury have been well done and are useful for measuring the utility of public health measures for accident prevention. The long-term outcome and hence the complications of neurological injury are not fully described (Eisenberg *et al.*, 1985). This is an area in which studies from different countries cannot be considered to be equivalent because the incidence of severe head injury is largely related to road traffic accidents and

violence. A country that tightly controls seatbelt use, driving speeds and "drink–driving", and where handguns are illegal, is likely to have fewer head injuries than one where the converse is true. An area that is less clear and far more controversial is the relationship of head injury to subsequent neurological disorders, e.g. multiple sclerosis and meningioma.

1.3.8 Hereditary ataxias

Definitions used

The hereditary ataxias are a group of disorders characterised by genetic inheritance, which may be dominant or recessive, symptoms and signs of cerebellar pathology, and, in many, symptoms and signs of the involvement of other neurological systems, e.g. peripheral nerves or corticospinal tracts (Harding, 1989).

Problems

Little is known about the epidemiology of the ataxias. In the past, studies of these conditions have relied on clinical syndromes. Hereditary ataxias are a heterogeneous group of disorders and the definition of the syndromes is in a state of flux because recent work in molecular biology and genetics highlights phenotypic variation. It is probable that, clinical definitions will no longer be the mainstay of the diagnosis of these disorders.

Epidemiology

A study of the prevalence of all the genetically determined ataxias and spastic paraplegias was carried out in the community in western Norway in the early 1970s. Friedreich's ataxia had a prevalence of 0.01/1,000. Spinocerebellar ataxia in the dominant form was found to have a prevalence of 0.04/1,000; the recessive form, with a predominantly spinocerebellar syndrome, had a prevalence of 0.02/1,000, and with predominantly cerebellar symptoms it had one of 0.01/1,000. Hereditary spastic paraplegia that was dominantly inherited was found in 0.12/1,000, and the recessive form in 0.02/1,000 (Refsum *et al.*, 1978).

Interpretation and conclusion

The epidemiological study of these conditions predates recent advances in their genetic and radiological investigation; further studies may well be helpful in our understanding

of these conditions.

1.3.9 Idiopathic intracranial hypertension (IIH)

Definitions used

IIH is also referred to as benign intracranial hypertension and pseudotumour cerebri. It is a condition of unknown aetiology, which may result in headache, chronic papilloedema without localising signs, and occasionally nerve VI palsy. The diagnosis is made in an alert patient with raised cerebrospinal fluid (CSF) pressure, acellular CSF, with no localising signs and neuroimaging being normal or showing an empty sella, in the absence of another cause of raised intracranial pressure.

Problems

The case definition is clear-cut. It seems likely that the cases diagnosed were only a proportion of those who have the condition. Many neurologists feel that there is some spontaneous remission but the natural history is unknown and remission will affect the prevalence rate.

Epidemiology

In Rochester, USA, the reported crude incidence was 1/100,000. The highest crude incidence is from Libya at 2/100,000.

Obesity (odds ratio [OR] = 18; CL = 7–50), recent weight gain (OR = 3; CL = 1–11) and female sex are risk factors (Radhakrishnan *et al.*, 1993). However, case–control studies have shown no association with menstrual irregularities, pregnancy, endocrinopathies, oral contraception, steroids or vitamins, all of which have been invoked as associations (Ireland *et al.*, 1990; Guiseffe *et al.*, 1991).

In the Rochester study, over a mean follow-up of 2.7 years, 3 of 18 eyes developed mild visual loss; none became severely visually impaired (Radhakrishnan *et al.*, 1993). A risk of binocular blindness of around 4% has been reported from clinic populations (Wall *et al.*, 1991). This discrepancy illustrates the tendency of clinic series to over-estimate severity when compared with community-based studies.

Interpretation and conclusion

The reported difference in incidences from the USA and Libya is unexplained and may reflect a younger population, cultural differences or a genetic effect (Radhakrishnan *et*

al., 1993).

The origin of IIH is poorly understood. It seems clear that female sex, age and weight are risk factors. As one of the main outcomes in IIH is visual impairment, the statistical methods used have to take "paired organs" into account; this has not been done in many studies looking at the outcome of IIH.

1.3.10 Infection

1.3.10.1 Bacterial meningitis

Definitions used

Bacterial meningitis is defined as an infection of the CNS with signs of meningism and polymorphs in the CSF, and/or bacteria grown in CSF with an appropriate clinical picture, or meningeal pus shown at necroscopy.

Problems

There are many bacteria that can cause meningitis; there are, however, three that account for most cases: *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Their distribution varies and epidemics may occur. Other organisms are more frequently seen in the immunocompromised individual or in those at the extremes of age. In areas with poor access to medical care, deaths of obscure or non-specific causes in children include some deaths from meningitis (Fraser *et al.*, 1975).

Epidemiology

Bacterial meningitis has an incidence of 5–10/100,000 p.a. (Brewis *et al.*, 1966; Fraser *et al.*, 1973b, 1975; Filice *et al.*, 1978). In 1978, it was reported that the relative incidences of the three most common infecting bacteria, *H. influenzae*, *N. meningitidis* and *Strep. pneumoniae*, were 2–5/100,000 p.a., 1–4/100,000 p.a. and 1–2/100,000 p.a., respectively. The case fatality rates were 5–14% for *H. influenzae*, 7–29% for *N. meningitidis* and 23–38% for *Strep. pneumoniae* (Filice *et al.*, 1978).

The Rochester group compared the incidence of meningitis between 1935–1946, when it was 6.3/100,000 p.a., and 1959–1970, when it was 9.8/100,000 p.a. In the second period, there was an increase in *haemophilus* infections overall and in atypical

meningitides in those aged over 60 years. This last group had a high case fatality rate. The pneumococcal and meningococcal incidence rates stayed the same (Fraser *et al.*, 1973b).

Several studies of the incidence of meningitis were carried out in the USA in the early 1970s, presumably spurred by the development of new vaccines. They coincide with the period during which the increased risk of pneumococcal infection in sickle-cell anaemia was being investigated, but was not yet an accepted finding, so the risk to "blacks" does not identify those with sickle-cell disease (Table 8).

Table 8. Incidence rates for meningitis in the USA in the 1970s

Region Studied	Incidence of meningitis /100,000 p.a.		Reference
Charleston County	Whites 6	Blacks 19	Fraser *et al.*, 1973a
Tennessee	Rural 5	Urban 8	Floyd *et al.*, 1974
Bernadillo County	Overall 7	Blacks 14	Fraser *et al.*, 1974

The authors tried to explain the divergence socioeconomically because the black population was far more deprived than the white. However, the meningitis did not correlate well with financial measures because of the hidden confounder: sickle-cell disease.

Risk factors for bacterial meningitis are diverse. Age is an important factor, the highest rates being among neonates, young children and then elderly people. Other conditions predispose to its development, including dural defects, sinus and ear infections (especially if chronic), hypogammaglobulinaemia and hyposplenism. In some American studies, Amerindians and blacks had higher adjusted incidence rates, which may in part be related to socioeconomic factors, because overcrowding plays a role in meningococcal spread. There are endemic areas such as the sub-Saharan meningitis belt. Outbreaks are known to occur in high-density living – in the UK this is notable in student hostels. There has been an effective vaccine against certain meningococcal strains since the late 1960s, and for *Haemophilus* sp. since the late 1970s (Filice *et al.*, 1978).

The long-term outcome for neurological deficit or epilepsy in patients who have had meningitis is unknown

Interpretation and conclusion

These are conditions that are reported to the government agencies for control of infectious diseases in many countries. Outbreaks and the emergence of bacterial resistance are monitored, so little further epidemiological work is needed. The long-term neurological outcome has been neglected more and could warrant further study.

1.3.10.2 Aseptic meningitis and viral encephalitis

Definitions used

Viral encephalitis is defined as a condition of acute or subacute onset, with neurological symptoms or signs indicative of brain parenchymal involvement – seizures, coma, focal neurological signs or impairment of mental function – in the absence of evidence of other conditions or non-viral infections. Mild obtundation and febrile convulsions were not considered to be encephalitic.

Aseptic meningitis is defined as a benign self-limiting condition of suspected or demonstrated viral origin, with fever, meningism, sterile CSF pleocytosis, but no evidence of parenchymal brain involvement.

Problems

The definition of aseptic meningitis requires a lumbar puncture result. This means that a factor in the epidemiology is the availability of doctors to perform this investigation, and the threshold at which they do it. There are good clinical reasons for a lower threshold in very young children, but the rate among immunocompetent adults is likely to be affected by sociological factors, such as clinical confidence, restraints on resources and litigation patterns.

Viral encephalitis can be difficult to separate from other encephalopathic illnesses and mild cases may never be diagnosed.

Epidemiology

The Rochester group has reported the incidence of aseptic meningitis and encephalitis from 1950 to 1981 (Beghi *et al.*, 1984). They report overall rates of 11 (10–12)/100,000 p.a. for the former and 7/100,000 for the latter. The incidence of viral

encephalitis was 7.4/100,000 p.a. in Carlisle (Brewis *et al.*, 1966).

Males in Rochester experienced significantly more of both these conditions, the effect being more significant in the aseptic meningitis group; however, this was across all ages including infancy. The rates for aseptic meningitis showed a significant rise in the most recent interval of 1975–81, with an incidence for all ages of 18 (14–21)/100,000 p.a. compared with 6.4–14/100,000 for preceding years. The increase was largely accounted for by a sixfold increase among children under 1 years and was the result of an identified enterovirus epidemic in the area in 1981; once these cases were excluded the increase was not significant. There was no variation in age group incidence rates over time for encephalitis, with young age being associated with increased frequency of the disorder. Viral encephalitis had a low fatality rate at 3.8%.

Despite the benign reputation of aseptic meningitis, 5% of patients had mild residua that were not detailed. Both conditions showed significant seasonal variation with peak rates in August and September.

Interpretation and conclusion

These rates must be treated with caution because some of the figures predate immunisation programmes for childhood exanthemas, which may underlie both these conditions. Specific disease components in the UK and the USA may differ, with significant effects on incidence and outcome. The criteria for performing a lumbar puncture may also differ and, because one criterion for diagnosis of aseptic meningitis is the presence of cells in the CSF, this has an effect on the reported incidence.

This is a fairly problematic area because any clear-cut case definition disguises clinical difficulty: when should fairly non-specific symptoms be investigated, and what constitutes unequivocal evidence of brain parenchymal involvement? The case definition ensures that viral encephalitis is at the severe end of this spectrum. It may be a devastating illness despite modern antiviral treatments and, in many cases, the viral agent remains unidentified. This could be an area of useful investigation.

1.3.11 Motor neuron disease (MND)

Definitions used

MND is defined as a progressive disorder of the upper and lower motor neurons,

which causes weakness of the bulbar, limb, thoracic and abdominal muscles (Leigh *et al.*, 1994). It is diagnosed in the presence of a progressive pure motor syndrome (atypical features are sensory signs, parkinsonism and dementia) according to the El Escorial criteria (Table 9).

Table 9. The El Escorial criteria for the diagnosis of MND (World Federation of Neurology Research Group on Neuromuscular Diseases, 1994b)

Definite:	UMN and LMN lesions in 3 body regions
Probable:	UMN and LMN lesions in 2 regions with the UMN rostral to LMN
Possible:	UMN and LMN lesions in one region or UMN lesions in 2 or 3 regions
Suspected:	LMN in 2 or 3 regions

Problems

MND is notoriously difficult to diagnose early in its course. It may be mistaken for a number of other neurological conditions. In a recent cohort, 10% had alternative diagnoses at follow-up (Davenport *et al.*, 1996).

Epidemiology

The incidence is between 1 and 2/100,000 p.a. (Brewis *et al.*, 1966; Juergens *et al.*, 1980). Guam had a high incidence, around 87/100,000 p.a., earlier this century, but the rate had fallen to 5/100,000 p.a. in 1985. No explanation has been found and, although dietary factors were once believed to be the cause, this has not been borne out by epidemiological investigations (Leigh *et al.*, 1994).

Reported prevalence figures vary considerably, the range being 3.6–11/100,000 (Kondo, 1978). The cumulative risk of dying from MND up to age 80 years is 1 in 688 for men and 1 in 938 for women (Annegers *et al.*, 1991). The disease is more common in men (3:2) and with increasing age, particularly after 50 years (Juergens *et al.*, 1980; Li *et al.*, 1985). Ten per cent of patients have a family history of MND; the familial form is indistinguishable from the sporadic form. Some familial and some sporadic MND are associated with a mutation in the superoxide dismutase gene.

Apart from the superoxide dismutase gene, the search for risk factors has been unproductive despite well-designed studies in the general community and in areas and groups that have a high incidence.

Median survival is 3.5 years from onset of symptoms: 28% survive to 5 years, 10% to

10 years. A UK-based study reported that 57% of MND patients have dysphagia and 25% were totally dependent for all aspects of daily living (Leigh *et al.*, 1994). Recovery has never been reported.

Interpretation and conclusion

Studies of the incidence of MND give uniform figures, with, more recently, increased diagnosis among older age groups. Case–control studies have failed to find risk factors and so have geographical clusters (it seems that the MND syndrome of Guam was not the same condition – it is now disappearing again for unknown reasons). Genetic neuroepidemiological studies are under way.

1.3.12 Multiple sclerosis

Definitions used

Multiple sclerosis (MS) is a disease affecting the CNS white matter, causing intermittent demyelination. The pathological lesion is a plaque of demyelination, the temporospatial properties of which affect the presentation of and the problems experienced by the patient. At least two lesions, separated both anatomically and in time, are required for diagnosis. The most common definition used is that in the "Poser criteria", shown in Table 10 (see over). As yet, no internationally agreed criteria include the place of MRI in the diagnosis of MS, despite its recognised importance clinically.

Three clinical patterns are recognised: relapsing and remitting, primary progressive and secondary progressive. Isolated episodes of demyelination are described according to their location (transverse myelitits or optic neuritis), or their timing, as with acute demyelinating encephalomyelitis.

Problems

The initial problem is case definition because it is a clinical diagnosis with variable degrees of certainty (possible, probable or definite). Certain patients who are considered to have MS fail to fulfil diagnostic criteria for research, notably those with primary progressive disease.

Also, MS poses difficulties in epidemiology because there may be a long time from the

first symptom to diagnosis. This makes studies of causality difficult to carry out (Kahana *et al.*, 1996). As it is a rare condition with a long latency, no cohort study has been carried out (Wolfson *et al.*, 1997).

As it seems likely that a number of factors interact to cause the disease, a large number of cases are required to achieve statistical power in studies examining aetiological factors.

Table 10. The "Poser criteria" for the diagnosis and classification of multiple sclerosis (Poser *et al.*, 1983)

In an individual aged between 10 and 59 years	
An attack of symptoms ascribable to demyelination in the CNS, must last >24 hours, may be subjective, at least one month apart.	
Paraclinical signs include: raised ambient temperature causing a deterioration in clinical state, positive evoked potentials, imaging or urology studies	
a) Clinically definite MS	Two attacks separated in time and place and signs of two lesions
	or two attacks with signs of a lesion and a paraclinical sign
b) Laboratory supported MS	Oligoclonal bands
	and two attacks, with signs of a lesion
	or one attack and signs of two lesions
	or one attack, signs of a lesion and a paraclinical sign
c) Clinically probable MS	two attacks and signs of one lesion
	or one attack with signs of a lesion and a paraclinical sign
	or one attack and signs of two lesions
d) Laboratory supported probable MS	oligoclonal bands and two attacks

Epidemiology

The incidence is between 2 and 8/100,000 p.a. (Brewis *et al.*, 1966; Millar, 1980; Shepherd *et al.*, 1980).

There is evidence of temporal heterogeneity in incidence; there appears to be an increase in low-frequency areas, although this can at least be partly explained by improvements in case ascertainment. In addition, there appears to be a fall-off in the incidence in areas with high incidence rates. This may be the result of improved case

ascertainment of rarer mimics of MS, such as systemic lupus erythematosus, sarcoid and Beçhet's disease. There have been sharp and as yet unexplained increases in frequencies after World War II in the Faroe Islands, Iceland and Sardinia.

The prevalence varies with latitude in the UK and Australasia, although this is contentious (Miller *et al.*, 1990; Rice Oxley *et al.*, 1995; Robertson *et al.*, 1995). Rates of between 80 and 168/100,000 are reported. It has been estimated that about 1/300 of the population aged 40–59 years in north-east Scotland were affected in 1973 (Shepherd *et al.*, 1980; Collaborative Group for the Study of Epilepsy, 1992; McDonnell *et al.*, 1998).

MS has an uneven geographical distribution with the highest rates in the UK, Denmark and Scandinavia, and the lowest towards the equator in populations with low numbers of northern European settlers. In communities within the same geographical area, Caucasians have a predilection for the disease (Wolfson *et al.*, 1997). With migration, individuals retain the risk of their place of origin if they emigrate before the age of 10–15 years (Elian *et al.*, 1990). However, the effect of migration after this age is stronger if emigrating from a high-risk area than if immigrating to a high-risk area (Hodge *et al.*, 1997): the immigrée population acquiring an IR between that of the country of origin and the country they inhabit. Low temperature and high humidity and/or precipitation in winter correlate positively with incidence rates for MS (Lauer, 1997b). However, considerable controversy surrounds the relative importance of genes and environment in the causation of MS (Compston, 1990).

A genetic link, which in itself is not sufficient to cause the disease, is supported by a number of observations. There is a 10- to 50-fold increase in risk of developing the disease in those who have relatives with MS. The concordance rate in monozygotic twins supports the importance of genes in the propensity for developing MS, and suggests that at least two genes are likely to be involved. It is probable that one of these genes is the common Caucasian MHC class II type HLA-DR2, but the role of other genes is less clear. In those diagnosed with MS, a negative family history is a better prognostic feature than a positive one (Phadke, 1990). However, it should be borne in mind that the time clustering in some communities, as in the Faroe Islands and Sardinia, argues against the importance of genes (Riise, 1997b).

The medical profession and patients' partners are not at increased risk (Compston, 1990). However, there have been case–control studies which looked at infection with viruses and reported an association between infection with various viruses and the development of MS (Hodge *et al.*, 1997, Riise, 1997a). In fact, the strongest correlation is not with any one viral agent but with late acquisition of at least one viral illness (Granieri *et al.*, 1997).

A link between trauma and development of either MS or exacerbations thereof is weak, but may just be significant for disease development; it does not appear to trigger relapses (Riise, 1997a).

A twofold higher rate of MS was found among painters, compared with other blue collar workers in Norway; this has led to the hypothesis that exposure to organic solvents may be a risk factor (Riise, 1997a).

Diet – given its wide geographical and ethnic variability – has been studied a great deal. The most consistent reports are correlation between MS and dietary parameters that reflect the consumption of animal fat, meat and animal protein. The inverse relationship to fish and vegetables is smaller in magnitude and probably reflects confounding as a result of replacement of meat in the diets of those eating less (Lauer, 1997a). There is an association between MS and certain forms of cancer, notably those that are linked to consumption of animal products and particularly animal fat (e.g. colorectal and rectal cancers) (Lauer, 1997b).

Among prevalent cases, the three clinical patterns are seen: 31% relapsing and remitting, 37% primary progressive and 31% secondary progressive (Minderhoud *et al.*, 1988). In the Harris report, 70% of patients with MS living at home have some disability, which ties in with the finding that 20–40% of patients have benign MS (minimal permanent disability after prolonged observation – usually > 10 years) (McAlpine, 1961; Shepherd *et al.*, 1980; Thompson *et al.*, 1986; Phadke, 1990; McDonnell *et al.*, 1998).

The incidence and prevalence of demyelinating diseases not fulfilling the criteria for MS are unknown (Weinshenker, 1996). The point prevalence of optic neuritis in Rochester was noted to be 10/100,000 (Kurtzke, 1984).

Interpretation and conclusion

Although the incidence and prevalence of MS are well described, the cause remains obscure. Studies of risk factors are marred by retrospective design and hence recall bias in an illness; this particularly affects studies of illnesses with long latency. For a prospective study of risk factors, a method that produced such good results in atherosclerotic conditions would be hampered by the low incidence. The reason for the change in incidence is not known. The numbers of prevalent cases with secondary problems, such as central pain syndromes, neurogenic bladder and epilepsy, are not defined in community-based studies.

1.3.13 Myasthenia gravis (MG)

Definitions used

Myasthenia gravis is an autoimmune condition in which voluntary muscle develops weakness as a result of the presence of antibodies to the post-synaptic acetylcholine receptors at the neuromuscular junction. It is defined as the presence of rapid fatigue in one or more muscle groups, and weakness aggravated by exercise and relieved by rest, which shows a significant response to anticholinesterase drugs. The presence of acetylcholine receptor antibodies and decrement on electromyography (EMG) support the diagnosis. The exclusion of the Lambert–Eaton syndrome is clinical with help from EMG (Christensen *et al.*, 1993; World Federation of Neurology Research Group on Neuromuscular Diseases, 1994a).

Problems

Myasthenia gravis is a relatively rare condition which may be under-diagnosed in its mildest or earliest manifestations. Certainly, in elderly people who have multiple pathologies, fatigue may not be appreciated as "rapid fatigue in one or more muscle groups". Treatment may abolish signs.

Epidemiology

A retrospective community-based study of myasthenia gravis in western Denmark between 1975 and 1989 found an incidence of 0.5/100,000 p.a. (Christensen *et al.*, 1993). A retrospective estimate of incidence in Sardinia estimated a rate of 0.8 (0.5–1.2)/100,000 p.a. (Aiello *et al.*, 1997).

The prevalence in Denmark was 0.08/1,000. The prevalence rose from 0.03/1,000 in

1977 to 0.07/1,000 in 1987; such an increase has also been reported from Sardinia and Norway (Christensen *et al.*, 1993). The prevalence in Sardinia was 0.1 (CL = 0.08–0.16)/1,000 based on a community sample of over a quarter of a million (Aiello *et al.*, 1997). The most recently reported prevalence was in Cambridge where a figure of 0.15 (0.12–0.18)/1,000 was found for an incidence of 1/100,000 p.a. (Robertson *et al.*, 1998). Other prevalence and incidence figures are in broad agreement with these, with ranges of 0.25–0.5/100,000 p.a. for incidence and 0.05–0.1/100,000 for prevalence.

Myasthenia gravis most commonly affects women in early adult life, with a second peak in older men. It is associated with other organ-specific autoimmune diseases; this association is more marked in women (6% of men and 38% of women with myasthenia gravis had other autoimmune disorders) (Robertson *et al.*, 1998).

In Sardinia, they found moderate-to-severe disability in 51%; however, the classification of disability used a protocol that described the natural history of different presentations of myasthenia gravis and not the degree to which the patient was impaired (Osserman *et al.*, 1971). Of those who were known to have had myasthenia gravis in Denmark, 21% had resolved and 18% were moderately or significantly disabled (Christensen *et al.*, 1993).

It should be noted that early and retrospective studies of myasthenia gravis report around 10–14% of ocular cases, whereas the most recent studies report around 33% of cases as ocular (Robertson *et al.*, 1998).

Myasthenia gravis is a condition with a significant direct mortality rate. Despite improvements in care, which may increase prevalence, immunosuppressive regimens are used and control of the condition carries treatment-related morbidity and mortality.

Interpretation

There are few data on myasthenia gravis. The reported prevalence rates seem low for a treatable condition of such an incidence, although more recent studies, such as the Cambridge study, give more plausible prevalences. More recent studies have shown increased percentages of ocular myasthenia gravis, which has been used to support the argument that more mild cases are being seen. However, this may also be a reflection of treatment efficacy.

1.3.14 Parkinson's disease

Definitions used

The case definitions of idiopathic Parkinson's disease, "Parkinson's plus" syndromes and parkinsonism are difficult. Various case definitions have been used in studies of Parkinson's disease. The case definition used in the Aberdeen study was at least two of the cardinal signs of Parkinson's disease: resting tremor, rigidity, bradykinesia and impaired postural reflexes. This study excluded patients with a history or signs consistent with atherosclerotic parkinsonism, and also those who had been on neuroleptics or metoclopramide during the 6 months before the study and who had not reported parkinsonian symptoms before that period (Mutch *et al.*, 1986). Other studies have required one of three cardinal signs with other supportive investigations and different exclusion criteria (Anderson *et al.*, 1998). By contrast, the Rochester study required one of the following: a diagnosis made by a neurologist, demonstration of all three major manifestations (resting tremor, bradykinesia and rigidity), demonstration of the glabellar tap, facial rigidity and asymmetrical or unilateral bradykinesia and rigidity, or classic, histological, idiopathic Parkinson's disease. Moreover, patients who developed parkinsonism on medication, which persisted for 12 months after medication was withdrawn, were considered to have drug-induced parkinsonism; if the syndrome was transient, however, patients were not included in the study. Patients who became symptomatic while taking neuroleptic drugs and who had continuing symptoms 6 months after stopping medication were counted as having idiopathic Parkinson's disease (Kurtzke, 1984) .

Problems

There is variability between the studies which makes comparison difficult (Anderson *et al.*, 1998). Moreover the signs are not invariable and patients will exhibit some signs and not others dependent on the treatment and the severity of illness. For example, 70% of patients will have resting tremor at diagnosis (Hoehn *et al.*, 1967). Some studies use drug tracer methodology, which is a useful additional technique for case ascertainment but cannot substitute for clinical assessment. (Some patients will be put on trials of L-dopa for parkinsonism that is not Parkinson's disease and may stay on this medication long term; other patients with Parkinson's disease may not want to start medication despite the diagnosis. Both of these will affect the results of drug

tracing.)

Other conditions may mimic Parkinson's disease, such as cerebral atherosclerosis, space-occupying lesions and other neurodegenerative conditions. Producing a case definition that reliably excludes these conditions is difficult; in one clinic-based postmortem series, reported misdiagnosis by movement disorder specialists was high (Hughes *et al.*, 1992). There is the problem of dual pathology in elderly people and how to decide which illness contributes most or exclusively to a parkinsonian syndrome.

The frequency of Parkinson's disease is closely related to age and the changes in population demographics are marked. Thus, rates may seem low for studies done in earlier decades and from countries where there are fewer elderly people. Before making comparisons, the rates must be adjusted to a single standard population.

Epidemiology

The incidence lies between 12.2 and 18.2/100,000 p.a. (Brewis *et al.*, 1966; Rajput *et al.*, 1984b). The higher figure from the Rochester group includes atherosclerotic cases (14% of all cases), and an incidence of 20.7/100,000 p.a. was reported when drug-induced cases (7% of cases) were included.

The prevalence is not always easy to estimate; this results partly from treatment being sufficiently efficacious to abolish signs of illness in early disease. Moreover, atherosclerotic disease may mimic Parkinson's disease, as do the side effects of the neuroleptic family of drugs. Worldwide, the prevalences standardised to the population of the USA in 1970 are between 0.6 and 2.3/1,000 (Brewis *et al.*, 1966; Mutch *et al.*, 1986; Chio *et al.*, 1998).

Age is a key risk factor for Parkinson's disease. The prevalence rate of parkinsonian signs on examination rises with age, from 14.9% at age 65–74 years, through 29.5% at 75–84 years, to 52.4% at 85 years or more (Bennett *et al.*, 1996). From door-to-door surveys of Parkinson's disease, it can be estimated that the prevalence is 2 (CL = 1.6–2.4)/1,000 (Chio *et al.*, 1998). Sex is not a factor (Zhang *et al.*, 1993). Geographical variation has been reported, with the lowest rates for both incidence and prevalence in China, but it seems likely that study design was not optimal for case ascertainment.

Further study of this low incidence area may be valuable (Zhang *et al.*, 1993). There has been much debate about the protective effect of smoking in Parkinson's disease. It remains unclear whether this is a true effect or whether there is selected mortality or even reverse causality (Ben-Shlomo, 1996).

Before the advent of L-dopa treatment, 28% of patients with Parkinson's disease were dead or disabled to the point that they required help in feeding or dressing within 5 years of diagnosis, and 90% by 15 years (Hoehn *et al.*, 1967). More modern studies reported that 35% of patients were considerably disabled and 10% confined to a wheelchair or bedbound (Mutch *et al.*, 1986). A recent study reported that 14%, 15% and 4% of patients in the community were at Hoehn and Yahr stage III, IV and V, respectively, reflecting considerable disability (Hoehn *et al.*, 1967; Chio *et al.*, 1998). The Harris report estimated that Parkinson's disease accounted for 3% of the severely handicapped living at home. A survey has further found that 33% also have problems of mood or intellect.

Mortality is increased in patients with Parkinson's disease, with a risk of death raised by a factor of 2 (CL = 1.6–2.6); this risk is particularly increased if there is a gait disturbance (Bennett *et al.*, 1996).

Interpretation and conclusion

There are difficulties in comparing studies as a result of inadequate case definition. There is some evidence of geographical differences. The study of Parkinson's disease could be productive, especially in view of the possible interaction of putative environmental factors with disease expression. To address this appropriately, studies need to be designed to look at these factors experimentally.

1.3.15 Peripheral neuropathies

1.3.15.1 Polyneuropathy

Definitions used

Polyneuropathy causes a bilateral symmetrical disturbance of peripheral nerve function, which may be motor, sensory or autonomic, or any combination of these modalities. A wide range of aetiologies including toxins may be implicated, but cryptogenic polyneuropathy accounts for a relatively high percentage of cases. In one clinic study, 13% of patients with polyneuropathy followed for at least one year were thought to

have cryptogenic polyneuropathy (McLeod *et al.*, 1984), but higher rates are reported elsewhere (Dyck *et al.*, 1981).

Problems

Many polyneuropathies may be asymptomatic and these will be picked up only if they are found incidentally or sought out as in people with diabetes.

The diagnosis of the different underlying causes requires appropriate facilities.

Epidemiology

There are no good epidemiological studies of the polyneuropathies in general (Hughes, 1995).

The hereditary neuropathies are thought to account for most of the undiagnosed neuropathies (Dyck *et al.*, 1981). Their prevalence has variously been reported as from 0.02 to 0.41/1,000 (Schoenberg *et al.*, 1993). A study of the Charcot–Marie–Tooth disease in Norway identified a prevalence of 0.36/1,000 for the autosomal dominant form, 0.01/1,000 for the autosomal recessive form and 0.04/1,000 for the X-linked form (Refsum *et al.*, 1978). In northern Sweden, the prevalence was 0.2/1,000, among whom 80% had type 1 and 15% had severe disability, including 2% who were wheelchair-bound (Holmberg, 1993).

Estimates of neuropathy in patients with cancer suggest that 1–5% are affected. The type of tumour and the chemotherapeutic agents used will affect this rate significantly. Paraprotein-related neuropathies are said to account for 10% of unexplained neuropathies.

Interpretation

There are no good community-based studies of neuropathies and most reports are from tertiary centre clinics, whose populations are biased to the point of being uninterpretable at a community level.

Conclusion

There is a need for basic descriptive epidemiology of the neuropathies. Given the significant number that are cryptogenic, and the fact that toxins play an important role, it would not be unreasonable to hope that analytical epidemiology may identify

additional risk factors.

1.3.15.2 Diabetic polyneuropathy

Definitions used

Case definition of diabetic neuropathy has been a fairly complicated issue. A large European multicentre study – the EURODIAB IDDM Complications Study – summarises the differing definitions used. They report a large-scale, clinic-based study and included those patients who had any two of the factors listed in Table 11 (Tesfaye *et al.*, 1996).

Table 11. Inclusion criteria for EURODIAB IDDM complications study

1.	The presence of one or more symptoms: (a) numbness or deadness in the feet; (b) deep or burning pains in the legs; (c) prickling sensation in the feet; (d) unusual difficulty in climbing the stairs; (e) difficulty controlling the bladder; (f) any trouble with nocturnal diarrhoea; and (g) in men with problems with sexual intercourse: obtaining an erection, sustaining an erection, or lack of spontaneous erections at night or in the morning.
2.	Absence of two or more ankle or knee reflexes.
3.	Abnormal age-adjusted vibration threshold measures.
4.	Abnormal autonomic function measures using Ewings' definitions of postural hypotension (drop in systolic blood pressure of > 30 mmHg and/or relative risk ratio < 1).

It should be noted that the two forms of diabetes present differently in terms of neuropathy. People with type 2 or non-insulin-dependent diabetes (NIDDM) often present with slowly evolving symptoms or are asymptomatic; polyneuropathy is not infrequently present at diagnosis. People with type 1 or insulin-dependent diabetes (IDDM) are usually acutely unwell at presentation and it is rare for peripheral nerve damage to be present at diagnosis (Melton *et al.*, 1987).

Problems

The case definition used by EURODIAB is clearly not practical in the community, unless this is the focus of a study with sufficient resources. Also, it lacks sufficient

specificity to exclude other conditions.

The case definition would have to be designed so that causal factors could be studied – in order to find cases early in the development of this complication. To do this, it seems inevitable that better information would be gained from a presymptomatic diagnosis which would require more resources for case finding (Melton *et al.*, 1987). Controls would have to be used because there is a background rate of neuropathy from other causes in the community. Some instruments have established normal ranges, which may help (Bloom *et al.*, 1984).

Epidemiology

There is no study of the incidence of diabetic polyneuropathy. The range of patients affected at the time of first diagnosis of diabetes has been reported as 0–100% (Melton *et al.*, 1987). The prevalence of diabetic neuropathy has been studied in Rochester, USA (Dyck *et al.*, 1993) where 1.3% of the population had diabetes, 26.8% of those with diabetes had type 1 and 73.2% type 2. The breakdown of neuropathies found is shown in Table 12.

Table 12. Prevalence of neuropathies in people with diabetes (Dyck *et al.*, 1993)

Type of neuropathy	Prevalence (%) in patients with	
	Type 1 diabetes	Type 2 diabetes
Any neuropathy	66	
Polyneuropathy	54	45
Symptomatic polyneuropathy	15	13
Severe polyneuropathy (unable to stand on heels)	6	1
Asymptomatic carpal tunnel syndrome	22	29
Symptomatic carpal tunnel syndrome	11	6
Autonomic neuropathies	7	5

Prevalence of polyneuropathy in people with diabetes is proportional to the duration of illness, although 3% of adults have neuropathy at or before the diagnosis of diabetes. A door-to-door survey of symptomatic diabetic neuropathy in Sicily reported a crude prevalence rate of 3/1,000 (Savettieri *et al.*, 1993). The Oxford community-based

study of diabetic neuropathy defined it as a bilateral loss of distal vibration sense. The prevalence of diabetes in the population was 1%; 17% of patients with diabetes aged 20–59 years, 42% of patients aged 60–69 years and 10% of those aged over 70 years fulfilled the criteria for diabetic neuropathy. A rough calculation of the point prevalence of diabetic polyneuropathy gives 2 (1.86, 2.99)/1,000 of the general population (Neil *et al.*, 1989).

The EURODIAB IDDM Complications Study explored the associations of polyneuropathy with measures of diabetic severity and control, using stratification by adjusting for age, duration of diabetes and levels of HbA_{1c}. The control group was the whole diabetic clinic population who did not have neuropathy.

Factors examined are shown in Table 13. On stepwise logistic regression analysis, the independent predictors were weight, current smoking, severe ketoacidosis, macroalbuminuria, background and proliferative retinopathy, and high fasting plasma triglycerides, as well as age and duration of diabetes. There was a lower prevalence of neuropathy among those with no albuminuria, microalbuminuria and macroalbuminuria. This study correlates well with other clinic-based studies (Tesfaye *et al.*, 1996).

Table 13. Variables associated with neuropathy in a population of people with diabetes

Factors associated with neuropathy	Factors not correlated with neuropathy
Increasing height	Age at diagnosis of diabetes
Diastolic blood pressure (adjusted for age)	LDL-cholesterol levels
Current smoking	Total cholesterol
Reduced HDL-cholesterol	
Raised fasting triglyceride	
Severe ketoacidosis	
Cardiovascular diabetic complications	
Retinopathy	
Albumin excretion	

HDL, high-density lipoprotein; LDL low-density lipoprotein

There are a number of clinic-based studies that have examined patients with diabetes for neuropathy. The numbers of patients examined and the criteria for diagnosis of neuropathy have varied, leading to rates of neuropathy that are disparate (Table 14).

Table 14. Reported prevalence of symptoms and signs of neuropathy in diabetes

Source	Measurement	No patients	neuropathy (%)
Cleveland 1953	Subjective complaints	261	62
Salford, Eng. 1953	General findings	100	57
Brussels 1965	Objective signs	1,175	21
Stockholm 1950	Objective signs	150	49
Rochester 1961	EMG, objective signs	103	42
Philadelphia 1958	Impotence	198	55
New York 1952	Skin vessel dilatation	16	44
London 1960	Abnormal Valsalva manoeuvre	337	20
Toronto 1961	Objective signs	100	52
Cincinnati 1951	General signs	77	35
Chicago 1966	Objective signs, motor conduction velocity	107	10
Aarhus 1968	Motor conduction velocity	14	100
London 1971	Motor conduction velocity	39	100
Edinburgh 1977	Motor conduction velocity, autonomic vascular tests	10	100

(Adapted from Melton *et al.*, 1987)

Interpretation and conclusions

It is difficult to compare those studies that use different case definitions. However, it is clear that diabetic neuropathy has a high prevalence in the community and may be asymptomatic. It is of clear clinical importance to find out why some patients develop complications of diabetes whereas others are spared.

1.3.15.3 Inflammatory neuropathy and Guillain–Barré syndrome (GBS)

Definitions used

The diagnostic criteria are a progressive motor weakness of more than one limb with areflexia, relative symmetry, progression over less than 4 weeks, mild sensory symptoms, cranial nerve involvement, autonomic dysfunction and no fever at onset. Investigative support includes raised CSF protein, with fewer than 10 lymphocytes and an EMG showing slowing or block of motor conduction. In contrast, the diagnosis is put in doubt by asymmetry of signs, bladder or bowel disturbance either at onset or persistently, more than 50 monocytes or polymorphonuclear white cells in the CSF, or a sharp sensory level (World Federation of Neurology Research Group on Neuromuscular Diseases, 1994a; Rees *et al.*, 1998).

In distinction, chronic inflammatory demyelinating polyneuropathy (CIDP) must have been progressive for more than a month. Sensory symptoms are more common.

Problems

Some mild cases of GBS are possibly missed in the community and atypical cases may be misdiagnosed.

Epidemiology

The incidence has been well studied and is about 1.5 (1.3–1.8)/100,000 p.a. (Rees *et al.*, 1998).

A correlation with infections and particularly with *Campylobacter* spp. has been demonstrated in different countries.

In one study, 20% were left with disability, 10% being unable to walk unaided at a year (Hughes, 1996). In a recent study, the mortality rate was 8%; 4% remained either bedbound or ventilator dependent and 9% were unable to walk unaided at 1 year (Rees *et al.*, 1998).

Interpretation and conclusion

GBS has been well studied and is an example of how community-based studies can be linked with analytical studies in neurology to produce clinically important information.

CIDP tends to get mixed up with polyneuropathies of cryptogenic origin. It would be rational to investigate it further as part of a community study of polyneuropathy.

1.3.15.4 Compressive neuropathy

Definitions used

Entrapment or compressive neuropathies are focal neuropathies caused by restriction or mechanical distortion of a nerve. These occur at particularly vulnerable points on nerves giving classic signs and/or symptoms; however, not all compressions are symptomatic (World Federation of Neurology Research Group on Neuromuscular Diseases, 1994a).

Epidemiology

Carpal tunnel syndrome has been studied and, given its high frequency, both symptomatic and asymptomatic, we have excluded it from our study. The other compressive neuropathies have not been studied epidemiologically (Hughes, 1995). A Franco-American collaboration found that the ratio of ulnar compression to carpal tunnel syndrome was 1:4, but this was in a clinic-based study (Seror *et al.*, 1993).

Interpretation and conclusion

There is no useful information for any to be made.

1.3.16 Plexopathy / Plexitis

Definitions used

Plexopathy is frequently a painful condition, which may be related to a number of conditions, e.g. diabetes, pressure from space-occupying lesions, malignant infiltration or radiation, but no underlying cause is uncovered in many cases. It may affect the lumbrosacral or brachial plexus. The latter is most commonly affected by an idiopathic condition – known as brachial neuritis or neuralgic amyotrophy. Little is known of the pathology and plexitis is an alt rnative term.

Epidemiology

There is one study of the incidence of brachial neuritis from Rochester, USA where a rate of 2/100,000 p.a. was found (Beghi *et al.*, 1985).

Conclusion

This appears to be an area that might benefit from neuroepidemiological attention, because so little is known about its causes, what affects its outcome and its prognosis.

1.3.17 Postherpetic neuralgia (PHN) and shingles

Definitions used

Shingles is a vesicular rash in a dermatomal distribution caused by herpes zoster.

PHN is persistent pain, lasting for more than a month, after an episode of shingles, which has the same distribution as the original rash.

Problems

This is a condition that is largely dealt with in primary care. It may be associated with malignancies or immunosuppression, so PHN may be regarded as a secondary problem. Patients may be referred to a number of different specialists for further management of the pain or the associated malignancy or immunosuppression.

Epidemiology

There are a number of studies based in the community which give quite divergent reports for the incidence of shingles. The range is 130–480/100,000 p.a. (Hope-Simpson, 1965; Ragozzino *et al.*, 1982; Schoenberg *et al.*, 1993). It has been reported that 9–10% of patients who have had shingles develop PHN (Ragozzino *et al.*, 1982). The Rochester study found that, in 45%, PHN lasted less than 8 weeks and, in 22%, more than 1 year.

PHN is more frequent in elderly people, which accounts for the reported bias towards women (Ragozzino *et al.*, 1982).

Conclusion

It could be useful to study the factors that influence the development of PHN after shingles; moreover, identification of the true percentage of patients who have associated pathologies could be explored.

1.3.18 Stroke

Definitions used

There are currently two widely used disease definitions used for stroke: (1) "rapidly developing clinical signs of a focal (or global) disturbance of cerebral function, with symptoms lasting at least 24 hours or leading to death, with no apparent cause other than of vascular origin" (NINDS, 1990); (2) "any one or all of a group of disorders including cerebral infarction, intracerebral haemorrhage, or subarachnoid

haemorrhage" (Atkinson *et al.*, 1989). Cerebral infarction accounts for 70–80% of acute stroke in the community, among which 80% are caused by cerebrovascular disease, 15–19% are from emboli and 5% from unusual causes (e.g. dissection, fibromuscular dysplasia, arteritis) (Thompson *et al.*, 1996). Infarction secondary to cerebrovascular disease encompasses both large- and small-vessel disease: large-vessel disease occurs when a thromboembolus or occlusion evolves from atheroma in a large artery such as the carotid and small-vessel disease is caused by occlusion of the small perforating arteries in the subcortical white matter. It seems likely that these two conditions share some risk factors but that they are disparate conditions. Transient ischaemic attacks (TIAs) are vascular episodes the symptoms and signs of which last less than 24 hours (Bamford *et al.*, 1988). Intracranial and subarachnoid haemorrhage accounts for 20–30% of strokes. Subdural haemorrhage, which presents either as stroke after trauma or subacutely with progressive neurological deficit, has not been studied epidemiologically.

Problems

The clinical definition of stroke is clearly defined and useful, provided that care is taken to exclude some conditions that may imitate the presentation of stroke. Studies vary in their definition of stroke subtypes.

As stroke is common, particularly in elderly people, it requires case ascertainment that is community based because many patients are never referred to specialist services. The case definition is clinical and the Oxford Community Stroke Study noted that the clinical diagnosis of stroke was highly specific with an error rate of only 1% (Bamford *et al.*, 1988). One difficulty is that, as the case definition for stroke is wide and the underlying pathological conditions are heterogeneous, studies of "stroke" as an entity may obscure important patterns in subgroups.

Stroke is a feared diagnosis, particularly among elderly people, and not all patients understand that transient symptoms may be strokes. This will affect the results of studies by post. Some patients with TIAs may not see their GP at all. Some patients will die suddenly from their first stroke and will therefore not be included in incidence studies. Conversely, stroke is a diagnosis that is invoked without confirmatory evidence when elderly people die at home.

Epidemiology

Stroke is the third most common cause of death in the UK and accounts for 80% of neurological deaths (Rudd *et al.*, 1997). The Oxford-based study reported the age-adjusted incidence for first-ever stroke or TIA as 200/100,000 p.a. (Bamford *et al.*, 1988). A more recent study in north-west England reported an overall age- and sex-adjusted incidence of 160 (150, 170)/100,000 p.a.; they noted, however, that towns had rates of 163–205/100,000 p.a. compared with rural rates of 118/100,000 p.a. (Du *et al.*, 1997).

The incidence rate of primary intracerebral haemorrhage is around 10% of all strokes (Bamford *et al.*, 1990).

The incidence of stroke, as a result of both primary intracerebral haemorrhage and infarction, declined in the 1970s and early 1980s, but may now have restabilised (Phillips *et al.*, 1980; Perkin, 1997). The figures from the Fourth National Morbidity Study, based on UK general practice, noted a fall in the mortality rate of stroke, coincident with a rise of 65% in the number of patients presenting with stroke in general practice (Ebrahim, 1995). As this figure is generated by the GDRP system of data collection, it seems likely that the effect is the result of an increased number of consultations per patient with a stroke, as a consequence of recent trends towards higher levels of intervention in hypertension in elderly people and use of warfarin for atrial fibrillation.

The data on recurrence after first stroke are limited, but can be approached by examining the placebo arm of intervention studies. The incidence rate was 3.6% p.a. in patients who have had a stroke, with a relative risk of 2.2 (1.5–3.4) for large-vessel disease with respect to small-vessel disease (Kappelle *et al.*, 1995). The Yorkshire community postal survey (discussed in detail below) reported that 13% of stroke survivors had experienced two strokes, and 7% three or more strokes (McGeddes *et al.*, 1996). The Copenhagen community study reported that 25% of their cases with prevalent stroke had had more than one stroke (Sorensen *et al.*, 1982).

If the background rate of first stroke is 200/100,000 p.a., with a 30% mortality rate at 3 weeks (Lyden, 1997), it can be estimated that there will be 28–35/100,000 people having "subsequent strokes" per year (not corrected for mortality after 3 months).

Studies of the prevalence of stroke patients in the community are relatively sparse. In Copenhagen in 1976, a prevalence of 5/1,000 was found (Sorensen *et al.*, 1982). Estimates in the USA, based on incidence studies, have given figures of 8/1,000. The figure currently used in the UK as a guide to purchasing services is 6/1,000 (McGeddes *et al.*, 1996).

There are no reports of the epidemiology of subdural haematoma.

Risk factors for ischaemic stroke are broadly similar to those for ischaemic heart and peripheral vascular disease: hypertension, age, male sex, race, smoking, diabetes and hyperuricaemia. More specifically, cerebral infection is a potent risk factor for stroke. TIAs, and even more strongly stroke, are indicators of risk for future stroke, and the frequency of recurring TIAs is proportional to risk (Shinton *et al.*, 1989; WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989).

Hypertension is the most important modifiable risk factor, with a threefold increase for stroke with borderline hypertension and an 18-fold increase with definite hypertension, the effect being stronger in men. Systolic, diastolic and combined hypertension are each a risk factor for stroke worldwide (WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989; SHEP Cooperative Research Group, 1991). All types of primary intracranial haemorrhage are strongly associated with hypertension (WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989; Anderson *et al.*, 1994).

Practically all forms of chronic heart disease are associated with ischaemic stroke. The lowest risk is for lone atrial fibrillation with a stroke rate of less than 3% p.a., rising 17-fold when associated with mitral stenosis (Halperin *et al.*, 1988). Clinically overt or covert impairment of cardiac function as a result of any cause carries the highest risk, particularly if associated with embolic risk or left ventricular hypertrophy (Thompson *et al.*, 1996). It is worth noting that, in developed countries, the incidence of rheumatic heart disease, which formerly accounted for most cases of valvular heart disease, has declined dramatically since the 1920s. Acute rheumatic fever affects less than 5/100,000 p.a. in developed countries (Neutze, 1988), but in developing countries it remains a problem because the prevalence of chronic rheumatic heart disease remains

high: 6/1,000 in schoolchildren (Gibson, 1988).

What is notable, however, is that the trends in frequency of stroke and coronary heart disease differ and appear to vary with different factors (Maheswaran *et al.*, 1997a). It has been reported that trends in stroke mortality in Greater London differ from those in south-east England, the mortality being lower for individuals born before 1921 who live in London compared with those who live in south-east England, but the stroke mortality rates decline less rapidly with each subsequent decade. This does not seem to be linked to markers for intrauterine deprivation or early socioeconomic status, nor does changing ethnicity account for all the change, although it may contribute, because the divergence of change of stroke mortality rates predates the large Commonwealth immigrations to London (Davey-Smith *et al.*, 1997; Maheswaran *et al.*, 1997a, 1997b; Uemichi *et al.*, 1997).

Smoking increases the risk of all types of stroke. The effect is more marked for ischaemic stroke in women and increases their risk by 60%. A meta-analysis of the relative risks of smoking with different types of stroke showed the biggest effect in ischaemic stroke with a relative risk for smokers of 1.9 (CL = 1.7, 2.2) (Shinton *et al.*, 1989; Grobbee *et al.*, 1996). On cessation of smoking, the risk is said to decline to normal in 5 years (WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989; Grobbee *et al.*, 1996). More rigorous analysis has, however, shown that a degree of increased risk can persist for up to two decades after stopping smoking (Parker *et al.*, 1997).

Antiplatelet therapy (aspirin or non-steroidal anti-inflammatory drugs) was associated with 27% of all primary intracerebral haemorrhages, and alcohol binges in 7% in a community-based stroke study in Australia. Unfortunately, no control figures were given for comparison (Anderson *et al.*, 1994).

Unmodifiable risk factors include age – an important predictor of stroke. Cerebral infarction has an incidence of 1% p.a. in those aged 65–74 years. Moreover, it accounts for 88% of deaths in the over-65s, compared with 10/100,000 in the under-45s. Men experience 30% more strokes overall, but in the later decades of life the percentage of women having a stroke is higher than for men, forming a curve that lags

by about a decade (Thompson *et al.*, 1996).

Race is another key factor in stroke. The incidence is higher and the age of onset lower in blacks in the USA. Among Hispanic people, the rate up to 75 years is similar to that for the US black population, but it drops above this age to lower than that for whites; this fall may be artefactual as a result of low numbers. American Asians have less coronary heart disease and more strokes (Howard *et al.*, 1994). In the UK, Afro-Caribbeans have the highest incidence of stroke and Indian men the highest stoke mortality rate – 53% above the average (Balarajan, 1991). There is a particularly high rate of intracranial haemorrhage among the Japanese.

The mortality rate for black American men with stroke was 55% versus 27% in white American men in 1991. One-third of this excess mortality could be explained by socioeconomic status, and one-third by the usual risk factors for stroke, but one-third remains unexplained. Studies of stroke at a population base include those from Oxford (Bamford *et al.*, 1988), Framington (Wolf *et al.*, 1978) and Rochester (Kurtzke, 1982). Despite their strengths, it is of interest that they failed to demonstrate the well-known racial differences in stroke frequency and severity, which are worse and more frequent in younger black and older white people (Howard *et al.*, 1994). This reflects their largely white population base and affects our ability to extrapolate the figures to ethnically diverse urban populations.

Factors that have been studied in stroke with inconsistent results in different studies have included obesity, platelet hypercoaguability, alcohol (both acute binges and chronic alcoholism), blood lipids, systemic infection and genetics (WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989) (Table 16 - see page 66).

Studies report that 24–34% of those who experience stroke die within 4 weeks (Wolfe *et al.*, 1993; Du *et al.*, 1997). There is some evidence of a decline in mortality rate, with the more recent estimate of 16–23% dying in the first 3 months (Lyden, 1997). In the Oxford Community Stroke Project, the mortality rate 1 year after infarction was 23% and 62% after primary intracerebral haemorrhage (Bamford *et al.*, 1990). The type of primary intracerebral haemorrhage affects mortality; the 28-day case fatality rate for lobar and deep haemorrhages was around 20% of all cases, cerebellar haemorrhages had a higher rate at 30%, and massive cortical haemorrhages at 54%;

brain-stem haemorrhages were uniformly fatal (Anderson *et al.*, 1994).

Stroke is a very important cause of neurological disability. Only 25% of patients recover fully (Lyden, 1997). Harris (1971) estimated that patients with stroke accounted for 24% of all the severe disability in the community (Harris, 1971). In Copenhagen, in 1976, it was reported that 60% of those in the community who had experienced stroke had residual neurological signs (Sorensen *et al.*, 1982). According to the Bristol Stroke Study, 40–45% of survivors of stroke are disabled at 3 months and 35% at 1 year (cited in Langton Hewer, 1993). This was confirmed in Australia where 43% (CL = 37–49%) of those surviving were handicapped at 1 year (Anderson *et al.*, 1995). It is further estimated that 75% of those disabled by stroke are aged over 65 years and many also have other illnesses (McGeddes *et al.*, 1996).

The community-based study in Yorkshire, which surveyed 18,827 people (around 1 in 10 of the population) aged over 55 years by postal piloted questionnaire, found 47 (CL = 43–52)/1,000 aged over 55 years had had a stroke (Table 15)

Table 15. Deficits after stroke (McGeddes *et al.*, 1996)

	Deficits (L/R %) among stroke survivors	
Deficit	**At time of stroke**	**On prevalence day**
Full recovery	23	
Speech difficulties	51	33
Difficulties in thinking	47	27
Left/right leg problems	39 / 38	33 / 27
Left/right arm difficulties	34 / 41	25 / 24
Left/right visual disturbance	27 / 17	15 / 11
Swallowing difficulties	18	13

Among those with residual problems, over half needed help with at least one of the 10 aspects of daily living in the questionnaire (five about mobility, the others about self-care). Residual impairments showed no age-related difference, although the frequency of previous stroke increased markedly with age as did the reported dependency

(McGeddes *et al.*, 1996).

Table 16. Risk factors for stroke

Factor	Relative risk	Attributable risk
Inherited biological traits		
Male	1.3	
Age (55-64 vs 75+)	5	
Family history	2.3	
SAH	7	
Social Characteristics		
SEC I	1	
SEC V	1.6	
Ethnic group black		
Male	1.1	
Female	1.4	
Physiological characteristics		
Hypertension	7	0.46-0.75
Cardiac disease	3	0.11
LVH	4.4	
AF	3.7	0.015 (age 50-59) 0.24 (age 80-89)
Previous TIA	5-13	0.1
Diabetes mellitus		
Male	4.1	0.18
Female	5.8	0.22
Epilepsy	4	
Snoring	3	
Infection	9	
Homocysteinuria	10	
Sickle-cell disease	10	
Fibrinogen >3.6 g/l	1.8	
Behavioural Traits		
Obesity	1.8	
Increased waist:hip ratio	1.5	
Physical activity	2.5	
Total cholesterol >5.7 mmol/l	2.9	
Acute alcohol intoxication	5	
Smoking	1.5	0.37
Potassium		
Male	2.6	
Female	4.6	
Hormone replacement therapy	0.53	

(Adapted from Rudd *et al.*, 1997). SEC, socioeconomic class.
LVH, left ventricular hypertrophy; AF, atrial fibrillation; TIA, transient ischaemic attack

Interpretation

Given the geographical, racial and socioeconomic factors involved in stroke, it can be difficult to extrapolate the epidemiological findings from one location to another. Care must be taken in the consideration of the subgroups of stroke, so that important

findings are not obscured by lumping together the diverse conditions that have an end-result of stroke, because even in stroke subtypes (e.g. primary intracerebral haemorrhage) there is statistically significant heterogeneity (Anderson *et al.*, 1994).

Conclusion

There is some evidence for alteration in stroke occurrence and mortality, but this is confounded by social aspects of studies and lack of uniformity in study design (Malmgren *et al.*, 1987). The impact of intervention in modifying important risk factors and the incidence rate of stroke has not been reported at a community level, although some studies are under way (Grobbee *et al.*, 1996). Attention should be turned to the epidemiological aspects of homogeneous subgroups of all types of stroke. The effect of stroke on the prevalence of neurological disability is relatively poorly studied. The possibility of limiting disability by intervention requires further work.

1.3.19 Subarachnoid haemorrhage (SAH)

Definitions used

SAH is a bleed into the subarachnoid space. The underlying pathology may be an aneurysm (in 80%), an arteriovenous malformation or a bleeding diathesis (each accounted for 4% in Rochester, USA) (Phillips *et al.*, 1980). In addition, trauma may be responsible, or no underlying cause may be found. It is diagnosed in the presence of "an atraumautic lumbar puncture yielding bloody cerebro-spinal fluid in the clinical setting of an acute, devastating neurological illness lacking focal signs at onset usually accompanied by headache and meningism" (Phillips *et al.*, 1980).

Problems

Subarachnoid haemorrhage does not follow the pattern of other stroke illnesses; indeed stroke is not always a sequel (WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1989). It may cause stroke and is sometimes included in stroke studies, but it is far less frequent than ischaemic stroke, so important factors may be overlooked in SAH when these pathologies are lumped together. Not infrequently, it is abruptly lethal and, particularly in elderly people, sudden death may be ascribed to more common causes when a postmortem examination is not done. If studies are not community based, early mortality of the most severely affected individuals will improve the

measured outcome.

SAH can be difficult to differentiate from primary intracerebral haemorrhage with subarachnoid extension, which has not figured in any discussion of the problems in the epidemiology of SAH. Some SAHs are not caused by any identifiable cause or anatomical lesion; some studies ignore this and group them under "presumed aneurysm".

Epidemiology

SAH has an incidence rate of 5% of all strokes or 8–15/100,000 p.a. (Gudmundsson, 1973; Hansen *et al.*, 1977; Phillips *et al.*, 1980; Bamford *et al.*, 1990). The prevalence in the community of those who had experienced a previous SAH was 45/100,00 in Rochester, USA in 1975 (Phillips *et al.*, 1980). It is associated with intracranial aneurysms, which have a prevalence rate of 1–8% in the population. Unruptured aneurysms at postmortem examination are associated with age and clinical presentation rises with each decade (McCormick *et al.*, 1965; Phillips *et al.*, 1980). Women are more frequently affected than men (3:2, $p < 0.01$ (Phillips *et al.*, 1980; Hawkes *et al.*, 1997)), and have more unruptured aneurysms in postmortem series (McCormick *et al.*, 1965). Hypertension, atherosclerosis and smoking (relative risk or RR = 2.9; CL = 2.5, 3.5) are also correlated (Shinton *et al.*, 1989). The effect of hypertension does not appear to be causal because the rate of SAH has not declined as would be expected with the increase in treatment of hypertension over the last few decades (Phillips *et al.*, 1980). SAH occurs in first-degree relatives of affected individuals at three to seven times the background rate (Bromberg *et al.*, 1995).

Half of those experiencing an SAH die (Lyden, 1997). More women than men aged over 40 years die from their bleed (Acheson *et al.*, 1980).

One of the serious early sequels is a second bleed from the aneurysm. Rebleeding, which is an end-point in some studies, is associated with a poor prognosis. The rebleed rate in Rochester, USA was calculated to be 2% per day for the first 10 days (i.e. 20% during these 10 days), and then 1.5% p.a. for 10 years. None of the 10 patients in the Rochester study who had had negative angiograms rebled over an average follow-up of 11 years (Phillips *et al.*, 1980).

A wide range of outcomes is reported after SAH. Between 24% (Bamford *et al.*, 1990) and 50% (Lyden, 1997) of those who survive are severely disabled. In another paper, 75% of survivors were neurologically normal or capable of resuming work (Phillips *et al.*, 1980).

Interpretation

One major problem with the Rochester study is that it does not consider non-aneurysmal bleeds separately from all SAHs. In fact, 11% had angiography, postmortem examination or both without evidence of a structural lesion (Phillips *et al.*, 1980). Long-term outcome and response to nimlodipine differ in this group.

No studies seem to have examined the different short-term and long-term outcomes: rebleed, death from SAH or other causes, subsequent neurological and neuropsychiatric outcomes.

Conclusion

Studies of SAH must be rigorously designed because any loss of cases early in the disorder is usually the result of severe fatal bleeds. The long-term outcomes for disability after SAH need to be assessed.

1.3.20 Syringomyelia

Definitions used

Syringomyelia is a condition in which a pathological longitudinal cyst, a syrinx, develops within the parenchymal grey matter of the spinal cord; the expansion of such a cyst causes mechanical disruption of spinal cord tracts and subsequent neurological deficit. More infrequently, similar lesions are found in the brain stem and are referred to as syringobulbia (Sarnat, 1989).

Problems

This is a rare condition which is notoriously difficult to diagnose.

Epidemiology

Two studies have looked at the epidemiology of this condition in the north of England.

In Carlisle the prevalence was found to be 0.09/1,000 (Brewis *et al.*, 1966). A more recent study in Newcastle upon Tyne found an incidence (retrospective) of 0.4/100,000 p.a. and a prevalence of 0.06/1,000. The sex ratio is equal and the average age of onset is the early 30s, but any age may be affected. Syringomyelia may be associated with the Chiari malformation, but it also occurs together with basal arachnoiditis and after trauma. On occasions, a non-communicating form may be found with a posterior fossa tumour. The occurrence of syringomyelia in families has been described in the literature (Foster, 1980).

Interpretation and conclusion

There is inadequate information on this condition, with only two studies. One predates MRI scanning, a key investigation for this disorder, and the other is retrospective.

1.3.21 Trigeminal neuralgia

Definitions

Idiopathic trigeminal neuralgia is defined as "a painful unilateral affliction of the face, characterised by brief electric shock-like (lacinating) pains". The pain must last less than 2 minutes, and have four of the following characteristics: distribution in one or more divisions of the trigeminal nerve; a quality of pain described as intense, sharp, superficial, stabbing or burning; trigger areas on the face or in the mouth; and freedom from symptoms between attacks. The pain must be in the absence of neurological deficit, and other causes of facial pain, including multiple sclerosis and brain-stem infarction, must be eliminated by the history, examination or investigation (Headache Classification Committee of the International Headache Society, 1988).

Problems

Facial pain is a relatively frequent complaint compared with the frequency of trigeminal neuralgia, and rigorous adherence to the criteria for diagnosis is important. However, the diagnosis is based on the history alone and hence the subjectivity of the patient and the doctor may easily confound case findings.

There are no community-based studies of trigeminal neuralgia.

1.3.22 The provision of neurosurgery

Although the provision of neurosurgery is not a "neurological disorder", we decided to

examine the incidence of neurosurgical interventions because this service issue is topical in the North Thames Health Authority and the Linkage study provided an ideal opportunity.

Definitions used

Within different studies, this may be examined in different ways, e.g. counting neurosurgical inpatients, the number of operations or the number of different patients operated on (to avoid recounting the same patient in staged procedures).

Problems

Description of neurosurgical practice at any point in time measures only current practice. The number of operations done for neurological conditions depends not only on the incidence of conditions amenable to surgery in the community, but also on such issues as service provision and sociological factors, as well as "need". Factors influencing the number of neurosurgical operations include the number of neurosurgeons, operating room availability, the speed with which they operate, their beliefs about the desirability of operative intervention for different conditions, the patients' willingness to be operated on, and how the surgeon is paid. In certain countries in Europe, for example, and in free market health-care systems, surgeons are paid a fee per item of service, whereas in the UK they are paid to provide surgical care for a given population. The rate of surgical intervention is highly dependent on the number of surgeons (Armstrong, 1983).

Epidemiology

In the USA, the number of neurosurgeons is 1/100,000 population, a much higher figure than in the UK. In Olmstead County during the period 1970–74, record linkage identified all patients who had had a neurosurgical intervention. This area has a population of just under 90,000 and there are seven staff neurosurgeons and 21 neurosurgical residents. They serve an area larger than Olmstead County, but the actual population served is omitted from the paper. They reported the following annual operation rates per 100,000: seven for brain tumour, four for intracranial aneurysm, 42 for lumbar disc removal, six for cervical disc removal, and one for evacuation of intracranial haematoma (Glista *et al.*, 1977).

Interpretation

It is important to recognise that the measurement of neurosurgical intervention is not a straightforward reflection of need. Such a belief led to health inequalities in the UK after the establishment of the NHS; because funding followed previous patterns, as noted since the mid-nineteenth century, facilities are over-represented in more affluent areas (Hacking, 1990).

Conclusion

This complex area is poorly described because the extant figures fail to discuss the sociological confounders. It is, however, an important area because the training of specialists and provision of infrastructure in which they work need a more rational basis.

1.3.23 Conclusion

Individual neurological conditions have been reviewed above. Although there is the basic descriptive epidemiology of some conditions, such as epilepsy and stroke, there are still questions (e.g. about long-term prognosis) even in these well-studied areas. In some areas of neuroepidemiology, the basic descriptive data are lacking, and it is in this context that the current study was felt to be necessary.

1.4 Febrile convulsions

Generally, febrile convulsions are considered to be a common and benign condition. However, there has been debate about their prognosis with regard to the development of subsequent epilepsy and neurological dysfunction.

1.4.1 Definitions and general discussion

A febrile convulsion, synonymous with febrile seizure, is defined as the occurrence of a seizure in a febrile child aged between 3 months and 6 years in the absence of a CNS infection or previous medical history of unprovoked seizures (National Institutes of Health Consensus Statement, 1980). Most frequently, they are generalised, single and brief. Although these were often thought to presage epilepsy and neurological sequelae (Gowers, 1881, pages 1–22), a more optimistic outlook was suggested by population-based studies. One concern is that, despite the apparently low risk of epilepsy after an FC, there are high numbers of patients attending epilepsy clinics who have experienced them.

Different studies have identified a range of features, which are said to affect their occurrence, recurrence and outcome for epilepsy. These include maternal and perinatal characteristics as well as those of the febrile illness itself and a given child's predisposition (Annegers *et al.*, 1979b; Sofijanov *et al.*, 1983; Verity *et al.*, 1985a; Annegers *et al.*, 1987; Wolf *et al.*, 1989; Berg *et al.*, 1990; Tsuboi *et al.*, 1991; Verity *et al.*, 1991; Berg *et al.*, 1992; Verity *et al.*, 1993). However, the extent to which these additional factors contribute to the increased risk of epilepsy and neurological sequelae after an FC is not known. The cumulative risk for epilepsy is related to the length and completeness of follow-up, which is often insufficient to throw light on their role in adult onset-epilepsy (Sander, 1993). Hence, the study of the long-term follow-up of prospectively defined, community-based cohorts with high retention rates is important to understand their natural history.

1.4.2 Epidemiology of FCs

Febrile convulsions occur in 2–4% of children between the ages of 18 months and 6 years. Pooled population-based studies have found that the mean age of first FC is 18 months with a range of 2–135 months (Hauser *et al.*, 1975; Nelson *et al.*, 1976; Ross *et al.*, 1980; Verity *et al.*, 1985a, 1985b). The incidence rate for children aged from 0

to 4 years was 62/1,000 per year and, for children between 5 and 9 years, 0.7/1,000 per year (Stanhope *et al.*, 1972). In the USA, the prevalence by the age of 7 years was 34.8/1,000 in whites and 42.4/1,000 in blacks (Nelson *et al.*, 1978a). In around 33% of children, FCs recurred at least once (range 29–41%) (Berg *et al.*, 1990). If data from population- and clinic-based studies are pooled separately, the recurrence rate for population studies was 32% (range 30–33%) (Nelson *et al.*, 1978a; Annegers *et al.*, 1987) and 36% (range 35–37%) in clinic-based studies (Knudsen, 1985a; Offringa *et al.*, 1992, 1994). A further 4–17% (pooled population studies 7%, pooled clinic-based studies 16%) went on to have two and 9% to have three or more recurrences; 1–11% of those who had a subsequent FC after a simple first FC went on to have complex features. The only clinic-based study that examined this outcome found 7%, and pooled community-based studies found 5% (Nelson *et al.*, 1978a; Offringa *et al.*, 1994). Twenty per cent of first FCs in population studies were complex – the same as in the clinic-based studies: 3–4% are focal or followed by Todd's paresis, 12–13% were repeated within 24 h, and 6–7% were prolonged (defined as (15 min). Thus, it appears that there is a bias in clinic-based studies, although this appears to be seen in seizure numbers and not in the features of the seizures themselves (Verity *et al.*, 1985a; Offringa *et al.*, 1994).

1.4.3 Outcome measures for the prognosis of FCs

The prognosis of FCs has been examined as the risk for recurrent FC, and long term for unprovoked seizures, epilepsy and/or neurodevelopmental delay. Recurrent FCs as an outcome measure are useful in as far as they describe the natural history of the condition, but their utility is limited because the concern is whether FCs cause any sequelae of importance. The difficulty in defining the risk of sequelae of FCs, as evinced by the volume of literature on the subject, implies that if FCs do cause disability it is unusual, subtle or late.

1.4.4 Risk factors for ever having FCs

In most studies, there are more boys, who accounted for 53–58% of cases (Nelson *et al.*, 1978a; Knudsen, 1985a; Annegers *et al.*, 1987; Tsuboi *et al.*, 1991; Offringa *et al.*, 1992; Berg *et al.*, 1996b). Various risk factors for ever having a FC have been reported (see Table 18 and 17).

Table 17. The absolute risk of FCs with respect to risk factors (from Bethune *et al.*, 1993)

Risk factors	Absolute risk (%)
No risk factor	2.2
Daycare	6.6
Second-degree relative had had FC	7.7
Child was thought to be "slow"	10.3
Late neonatal discharge	11.6
One first-degree relative had had FC	9.6
Two first-degree relatives had had FC	32.5
Any two factors	28 (range 20-73).

Table 18. Risk factors and their relation to FC

Risk factor	Effect reported	Study
Temperature	+	Friderichsen *et al.*, 1954; Rantala *et al.*, 1990 & 1995; Pruksananonda *et al.*, 1992; Hall *et al.*, 1994; Barone *et al.*, 1995; Berg *et al.*, 1995
	No effect	Barone *et al.*, 1995
Rate of rise of temperature	No effect	Berg, 1993
Family history of FC	+	Bethune *et al.*, 1993; Berg *et al.*, 1995
Family history of unprovoked seizures	+	Offringa *et al.*, 1994
Exanthem subitum	+	Rantala *et al.*, 1995
Haemoglobin, white blood cell count, electrolytes, C-reactive protein, lymphocyte count and activity, immunoglobulins, tumour necrosis factor and paracetamol ingestion	No effect	Rantala *et al.*, 1995
Reduced immunoglobulin class A	+	Lewis *et al.*, 1980; Eeg-Olofsson *et al.*, 1982; Isaacs *et al.*, 1984
Reduced zinc in blood & CSF	+	Burhanoglu *et al.*, 1996
Increased interleukin-1	+	Burhanoglu *et al.*, 1996
Copper, magnesium, protein levels	No effect	Burhanoglu *et al.*, 1996
Iron deficiency anaemia	+	Pisacane *et al.*, 1996
Maternal smoking in pregnancy	+	Cassano *et al.*, 1990; Berg *et al.*, 1995
Maternal drinking in pregnancy	+ Cassano *et al.*, 1990	No effect: Berg *et al.*, 1995
Complicated labour/ peripartum	+ Wolf *et al.*, 1989	No effect: Berg *et al.*, 1995
Twin births	No effect	Morimoto *et al.*, 1993
Breech delivery	+	Verity *et al.*, 1985b)
Late neonatal discharge	+	Bethune *et al.*, 1993
Day-care attendance	+: Bethune *et al.*, 1993	No effect: Berg *et al.*, 1995

1.4.5 Family history and genetics

Genetics has an important role in the occurrence and prognosis of FCs (Berkovic *et al.*, 1998). All studies that have examined this reported an increased rate of seizure disorders in the families of children with FCs.

Seventy-two per cent of children with FCs had no family history of any seizure; 28% had a family history of either FCs or unprovoked seizure (s); 18–24% had had FCs, 4–10% unprovoked seizure(s) and 4–5% both in the family (Offringa *et al.*, 1994). There was a 85.7% concordance rate for FCs in monozygotic twins compared with 16.7% in dizygotic twins (Sunami *et al.*, 1988). A correlation was shown between the proportion of affected relatives and the risk of recurrence. If no family member had had FCs, then risk of recurrence was 27%; if 0–0.5 family members had, it was 40%, and 83% if 0.5 or more (van Esch *et al.*, 1994).Other studies have also shown an association between a family history of FCs and recurrence, although the details are controversial (Nelson *et al.*, 1978a; Knudsen, 1985a; Verity *et al.*, 1985b; Berg *et al.*, 1990, 1992; Offringa *et al.*, 1992; Berg *et al.*, 1995, 1996b). A meta-analysis of factors augmenting recurrence rate showed that a first-degree family history of either FC or epilepsy increased the recurrence rate from 37.4% to 55.8% (Offringa *et al.*, 1994). It has been reported that the family history of multiple FCs often predicts multiple FCs at initial presentation.

The mode of inheritance may be autosomal dominant, recessive or polygenic. Most studies support the view that there are at least two forms of inheritance. A population-based complex segregation analysis starting with the incident FC proband suggested that single FCs – the majority – were probably polygenic with a 68±7% heritable component. In contrast, in a minority of families, there is an autosomal dominant pattern. Linkage analyses have so far reported four putative loci for autosomal dominant FCs (Rich *et al.*, 1987).

The effect of family history on long-term outcome measures has produced discrepant reports (Nelson *et al.*, 1978a). It has recently been postulated that there are several epilepsy syndromes that include affected cases with pure FCs (Berkovic *et al.*, 1998).

1.4.6 Neurodevelopmental delay and febrile convulsions

When children with neurodevelopmental delay have been included in FC studies, delay

was the strongest predictor of FC occurrence, recurrence and subsequent development of epilepsy (Nelson *et al.*, 1978a; Annegers *et al.*, 1979b; Wolf *et al.*, 1989; Berg *et al.*, 1996b). The evidence for an association with FC recurrence was weakest and was reported as either a small effect (Berg *et al.*, 1990) or not significant (Berg *et al.*, 1992). One hospital-based first seizure cohort analysed both the group as a whole and subgroups of children with or without neurodevelopmental abnormality. Multivariate techniques for the group as a whole identified neurodevelopmental abnormality (before the first FC) as a strong independent predictor of unprovoked seizures; they formed a group that seemed to be different because they were far less likely than the remainder of the cohort to have a family history of FCs or a young age at first FC. Moreover, when multivariate analysis was performed on the groups separately, although they shared the number of FCs as an independent predictor of unprovoked seizures, in the neurologically normal group complex features were only marginally significant (at $p = 0.09$) and duration of fever was not predictive; in the abnormal group, these two features were significant independent predictors of unprovoked seizures.

Occurrence of afebrile seizures after FCs increases the risk of developing neurological deficit independently of prior neurodevelopmental status (Nelson *et al.*, 1978a).

1.4.7 Age of onset

Although many paediatric textbooks state that the age of the first FC is an important factor in recurrence of FCs and unprovoked seizures, there is little evidence for this assertion. Studies of the age of onset of FCs have found this to be the strongest and most robust predictor of recurrence (Nelson *et al.*, 1978a; Verity *et al.*, 1985a; Knudsen, 1988; Wolf *et al.*, 1989; Berg *et al.*, 1990, 1992; Rantala *et al.*, 1994). For example, pooled estimates for first FC at less than 15 months showed recurrence rates of 48%, as opposed to 39.2% if less than 18 months and 22.5% in those children who presented at an older age. Studies of the long-term outcome for seizure disorders have shown variable results; one univariate analysis suggested that the outcome is poorer in children whose FC started early (Annegers *et al.*, 1979b); others fail to show any correlation (Nelson *et al.*, 1978a; Berg *et al.*, 1996b).

1.4.8 Types of infection associated with FC

The type of triggering infection has been proposed as a factor in both the initiation of

and continuing propensity for FCs. Most children presenting with FCs have good evidence for a viral illness, with far fewer having evidence of bacterial illness (Lewis *et al.*, 1979). Recently, human herpes virus-6 (HHV6, exantham subitum or roseola) has been discussed the most, but previous candidates have included rotavirus and cytomegalovirus (Rantala *et al.*, 1990; Pang *et al.*, 1996). Other infections purported to be associated with FC are toxocariasis (Arpino *et al.*, 1990) and toxoplasmosis (Critchley *et al.*, 1982).

1.4.9 The number of FCs experienced

It has been said that the number of FCs are an important risk factor for subsequent epilepsy, although not all studies have shown this (Nelson *et al.*, 1978a; Wolf *et al.*, 1989). Most studies have examined a single versus multiple FCs by univariate analysis (usually chi-squared analysis) (Stanhope *et al.*, 1972). A recent study has shown that, in all children with a first FC, and also in children with no prior neurodevelopmental delay or deficit, the number of FCs experienced was an independent predictor of unprovoked seizures on multivariate analysis. This was not the case for children with neurodevelopmental deficit before the first FC. When the group was stratified for family history of FCs, young age and low temperature at first FC – factors previously suggested as predicting FC recurrence – it was seen that, in patients at high risk of recurrence, the number of FCs experienced did not alter the risk of unprovoked seizures. However, in those at low risk of recurrence there was an increased risk of unprovoked seizures associated with recurrence (Berg *et al.*, 1996b).

1.4.10 Treatment and its effects on prognosis

There has been a great deal of controversy about the role of treatment in FCs. This resolves into a number of questions:

1. Are FCs in themselves harmful in terms of the event or sequelae?

2. If some are associated with poor neurodevelopmental outcome, is this the result of the FC, or a brain anomaly that predisposes to both the FC and the poor outcome?

3. Does prevention of FCs prevent poor outcomes?

Some studies lack an appropriate and clearly framed question. A number of studies

have examined the reduction of FCs with antiepileptic drugs; this seems to be a spurious outcome measure because FCs themselves do not necessarily cause harm. The pertinent outcome measure is subsequent epilepsy or neurodevelopmental abnormality. It has been demonstrated that continuous phenobarbital, sodium valproate and intermittent diazepam with fever reduced the rate of recurrent FCs – both simple and complex. Despite this, there was no improvement in the long-term prognosis for epilepsy or neurodevelopmental deficit in these children (Knudsen, 1985a, 1985b; Wolf *et al.*, 1989; Farwell *et al.*, 1990; Knudsen, 1991; Offringa *et al.*, 1991; Farwell *et al.*, 1992; Rosman *et al.*, 1993). Furthermore, the reduction of FC recurrence with both valproate and phenobarbital was not found in all studies (Newton, 1988). There was evidence of harm from prolonged prophylactic treatment, with adverse effects on attention, behaviour and learning (Wolf *et al.*, 1978; Farwell *et al.*, 1990, 1992) when phenobarbital (Newton, 1988) or sodium valproate was used (Newton, 1988; Shafer *et al.*, 1988), and less harm with diazepam (Rosman *et al.*, 1993). Some authorities have advised the use of antiepileptic drugs for FCs only when there are "frequent recurrences" (Joint Working Group of the Royal College of Physicians and the British Paediatric Association, 1991; Valman, 1993), and others only if FCs have been prolonged over 20 minutes or occur before the age of 9 months, or after a third FC (Rylance, 1990). Others have recommended them for complex features or in children with neurological deficit. This causes confusion among doctors, leading to variability in treatment and a tendency to over-treat (Hirtz *et al.*, 1986).

Two community-based studies mention treatment rates of 0.5% in Sweden (Forsgren *et al.*, 1997) and 13.7% in the UK (Verity *et al.*, 1991). There is little evidence of benefit in using antiepileptic drug therapy in FCs and clear evidence of harm; it can be advocated only under rare circumstances.

1.4.11 Complex FCs

Complex FCs are defined as FCs with one or more of the following features: prolonged beyond 15 min, recurring within 24 h, or with focal features either at onset or post-ictally.

It is generally held that the presence of complex features in the first or subsequent FC is the most important feature for the prognosis of FC for subsequent unprovoked

seizures (Wolf *et al.*, 1989), epilepsy (Nelson *et al.*, 1978a; Annegers *et al.*, 1979b) or neurodevelopmental deficit (Wolf *et al.*, 1989). Among the Rochester cohort who have been followed up for a maximum of 25 years, albeit with a loss to follow-up of almost 41%, it was found that focal features increased the risk of unprovoked seizures to 8% at 25 years of age; increased risk was for partial onset and not generalised seizure disorders (Annegers *et al.*, 1987).

FCs prolonged beyond 10 and 15 min have been associated with increased rates of unprovoked seizures (Annegers *et al.*, 1979b); however, some studies do not find this increase or any rise in neurodevelopmental deficit (Wolf *et al.*, 1989). Febrile status epilepticus ((30 min in duration) has been associated with catastrophic neurological outcome; it is interesting to note that, despite the apparent gravity of the condition, some community-based studies have found relatively good outcomes (Nelson *et al.*, 1978a; Shorvon, 1994). The Rochester cohort found a 7% risk of seizures in those experiencing FCs lasting 10–29 min; 3% developed unprovoked seizures (Annegers *et al.*, 1987).

Repeated FCs within 24 h have been correlated with poor outcome, although not in all reports (Wolf *et al.*, 1989).

1.4.12 The long-term risk of epilepsy and neurodevelopmental deficit

The risk of epilepsy and neurodevelopmental delay or disability is the cardinal reason for interest in FCs. Studies that have examined the prognosis for epilepsy from first FC in prospectively designed, community-based studies are listed in Table 19.

Table 19. Prospective community-based studies of prognosis for epilepsy after a first FC

Study	cohort (n)	Follow-up (years)	Percent with epilepsy
Nelson *et al.*, 1976 and 1978a	1706	7	2.0
Forsgren *et al.*, 1997	92	8.3	3.3
Verity *et al.*, 1985b and 1991	398	10	3.4
Annegers *et al.*, 1979b	687	10	4.5
Annegers *et al.*, 1987	687	25	7

For an accurate estimate of epilepsy risk, complete and lengthy follow-up is necessary (Shorvon, 1984; Annegers *et al.*, 1987). Case definition in a study may greatly influence the findings (e.g. exclusion of children with prior neurodevelopmental delay) (Verity *et al.*, 1985a, 1991). Until very recently, studies of FCs used rate ratios (Annegers *et al.*, 1990) or chi-squared statistical methods (Morris *et al.*, 1988), and ascribed differing levels of risk of epilepsy and other neurological sequelae to such risk factors as the presence of complex FCs, numbers of FCs, and a family history of FCs or epilepsy. A more appropriate method of measuring the strength of an association between a factor and a sequel is the odds ratios (ORs) in multivariate analysis; these have been used in only one relatively small cohort and led to non-significant findings as a result of wide confidence intervals (Forsgren *et al.*, 1997). This is in keeping with the short-term report of a prospective study that showed an increased rate of unprovoked seizures at 2 years in those who had experienced more FCs; the OR (95%CL) for unprovoked seizure by the age of 2 years in children who had experienced a FC was 4.2 (1.9, 6.6) compared with 20.4 (4.4, 36.4) in children who had had four FCs (Berg *et al.*, 1996b). Each study had differing lengths of follow-up and some excluded children with prior neurological disturbance. A multivariate analysis showed that, through use of five markers for risk (family history of FC or any seizure, temperature < 40 (C at first FC, multiple initial FC, age < 30 months), children could be divided according to risk of further FCs. The definition of neurodevelopmental sequelae is not straightforward. FCs occur in young children in whom development delay and neurological diagnosis are notoriously difficult. In one study, 413 children who had had FCs, but no subsequent unprovoked seizures, were tested psychologically and neurologically at 7 years of age. The control group was made up of siblings who had not experienced FCs. No differences were evident between the groups. This undermines the argument that subtle intellectual deficits are missed in children who have had FCs (Ellenberg *et al.*, 1978; Hauser, 1982).

1.4.13 Conclusions

The further study of the long-term outcome after FCs remains relevant, despite the extensive literature on the subject because the relationship between FCs and

subsequent epilepsy is still unclear.

There is an increased risk of neurodevelopmental deficit and epilepsy after FCs, but the factors responsible for this are not clear. It is still possible that reverse causality may be responsible for the observed associations.

FCs are heterogeneous, both clinically and genetically, and this requires further elaboration. Those children who have neurodevelopmental delay or other abnormality appear to form a separate group in terms of prognosis for epilepsy and other factors that are said to be predictive. This would support the view that they should be classified separately.

1.5 The prognosis of epilepsy

"Prognosis" refers to the possible outcomes of a disease and the frequency at which they can be expected to occur. Prognostic factors may include demographic features, disease-specific indicators (e.g. seizure frequency, aetiology of epilepsy) or co-morbidity. Such factors do not necessarily cause the outcome, but they are associated strongly with the outcome measured. They are distinct from risk factors – which are associated with the initial development of the disorder (Laupacis *et al.*, 1992).

Ideas about the outcome for epilepsy have been altered radically in the past century by study of its epidemiology. The prognosis for epilepsy comprises a number of measurable end-points: the prediction of recurrence after a single unprovoked seizure, the chance of remission after the diagnosis of epilepsy and the risk of premature death.

1.5.1 Recurrence of seizures after a first seizure

The overall risk of recurrence after the first seizure is an important aspect of prognosis. This has been examined previously in the NGPSE (Hart *et al.*, 1990), but is discussed briefly because it is so relevant to long-term prognosis. It should be borne in mind that factors affecting recurrence will not necessarily be the same as those leading to chronic epilepsy. A prospective study of seizure recurrence after a first generalised seizure, and seizure remission in the context of a placebo-controlled trial of medication after a first seizure, showed that factors associated with recurrence were not the same as those for poor prognosis for remission (Musicco *et al.*, 1997).

1.5.1.1 The rate of recurrence

Estimates vary for the risk of recurrence after a single seizure – from 27% to 81% (Thomas, 1959; Costeff, 1965; Blom *et al.*, 1978; Cleland *et al.*, 1981; Hauser *et al.*, 1982; Goodridge *et al.*, 1983a; Camfield *et al.*, 1985a, 1985b; Elwes *et al.*, 1985; Annegers *et al.*, 1986; Hopkins *et al.*, 1988; Hart *et al.*, 1990; Shinnar *et al.*, 1990; van Donselaar *et al.*, 1991a; Stroink *et al.*, 1998). The different results may be explained by methodological variations between studies (Hart *et al.*, 1990; Berg *et al.*, 1991).

The earlier after the initial seizure that patients are enrolled into a study, the higher the reported rates of recurrence. Late enrolment, studies in which there is delay between first seizure and assessment, or retrospective design biases studies towards lower

recurrence rates (Thomas, 1959; Costeff, 1965; Saunders *et al.*, 1975; Cleland *et al.*, 1981; Camfield *et al.*, 1985a; Logan *et al.*, 1998; Stroink *et al.*, 1998), because most recurrences occur within the first few weeks (Hart *et al.*, 1990) and the risk of seizure recurrence falls with time (Camfield *et al.*, 1985b; Hopkins *et al.*, 1988; Hauser *et al.*, 1990; Berg *et al.*, 1991).

As many as one-third of patients do not present until they had had more than two seizures (Elwes *et al.*, 1988) and so would be excluded from some studies of seizure recurrence (Cleland *et al.*, 1981; van Donselaar *et al.*, 1991a). Patients with generalised tonic–clonic seizures are likely to present earlier than those who have partial seizures, which may also bias studies.

Another important consideration is the frame of the study and selection bias. Studies based in EEG, neurology or paediatric clinics are not based on the same population as community-based ones – clinic-based groups have more severe seizure disorders (Blom *et al.*, 1978; Hauser *et al.*, 1982; Elwes *et al.*, 1985; Beghi *et al.*, 1988; Hopkins *et al.*, 1988).

Retrospective data will inevitably give a bias towards more severe cases with recurrence. Two retrospective studies of recurrence after first seizure report very different rates: Annegers *et al.* (1986) reported rates of 36% by 1 year and 56% by 5 years, compared with 81% overall by Goodridge and Shorvon (Goodridge *et al.*, 1983a, 1983b).

The only prospectively designed, community-based study of seizure recurrence is the NGPSE, which gave an overall rate of seizure recurrence of 67% by 1 year and 78% by 3 years (Hart *et al.*, 1990).

Single seizures have a lower incidence rate than epilepsy, implying that most patients will have two or more seizures. The alternative explanation – that single seizures are a more infrequent and different entity from epilepsy – does not seem biologically plausible.

1.5.1.2 Seizure recurrence after diagnosis of epilepsy

One study of seizure recurrence has looked at recurrence after two unprovoked seizures (Hauser *et al.*, 1998). It attempted to avoid some of the above-mentioned

biases by only recruiting patients within 24 h of a first seizure, but excluded patients who at first presentation could be said to have seizures once a medical history was taken. They report the recurrence rate after first seizure as 33% (CL = 26, 40); among those who had a second seizure there was a 57% (CL = 45, 70) chance of having a third at 1 year and 73% (CL =59, 87) at 4 years. Although it is stated that no patients who had a second seizure were lost to follow-up, no figure is given for loss to follow-up between first and second seizure, which makes interpretation difficult. In addition, its population is drawn from neurology patients and EEG referrals. There is an excess of male subjects who account for 70% of the group.

1.5.1.3 Factors affecting rate of recurrence

Several prognostic factors for recurrence have been identified, but they are not without controversy.

Age of onset below 10 years (Beghi *et al.*, 1988) or 16 years (Costeff, 1965; Blom *et al.*, 1978; Hirtz *et al.*, 1984; Hart *et al.*, 1990), or over 65 years (Hopkins *et al.*, 1988; Hart *et al.*, 1990; First Seizure Trial Group, 1993b; Musicco *et al.*, 1997) has been correlated with recurrence. This has not been replicated in other similar studies (Hauser *et al.*, 1982; Annegers *et al.*, 1986; Shinnar *et al.*, 1990). Sex does not correlate with prognosis for early recurrence (Hauser *et al.*, 1982; Annegers *et al.*, 1986).

Partial seizures are associated with poorer outcome for recurrence (Blom *et al.*, 1978; Goodridge *et al.*, 1983a; Hirtz *et al.*, 1984; Camfield *et al.*, 1985b; Annegers *et al.*, 1986; Hart *et al.*, 1990; Shinnar *et al.*, 1990), although not all studies examining seizure type have found this correlation (Hauser *et al.*, 1982). Nocturnal seizures (Hopkins *et al.*, 1988) and mixed seizure types (Beghi *et al.*, 1988) have also shown higher recurrence rates.

Aetiology also shows a correlation with prognosis; congenital neurological deficits predict higher rates of recurrence (Annegers *et al.*, 1986; Hart *et al.*, 1990). Seizures after stroke seem relatively benign; they are common, affecting 11.5% by 5 years, but half of these are single seizures from first cerebrovascular episode in a prospective community-based study (Burn *et al.*, 1997). Head injury may be associated with a higher rate of recurrence, but was reported in a study that had a low rate of recurrence

overall and it, together with other studies, fall within the range of expected seizure recurrence (Jennett *et al.*, 1960; Annegers *et al.*, 1980). Remote causes of epilepsy, which included conditions such as stroke or tumour, increased the rate of recurrence – in the Rochester study from 45% in idiopathic seizures to 77% (Blom *et al.*, 1978; Hauser *et al.*, 1982; Annegers *et al.*, 1986; Shinnar *et al.*, 1990; Berg *et al.*, 1991; Musicco *et al.*, 1997; Stroink *et al.*, 1998) – although other studies, which examined remote causes, either found that only tumours increased the recurrence rate (Hopkins *et al.*, 1988) or did not find an effect (Hart *et al.*, 1990). Abnormal neurological examination has been correlated to recurrence (Camfield *et al.*, 1985a; Annegers *et al.*, 1986).

Some underlying genetic syndromes entail a lifelong tendency to seizures, which may either respond to medication – as in juvenile myoclonic epilepsy (Timmings *et al.*, 1992) and autosomal dominant temporal lobe epilepsy (Berkovic *et al.*, 1996) – or not respond– as in nocturnal temporal lobe epilepsy (Bernasconi *et al.*, 1998); others have a very benign prognosis. Less specifically, a family history of seizure disorders increases the risk of recurrence (Hauser *et al.*, 1982).

The presence of an EEG abnormality is more controversial, but some studies have identified this as a risk factor for recurrence (Johnson *et al.*, 1972; Cleland *et al.*, 1981; Hauser *et al.*, 1982; Camfield *et al.*, 1985a; Annegers *et al.*, 1986; Shinnar *et al.*, 1990; Berg *et al.*, 1991; van Donselaar *et al.*, 1991b; First Seizure Trial Group 1993; Stroink *et al.*, 1998).

These factors reflect the heterogeneity underlying the diagnosis of "epilepsy" and imply that a differing case mix will influence reported recurrence rates.

1.5.1.4 Effect of medication on recurrence after a first seizure

In most epidemiological studies of epilepsy, the descriptive design does not influence the prescription of antiepileptic medication. This means that patients whose seizures are deemed to be more severe – in either seizure type or underlying aetiology – are more likely to be treated. This biases the results. Descriptive studies have found that the risk of seizure recurrence is not altered by medication (Hauser *et al.*, 1982; Hirtz *et al.*, 1984; Annegers *et al.*, 1986; Shinnar *et al.*, 1990), but studies have reported a

reduced chance of recurrence (Camfield *et al.*, 1985b; Hopkins *et al.*, 1988).

The only study that examines this appropriately, in the context of a placebo-controlled trial of antiepileptic drugs after a first seizure, found a threefold increased risk of seizure recurrence in the untreated group by 2 years (First Seizure Trial Group. 1993). There are some reservations about this study's design – it excluded patients with previous seizures and examined only generalised seizures.

1.5.2 The remission of epilepsy

Seizure freedom is the goal for the patient and the physician. Remission of epilepsy is the seizure-free period experienced by a patient who has had one or more seizures. It is usually defined as being of 1–5 years' duration. Terminal remission is when the remission continues to the end of follow-up. There are various factors that influence the likelihood of achieving and maintaining remission.

1.5.2.1 Methodological considerations

The interpretation of epidemiological studies requires an appreciation of potential pitfalls in study design.

1.5.2.1.1 Definition and classification of epilepsy

By convention, the diagnosis of epilepsy is made only after a second unprovoked seizure. Seizures can be the symptomatic expression of a wide range of conditions and, for this reason, the use of the term "the epilepsies" is more appropriate than "epilepsy" (Sander, 1993). Single, acute, symptomatic seizures and febrile convulsions are not considered to be epilepsy.

The study of the prognosis of epilepsy is confounded by the diversity of underlying diagnoses; it is in fact the prognosis of a diverse group of conditions of known aetiologies or cryptogenic origin. In addition to the differing risks for the underlying conditions, there are the risks of the seizures themselves.

1.5.2.1.2 The difficulty of diagnosis

The case definition of epilepsy is deceptively clear-cut: "two or more unprovoked epileptic seizures". A key difficulty is diagnosing the seizure. Seizures are brief, pleomorphic – albeit often stereotypical in an individual – and unpredictable. The diagnosis is based on the history of the episodes, with some support from

investigations. The witnessed account, even when it is available, may be difficult to interpret for many reasons, among which poor observation or capacity to describe the seizure and inaccuracy of second-hand accounts are common sources of error. In addition, there is variability in how clinicians interpret the information. This leads to diagnostic variation – for example, in some reports 20% of patients referred to specialist epilepsy clinics are diagnosed as not having epilepsy (Betts, 1983; Lesser, 1985). Interobserver reliability has been found to be as low as a kappa value of 0.58 in one study (van Donselaar *et al.*, 1991a). In the Rochester study, time from first seizure to diagnosis took over 6 months in 50% of patients and over 2 years in 30% (Hauser *et al.*, 1975). This lag time means that, when studies exclude patients without a definite diagnosis, considerable bias occurs; certain groups will be excluded more than others – elderly people, those with learning difficulties, those with infrequent or nocturnal seizures – as all these patients are less likely to be able to provide a clear account of the seizure. Most studies, except the NGPSE, do not address this important clinical issue (Blom *et al.*, 1978; Cleland *et al.*, 1981; Goodridge *et al.*, 1983a; Annegers *et al.*, 1986).

Adding to the difficulty of diagnosis are other paroxysmal conditions, the presentation of which may be confounded with epileptic seizures, such as syncope, vertigo, panic disorders, hyperventilation syndrome (Commission on Classification and Terminology of the ILAE, 1989). No investigation is definitive or highly reliable in the diagnosis of seizure disorders.

Seizures that occur during a metabolic disturbance or an acute illness are not considered as epilepsy because they are deemed to be caused by a pathological process, which, because of its transient nature, cannot be assumed to provoke further seizures; as a result, a continuing tendency to seizure activity will not occur. The distinction is, however, conventional and not the result of a clear-cut physiological demarcation.

The difficulty in diagnosis remains throughout the course of epilepsy; thus, non-epileptic seizures will inflate the figures for chronic epilepsy although it can be difficult to estimate how much they contribute to the 20–30% of patients who will suffer chronically (Shorvon, 1991).

Clearly, it is important that studies take the issue of diagnosis seriously, so that comparison of results may be made.

1.5.2.1.3 Difficulty in classification of epilepsy

A comprehensive syndromic classification was commissioned by the ILAE (Commission on Classification and Terminology of ILAE, 1989). It was drawn up with the intention of having a reliable clinical tool for the classification of epilepsy and to allow comparison between studies. However, it may be difficult to apply; one study that assessed its reliability found that this was only 50% (Feksi *et al.*, 1991).

In attempting to classify epilepsy, some syndromes are clear-cut, e.g. juvenile myoclonic epilepsy; however, despite extensive investigation and prolonged follow-up, many patients remain difficult to classify and, in addition, several aetiologies may underlie what is the "same" epileptic syndrome.

Moreover, the early remission of most epilepsies allows little time for observation and investigation of the active disorder. In most reliable studies, only half of the cases are classified. In children, this poses greater problems and one way of handling data is to group "disputable events" separately – when using such a demarcation it was found that these children had a 10% chance of seizure recurrence versus 54% overall (Stroink *et al.*, 1998).

1.5.2.1.4 Population characteristics

Only community-based studies provide the full breadth of the epilepsies because some patients may never be referred for specialist opinion and the choice of specialist is wide (The Research Committee of the Royal College of General Practitioners, 1960; Hart *et al.*, 1995). Clinic-based studies are influenced by referral patterns, patient characteristics and seizure severity; however, many studies are clinic based (Sato *et al.*, 1976; Lindsay *et al.*, 1979; Loiseau *et al.*, 1983a; Cavazzuti *et al.*, 1984; Camfield *et al.*, 1985b; Brorson *et al.*, 1987; Beghi *et al.*, 1988; Collaborative Group for the Study of Epilepsy, 1992; Tinuper *et al.*, 1996; Hadjipanayis *et al.*, 1997).

The community studied will also influence findings. In Rochester, USA the population is homogeneous, white, relatively affluent and of northern European descent (Hauser *et al.*, 1975; Glista *et al.*, 1977; Annegers *et al.*, 1979a).

1.5.2.1.5 Criteria for inclusion and exclusion

The criteria for inclusion and exclusion will affect outcome measures. The exclusion of patients who experience early recurrence seems likely to improve the overall prognosis. When single seizures are excluded, those patients with a lower tendency to recur are left out and remission rates are likely to be lower (Hauser *et al.*, 1975; Annegers *et al.*, 1979a; Ross *et al.*, 1980; Elwes *et al.*, 1988). Similarly, an atypical population with more severe seizures is selected if only patients taking AEDs are included (Collaborative Group for the Study of Epilepsy, 1992). Another bias that is difficult to interpret is added if only patients who have had an EEG are included (Shafer *et al.*, 1988). In one study, FCs were not excluded but lumped together with other seizure types (Thurston *et al.*, 1982). Some studies exclude patients with abnormal neurology before the seizure (Loiseau *et al.*, 1983a).

1.5.2.1.6 Temporal aspects

A turning point in the understanding of the natural history of seizure disorders came with the appreciation that patients should be followed from the same point in their illness – whether this is a first or second seizure, or first presentation. If this is not done, there is a tendency to find poor outcome because of the inclusion in the cohort of those with ongoing seizures and more severe epilepsy (Faxén, 1935; Shorvon, 1984; Sander, 1993). This underlies the poor prognosis of epilepsy reported in older studies (Gowers, 1881; Rodin, 1968).

Most patients, if they are going to remit, go into remission early in the course of their illness. For example, in the Rochester study the net probability of entering remission was 65% over 10 years but, if remission had not been achieved by 5 years, the chance of subsequent remission was only 35% (Annegers *et al.*, 1979a).

1.5.2.1.7 Definition of remission

Different definitions of remission lead to difficulty comparing studies. The time in remission varies from 1 to 5 years (Hauser *et al.*, 1975; Brorson *et al.*, 1987; Casetta *et al.*, 1997; Stroink *et al.*, 1998). Whether any seizure-free period is included as remission or only counted if it is terminal remission (Goodridge *et al.*, 1983a & b), and whether AED status is considered, are other sources of variability (Hauser *et al.*, 1975; Annegers *et al.*, 1979a).

Generally, AED status is not considered as part of the definition of remission, and many studies report both terminal and non-terminal remission rates.

1.5.2.1.8 Prospective design

Prospective studies yield better data because they can avoid bias by careful study design; information is available that may not have been recorded meticulously in normal clinical practice. This needs greater resources.

Length of follow-up is central to the prognosis of a chronic relapsing and remitting condition, and the further back a retrospective study delves the more bias must enter the study. Some of the Rochester data go back to 1935 (Annegers *et al.*, 1979a); this is the same year that Faxén wrote a critique of the definition of epilepsy, which seems so far removed from current concepts of seizure disorders (Faxén, 1935).

1.5.2.1.9 Length of follow-up

In a chronic disorder, the length of follow-up influences the remission rate. Studies of newly diagnosed patients followed for 1 or 2 years give high remission rates – of the order of 80% (Turnbull *et al.*, 1982; Beghi *et al.*, 1988; Stroink *et al.*, 1998). However, remission is only meaningful if the remission is lengthy and hence the follow-up must be prolonged. Prospectively designed studies are now reporting decades of follow-up data (Annegers *et al.*, 1979a; Kurtz *et al.*, 1998; Sillanpaa *et al.*, 1998).

1.5.2.1.10 Loss to follow-up

Loss to follow-up can damage the validity of a study because it cannot be assumed that those lost are identical or even similar to the rest of the group. Despite the statistical tenet that the non-responders do not resemble the responders, many groups have just ignored this problem (Casetta *et al.*, 1997).

An alternative way of handling those lost to follow-up in actuarial analysis is to assume that they have not remitted, which will decrease remission rates and give a pessimistic view of outcome.

1.5.2.1.11 Statistical analysis

Early in the course of their epilepsy, most patients will remit; fewer remit with the passage of time. For this reason, it is inappropriate to give the proportion of patients going into remission if the cohort is not being followed from the same point in the

illness.

Life-table analysis can handle only a single end-point but, in epilepsy, patients may go in and out of remission and may therefore need more sophisticated statistical analysis. If both cumulative and terminal remission are calculated, this can, to some extent, be accounted for. As only 12% of patients have this intermittent pattern, the bias may not be excessive (Goodridge *et al.*, 1983a).

In the statistical analysis of prognostic factors, the use of univariate analysis has confounded many studies. Unifactorial models are not appropriate for multifactorial disease. Coupled with the cut-off for statistical analysis of p (0.05, which means that one in twenty factors is found to be significant by chance alone, inevitably studies will not always agree.

A Cox proportional hazards method is multifactorial; the multivariable analysis enables the identification of dominant factors (which is not possible in single variate or Kaplan–Meier techniques). This is increasingly used to analyse the prognosis of epilepsy (Stroink *et al.*, 1998).

1.5.2.1.12 The effect of treatment on remission

The effect of treatment on epilepsy has been a confounder in many studies of the condition. When studying a condition, ideally one would want an unbiased set of factors acting on the whole cohort. If treatment is being used, as indeed it is in every modern descriptive study, this should be in a randomised fashion.

Interventional studies have demonstrated that most patients presenting with epilepsy entered long-term remission when treated (Shorvon *et al.*, 1978, 1982; Elwes *et al.*, 1984, 1985; Beghi *et al.*, 1988; Okuno *et al.*, 1989; Collaborative Group for the Study of Epilepsy, 1992; Mattson *et al.*, 1996). The studies that found a good prognosis for patients presenting with seizures were interpreted as causal – good prognosis was seen as a product of appropriate early intervention. It was argued by most authors at that time that treatment improved prognosis there is little evidence to uphold this view, and gathering evidence from interventional and epidemiological studies to refute it.

A recent study examining the effect of treating patients after their first or subsequent generalised tonic–clonic seizures has shown no difference in long-term (1 or 2 year)

remission rates (Musicco *et al.*, 1997).

Drug withdrawal is an important cause of seizure relapse (Medical Research Council Antiepileptic Drug Withdrawal Study Group. 1991).

1.5.2.2 Natural history

To study remission it is important to consider the natural history of the untreated condition. Epilepsy has had effective treatments since bromide salts were used in the 1850s, and so it has been difficult to study drug-naïve patients. The untreated patients in cohorts are unlikely to be similar to the treated patients and often have milder seizures (Keranen *et al.*, 1993).

1.5.2.2.1 Studies in developing countries

In conditions showing no remission and long survival, lifetime prevalence rates will approach prevalence rates, the difference being attributable to differential deaths caused by the condition or its complications. In the developed countries, the difference between these rates has been attributed to drug-induced remission. There is evidence that the incidence rates of epilepsy in the developing world are higher mainly as the result of acute bacterial infection, chronic viral and parasitic infection, poor neonatal outcome and accidents (Shorvon *et al.*, 1988; Sander, 1993). Prevalence rates should be higher in developing countries (allowing for related mortality) if the notion that failure to provide early treatment for epilepsy promoted chronicity and intractability was true. However, large studies of the epidemiology of epilepsy in these countries have reported rates that are very similar to those in the developed world (Juul-Jensen *et al.*, 1983; Tekle Haimanot *et al.*, 1990). There are exceptions to this, but these studies are in groups that have high rates of inherited neurodegenerative disorders, such as the Wapogoro of Tanzania and residents of Gran Bassau county, Liberia (Aall-Jilek, 1965; Jilek *et al.*, 1970; Goudsmit *et al.*, 1983; van der Waals *et al.*, 1983; Rwiza *et al.*, 1992).

In Ecuador, a population-based study found a cumulative incidence rate of 1.9% among a population of 75,000, the prevalence rate of active epilepsy being 0.7%, which implies a remission rate of at least 50% (Placencia *et al.*, 1992). Similar observations were made in a smaller study from Malawi (Watts, 1992). This supports

the idea that spontaneous remission may occur (Sander, 1993).

An additional argument against the development of intractability is that studies have shown good response rates for treatment initiated in unselected drug-naïve patients after many years of active epilepsy (Aall-Jilek, 1965; Jilek *et al.*, 1970; Watts, 1989, 1992; Pal *et al.*, 1998).

1.5.2.3 Overall remission rates from hospital-based studies

1.5.2.3.1 Retrospective studies

Despite the biases discussed above, there have been a large number of studies in recent decades that are clinic based and retrospective. The Japanese group have examined the outcome of seizures among 1,868 patients seen in 20 clinics. Follow-up was problematic because these patients constituted only 42% of those who had attended these clinics during the frame of the study. The remission rates for 3, 5 and 10 years were around 58% (Okuma *et al.*, 1981). In Aarhus, Denmark, a study of remission in 1,505 patients registered at diagnosis found that 47% of patients with primary generalised epilepsy were in remission compared with 28% of those with complex partial seizures; these were crude percentages without a long follow-up (Juul-Jensen, 1964).

1.5.2.3.2 Studies of newly diagnosed patients

Studies in clinic-based populations have reported the effect of treatment among newly diagnosed patients (Callaghan *et al.*, 1978; Shorvon *et al.*, 1978; Strandjord *et al.*, 1980; Shakir *et al.*, 1981; Turnbull *et al.*, 1982; Elwes *et al.*, 1984; Callaghan *et al.*, 1985; Mattson *et al.*, 1985; Collaborative Group for the Study of Epilepsy, 1992). Despite some differences in their case ascertainment, they discuss the outcome in terms of remission of seizures of 1, 2 or 5 years. The reported 1-year remission rates vary between 58% and 95%, most falling between 65% and 80% (Stroink *et al.*, 1998).

There is less unanimity over what features predict poorer outcomes. Partial seizures are thought to have a worse prognosis for seizure control than generalised seizures (whether from generalised epilepsy or in patients with secondarily generalised seizures only) (Mattson *et al.*, 1985). Multiple seizure types have also been linked with worse prognosis, as have associated neurological deficits and behavioural or psychiatric

disturbance (Beghi *et al.*, 1988; Collaborative Group for the Study of Epilepsy, 1992). A poorer outcome has been reported in those who had experienced a high-frequency tonic–clonic seizure before receiving any treatment (Elwes *et al.*, 1985; Collaborative Group for the Study of Epilepsy, 1992). In one study, there was a worse prognosis if there was a family history of epilepsy (Elwes *et al.*, 1985).

There are only clinic-based studies for prognosis of specific epilepsy syndromes. Benign partial epilepsy with centrotemporal spikes has a very good prognosis and practically all patients remit by puberty (Loiseau *et al.*, 1988; Bouma *et al.*, 1997). In contrast, typical absence epilepsy has a worse prognosis than was previously believed and two-thirds of patients remit (Loiseau *et al.*, 1983b; Bouma *et al.*, 1996; Stroink *et al.*, 1998).

1.5.2.4 Population-based studies of remission

Retrospective studies have also described the remission of seizures in patients diagnosed with epilepsy and started on antiepileptic medication at some point in the past.

In the UK, patients with chronic grand mal epilepsy were surveyed and 42% had no seizures during that year (The Research Committee of the Royal College of General Practitioners, 1960).

In the Rochester study, remission was defined as 5 years without seizures; at a year after diagnosis, 42% had entered into a period of remission and at 10 years 65% were in remission; at 15 years 76% were in a 5-year remission (Hauser *et al.*, 1975; Annegers *et al.*, 1979a).

The Tonbridge general practice study, in which remission was defined as a 2-year period without seizures, showed similarly that 73% of patients overall were in remission (Goodridge *et al.*, 1983b, 1983a).

In both Rochester and Tonbridge, most of the patients who entered into remission had done so by the end of the first 2 years. So, as time passed from diagnosis, the chance of treated active epilepsy remitting diminished.

1.5.2.5 Drug-withdrawal studies

As 70–80% of patients on AEDs become seizure free, it is common clinical practice to consider withdrawal once a patient has been in remission for a "reasonable" length of time. A number of studies address this issue (Juul-Jensen, 1964; Sakamoto *et al.*, 1978; Thurston *et al.*, 1982; Todt, 1984; Callaghan *et al.*, 1985; Shinnar *et al.*, 1985; Bouma *et al.*, 1987; Oller-Daurella *et al.*, 1987; Overweg *et al.*, 1987; Arts *et al.*, 1988; Matricardi *et al.*, 1989; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993; Peters *et al.*, 1998). The range of probability of relapse has varied from 11% to 41%. Studies of childhood epilepsies fall into the bottom end of this range and adult studies towards the upper end of the range. The rate of relapse is highest in the early months after withdrawal (Todt, 1984; Arts *et al.*, 1988; Matricardi *et al.*, 1989).

There is considerable variation in methodology. Older studies considered a reasonable seizure-free period or minimum treatment time to be up to 5 years (Oller-Daurella *et al.*, 1987). More recent studies tend to consider shorter periods (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993; Peters *et al.*, 1998). A prospective comparison of prognosis in children undergoing AED withdrawal after 6 or 12 months of seizure freedom found no difference in outcome (Shinnar *et al.*, 1985; Oller-Daurella *et al.*, 1987; Peters *et al.*, 1998). Exclusion criteria have varied; some investigators considered it unreasonable to withdraw medication if either the EEG had not returned to normal (Arts *et al.*, 1988) or the patient had a neurological deficit (Matricardi *et al.*, 1989). Patients whose seizures relapsed during the withdrawal period, rather than after complete withdrawal, were excluded from analysis in one study (Matricardi *et al.*, 1989).

The study that is not only the largest but also the best designed (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, 1993) found a risk of relapse of 41% within 2 years of drug withdrawal, compared with a rate of 22% among the group randomised to continuing with medication. This divergence between relapse rates was maximal between 1 and 2 years; after this, the risk of relapse was higher in those "remaining on treatment". This counterintuitive finding is most probably the result of the decision of patients, with or without medical supervision, to stop their medication, but because this is an assumption it needs to be treated

circumspectly. It would appear, however, that a substantial number of patients are in remission and will remain so without AEDs, whereas another group depend on their medication for seizure control.

It may be useful to examine not only the course of the drug withdrawal in such patients, but also how this relates to initial seizures and response to AEDs (Walker *et al.*, 1997).

Drug-withdrawal studies have found the following factors related to poor outcome:

- total number of seizures (Juul-Jensen, 1964; Emerson *et al.*, 1981),
- short seizure-free period (Matricardi *et al.*, 1989; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, 1993),
- seizures after starting antiepileptic medication (Thurston *et al.*, 1982; Oller-Daurella *et al.*, 1987; Gherpelli *et al.*, 1992; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993),
- polytherapy (Arts *et al.*, 1988; Matricardi *et al.*, 1989; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, 1993),
- duration of treatment (Callaghan *et al.*, 1988),
- generalised tonic–clonic seizures (Oller-Daurella *et al.*, 1987; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, 1993),
- myoclonus (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, 1993),
- partial seizures (Thurston *et al.*, 1982; Callaghan *et al.*, 1988; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991; Braathen *et al.*, 1996; Peters *et al.*, 1998),
- multiple seizure types (Thurston *et al.*, 1982; Oller-Daurella *et al.*, 1987),
- an abnormal EEG (Emerson *et al.*, 1981; Todt, 1984; Shinnar *et al.*, 1985; Callaghan *et al.*, 1988; Matricardi *et al.*, 1989; Gherpelli *et al.*, 1992; Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993; Andersson *et al.*, 1997; Braathen *et al.*, 1997; Peters *et al.*, 1998),
- symptomatic epilepsy (Thurston *et al.*, 1982; Thurston *et al.*, 1982; Todt, 1984; Oller-Daurella *et al.*, 1987; Matricardi *et al.*, 1989; Gherpelli *et al.*, 1992; Tinuper *et al.*, 1996; Peters *et al.*, 1998),

- previous FCs (Shinnar *et al.*, 1985),
- withdrawal of medication in adolescence (Todt, 1984),
- none of these (Bouma *et al.*, 1987).

1.5.2.6 Factors affecting prognosis for remission

1.5.2.6.1 Age

The effect of age on prognosis appears to follow a J-shaped curve. Most studies have found that early onset has a better prognosis than later-onset epilepsy (Hauser *et al.*, 1975; Annegers *et al.*, 1979a; Shafer *et al.*, 1988). However, studies that have included enough children show that prognosis is worse if epilepsy starts in the first year or two of life (Berg *et al.*, 1996a), reducing the 4-year remission rate from 69% to 47% in one study (Emerson *et al.*, 1981).

There is an interaction between aetiology and age in young-onset epilepsy – children with spastic quadriparesis accounted for 75% of children whose onset of epilepsy was under 2 years – a lower age of onset than in control epilepsy groups (Hadjipanayis *et al.*, 1997); similarly infantile spasms start before 1 year and have a particularly poor prognosis (in one study only 16% were alive without sequelae (Cavazzuti *et al.*, 1984)). On the other hand, some of the benign epilepsies of childhood start later, such as benign partial epilepsy with centrotemporal spikes, where the onset is between 3 years and puberty, or absence epilepsy starting at around age 6–8 years.

1.5.2.6.2 Seizure type

It is generally held that seizure type has a strong effect on prognosis; however, a close examination of the literature reveals that studies do not classify seizures in a way that allows easy comparison and, in addition, some findings are contradictory.

Partial seizures are thought to have a worse prognosis for seizure control than generalised seizures (whether from generalised epilepsy or in patients with secondarily generalised seizures only) (Blom *et al.*, 1978; Juul-Jensen *et al.*, 1983; Mattson *et al.*, 1985; Shinnar *et al.*, 1985; Braathen *et al.*, 1996; Sillanpaa *et al.*, 1998). The following have also been linked with worse prognosis:

- multiple seizure types (Thurston *et al.*, 1982; Brorson *et al.*, 1987; Collaborative Group for the Study of Epilepsy, 1992),

- atonic seizures (Sillanpaa *et al.*, 1998),
- infantile spasms (Berg *et al.*, 1996a),
- generalised tonic–clonic seizures (Shafer *et al.*, 1988),
- status epilepticus (Blom *et al.*, 1978; Sillanpaa, 1993; Hesdorffer *et al.*, 1998).

Some studies have not found seizure type to be helpful for prognostication (Cockerell *et al.*, 1995; Casetta *et al.*, 1997).

1.5.2.6.3 Aetiology

Unlike clinic-based or retrospective studies (Okuma *et al.*, 1981; Loiseau *et al.*, 1983a; Shafer *et al.*, 1988; Engel, 1998; Semah *et al.*, 1998), it has been shown that there is little difference in prognosis between idiopathic epilepsy and symptomatic epilepsies in prospectively designed, community-based studies (Goodridge *et al.*, 1983a & b). For example, in Rochester, USA 74% of patients with idiopathic epilepsy entered 5-year remission, which was not significantly different from the symptomatic group (Annegers *et al.*, 1979a). In this study, however, the subgroup of symptomatic epilepsy who had congenital neurological dysfunction did far worse and only 46% had entered remission at 20 years. The finding that remote symptomatic seizures in young children do worse than idiopathic seizures in children is supported by a number of other studies (Brorson *et al.*, 1987; Sillanpaa, 1993; Berg *et al.*, 1996a; Sillanpaa *et al.*, 1998).

1.5.2.6.4 Electroencephalographic findings

The study of the importance of EEG abnormality has been hampered by the clinic-based nature of the investigation, limiting the extrapolation of findings to the community. For example, in the large community-based cohort from Rochester, where there is ready access to medical investigations, 71% had had an EEG; it is reasonable to believe that those who were not investigated differed from the rest of the group (Shafer *et al.*, 1988).

The association of different types of abnormalities in specified subgroups has been correlated with poor prognosis for remission, i.e. generalised activity on the EEG in patients with generalised tonic–clonic seizures (Shafer *et al.*, 1988), abnormal background or paroxysmal activity in complex partial seizures (Loiseau *et al.*, 1983a), paroxysmal frontal or anterior temporal regions (Okuma *et al.*, 1981), among others.

However, not all studies show an effect (Sillanpaa *et al.*, 1995; Casetta *et al.*, 1997).

Another limiting factor in studies of EEG abnormality and prognosis for remission is that some studies based inclusion criteria on the results of the EEG (Lindsay *et al.*, 1979; Lindsay *et al.*, 1980; Shafer *et al.*, 1988).

1.5.2.6.5 Early seizure pattern and its effect on subsequent remission

The temporal pattern of epilepsy has been neglected. There are only two reported studies (Goodridge *et al.*, 1983b, 1983a; Sander *et al.*, 1987). One described the pattern of seizures in 181 patients with chronic epilepsy who attended an epilepsy clinic, and the other of 180 patients identified in the community. These groups were comparable in terms of age and length of history. Three patterns of epilepsy were described: a burst pattern (seizures at outset with early prolonged remission), intermittent (as for burst pattern, although after a remission of at least 2 years there was a relapse) and continuous seizures from outset. The burst pattern accounted for 65% of cases in the community, 25% having continuous epilepsy from the outset, and 12% had remission followed by relapse. This contrasted with those attending the specialist clinic, where only 22% had ever experienced a remission at any stage in their condition (Goodridge *et al.*, 1983a & b). Thus, the statement that epilepsy is a chronic remitting and relapsing condition can be applied only to a minority of patients who have seizures.

A separate issue is whether number or frequency of seizures at the onset of the disorder is predictive of remission. A worse prognosis has been reported in those who experienced high-frequency tonic–clonic seizures before receiving any treatment (Elwes *et al.*, 1985; Beghi *et al.*, 1988; Collaborative Group for the Study of Epilepsy, 1992; Camfield *et al.*, 1996), or without reference to medication (Elwes *et al.*, 1984; Brorson *et al.*, 1987; Reynolds *et al.*, 1989; Sillanpaa, 1993, 1998).

1.5.2.6.6 Other prognostic factors

A family history of epilepsy has been correlated with a worse prognosis (Elwes *et al.*, 1984, 1985), but this was not found in other studies (Casetta *et al.*, 1997).

1.5.3 Mortality from epilepsy

There is an increased mortality rate among patients with epilepsy. This has a peak in

the first year after diagnosis as a result of those causes of epilepsy that have high case fatality, such as secondary brain tumours, subarachnoid haemorrhage and stroke (Cockerell *et al.*, 1994). However, the mortality rate remains elevated, particularly among young adults with severe active epilepsy. This finding is consistent in many studies. Mortality is particularly high in those with cryptogenic seizures, and idiopathic epilepsy and severe active epilepsy; however, the standardised mortality ratio (SMR) for patients whose seizures are in remission is also high at around 1.8 (Zielinski, 1974a; Hauser *et al.*, 1980; ILAE Commission Report, 1997).

Demographic features are important; men have higher SMRs than women with epilepsy, especially in those aged up to 40 years where death as a result of other causes is infrequent. Among the over-75s, in whom the death rate is high, the added risk of epilepsy is much smaller.

Seizure type is important: absence seizures in isolation display no excess mortality, whereas myoclonic seizures have an SMR of 4.1 (Hauser *et al.*, 1980).

The most common causes of death among those with epilepsy are chest infections, neoplasia, and epilepsy-related deaths and accidents. Bronchopneumonia is the most common cause of increased SMR in this group, with a rate of 1.7–7.9 (Zielinski, 1974b; Hauser *et al.*, 1980; Klenerman *et al.*, 1993). It has been postulated that this is because of peri-ictal aspiration.

Tumours, with or without the inclusion of brain tumours, are more frequent in patients with epilepsy (Zielinski, 1974a; Hauser *et al.*, 1980; Klenerman *et al.*, 1993). However this seems to be caused by cancer diagnosed before the diagnosis of epilepsy (Zielinski, 1974b; Hauser *et al.*, 1980).

Epilepsy-related deaths are divided into those caused by status epilepticus, sudden unexpected death (SUDEP) or accidents. It has been postulated that death associated with a seizure is the result of autonomic instability, including apnoea, bradycardia and cardiac arrhythmia, which can be recorded during seizures (Nashef *et al.*, 1996). The difference between seizure-related death and SUDEP is that, in the former, the seizure is witnessed; in the latter, a patient with epilepsy is found dead and there is no cause found *post mortem*. The annual incidence of SUDEP in an outpatient cohort of a

specialist epilepsy service was 1 in 200 patients with chronic epilepsy (Nashef *et al.*, 1995).

SMRs for accidents and trauma are raised. Suicide is increased among those with epilepsy, especially if severe, of relatively recent onset and arising in the temporal lobe (Zielinski, 1974b). The NGPSE cohort has not demonstrated this as a cause of excess mortality, despite the inclusion of people whose epilepsy falls into these categories (Cockerell *et al.*, 1994).

Methods

2.1 General Practice – National Hospital for Neurology and Neurosurgery Linkage Study Design and Registration

2.1.1 Background

The incidence and prevalence of neurological conditions are important to plan health-care provision and measure health outcomes (Schoenberg, 1977; Charlton, 1996). Knowledge of the background frequency of neurological conditions is one of the tools that allows the physician to make accurate diagnoses (Longstreth *et al.*, 1987). To avoid bias, the rates should be based on surveys conducted at community level. The study was designed to enable the ascertainment of the incidence and lifetime prevalence of all neurological conditions in an urban community.

2.1.2 Population size

A population of around 100,000 was chosen because this would be sufficiently large to generate high numbers of the more common neurological conditions and, with the passage of time, good numbers of less frequent diagnoses.

2.1.3 Population base

The population frame of these studies was an unselected population covered by 13 general practices in the National Hospital for Neurology and Neurosurgery (NHNN) – GP Linkage Scheme. These practices serve 100,230 people – an administratively defined but otherwise unselected urban population[3].

We chose the practices in the following way. Having obtained a list of all local practices from the relevant Family Health Services Authorities we wrote to all those above a certain size in central London.We approached all those who expressed an interest in the study. Our requirements were that the practices should have a computerised age and sex register and that were happy to cooperate with all elements of the study; including the notes searches. Many practices, particularly those with limited space, did not wish to join a study which required this degree of commitment;

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[3] Although some studies have shown this to be relative because doctors who are female, or speak particular languages, and practices that offer particular services may skew the populations and because some patients will seek a GP based on such criteria (Scrivener *et al.*, 1995).

this was the main reason for rejection. As patients do not choose which practice they attend for the condition they will get the future the choice of practices should not influence incidence.

Of the thirteen practices four were fund-holding.

Inevitably patients were referred elsewhere, this was particularly the case for several referral types: -

- Within hospital referrals, which account for many outpatient referrals - i.e. patients seen in a local hospital for one condition might be referred to the attending consultant neurologist for an opinion.
- London is largely covered by a GP out of hours cooperative and patients with requiring emergency treatment e.g. for stroke would be admitted to the appropriate local hospital.
- Patients who attended casualty with neurological symptoms might be referred to neurologists via the casualty officier's usual channels.

In three of these practices, comprising around a quarter of this population, lifetime prevalence was surveyed. A pilot study of the system has been reported (Cockerell *et al.*, 1996).

The demographics of this population were monitored over time for migration and births and deaths, using each general practice's computerised demographic register. Small area statistics, which ascribe census data to small wards, were used to stratify for ethnicity and social class (Jarman, 1983; Majeed *et al.*, 1995).

2.1.4 Restricted population sets

As the frequency of an observed event increases, the confidence limits of the observed frequencies will diminish. However, errors in case finding are increased by the width of a search. Hence, it was decided to study certain conditions (diabetic polyneuropathy) in a subset of the population.

To survey lifetime prevalence, the subset population, amounting to a quarter of the incident study population, was used because prevalence tends to be higher than incidence and a smaller population would provide sufficient cases. This subset was

based in three of the practices.

2.1.5 General practice population

Each GP is responsible for the primary care and referral of all the patients on his or her list, and is usually the first doctor whom a patient sees. When patients change GPs, their health-care record is automatically sent via the National Health Service Central Register (NHSCR) to the new GP. The central register is also informed of all deaths and their cause. This ensures that, for every individual in the country, there is a traceable, unique record. This system is ideal for long-term, population-based studies; all individuals registered in studies can be traced efficiently, unless they emigrate.

2.1.6 National Hospital for Neurology and Neurosurgery

The NHNN is a tertiary referral centre for neurology in central London. A dedicated clinic was the basis of the facilitated link between general practice and the NHNN outpatients service.

2.1.7 Case ascertainment

Multiple methods for case finding were used to ensure complete ascertainment.

1. Patients were referred by their GP to the "linkage clinic" at the NHNN for a specialist opinion. Most patients were assessed within 2 weeks of referral. The reason for referral was noted. If, after assessment and appropriate investigation, a new neurological diagnosis was made it was recorded as an incident diagnosis.

2. Doctors in the practices were asked to inform the study office of any patient with a newly diagnosed or suspected neurological diagnosis, whether the diagnosis was made within primary care, accident and emergency or other specialist services. Neurological diagnoses were entered on to practice computers, copies of all relevant correspondence were kept and "neurology books"– where short notes about patients with suspected or confirmed diagnoses – were kept. In certain practices, all accident and emergency cards were also kept for review. The researcher (BKM) maintained a high profile through regular visits and easy access via mail or mobile telephone to discuss neurological queries and referrals.

3. The computers in the general practices were searched regularly for neurological diagnoses. Further, those drugs that are used with relative specificity in neurology were also searched for.

4. Using the patient administration system at the NHNN, patients from the general practices involved, who had been patients during the study period, were identified; this acted as a check on the hospital-based records.

5. A pilot search was carried out half-way through the study. This consisted of a random hand search of 4% of GP-held patient records (Lloyd George notes), including letters from specialists. Incident neurological cases were identified and compared with the office records.

6. A full search was carried out in all practices at the end of the observation period by examining all the population's (100,230) primary care notes. The age and sex of the patients whose notes were examined were recorded. The search was carried out by medical students who were trained and supervised to identify incident neurological diagnoses in the hand-written notes and correspondence (including "over-75" and diabetes record cards). They were instructed to be over-inclusive and to take note of any cases where they were uncertain. All the sets of notes identified as positives by the students were examined by a neurologist to check diagnostic criteria. All available hospital correspondence and notes were examined and the date of diagnosis established. Information necessary for disease classification was noted. This information was compared with the office records to estimate the accuracy of daily data collection.

7. The lifetime prevalence survey was based on information obtained from computer searches in general practices, and from the NHNN and the hand search of all the notes in three of the practices. The notes of all identified cases were examined to verify diagnosis by the author.

2.1.8 Quality control

To check the sensitivity of the audit, a random selection of 2% of notes from the practices was examined by an independent neurology trainee, who was blind to the data already collected.

2.1.9 Data collection

Registration of patients began in 1994; this report covers the period from 1/1/1995 to 1/7/1996.

The incidence date for a diagnosis was taken as the day that the diagnosis was made by either clinic date or date of entry in the GP notes. For example, if a patient had tingling and numbness on a number of occasions, and subsequently multiple sclerosis was diagnosed, the incidence date was that of the diagnosis, not the preceding and probably linked symptoms

2.1.10 Statistical methods

The denominator population was taken as the number of NHS patients registered with the practices. Demographics were collected at 6-monthly intervals during the study. As an urban population is mobile, the details of patients registering with and leaving the practice, and those who died, were collected. Given the prospective nature of data collection and population mobility, incidence rates were calculated for the population of 1 July 1996 plus those who died and half of those who left during the period. This correction was felt to be appropriate because, on average, that population had been present for half the time of the incidence study and the adjustment would give a minimum incidence rate. The denominator population for the lifetime prevalence was the population on 1 July 1996 in the three practices studied.

Incidence per 100,000 p.a. and lifetime prevalence per 1,000 are given after adjustment to the UK population figures from the 1991 census. Confidence limits were calculated using the Poisson distribution variables for small numbers (Haenszel *et al.*, 1962). All figures are given to one significant place. For stroke, epilepsy and Parkinson's disease, age-specific rates were also calculated.

2.1.11 Case definitions

See Appendix 2.

2.1.12 Exclusions

We excluded certain conditions that were borderline between two specialties, or of high frequency and low specificity (Table 20 - see over).

Table 20. Conditions excluded from the incidence and prevalence studies

Bells palsy
Benign position vertigo
Carpal tunnel syndrome
Back pain and sciatica
Ear conditions and idiopathic deafness (provided not related to other neurology)
Eye conditions anterior to the optic disc (although retinal stroke was included)
Menière's disease
Migraine
Plagiocephaly
Senile dementia
Tension headache

2.1.13 Criteria for registration

All patients registered as NHS patients, under the care of the 13 general practices involved in the study, and who had a newly diagnosed neurological conditions, were registered on the study.

2.1.14 On registration

Patient and clinical details were collected for each patient. Details were kept on SPSS software. The patients were flagged at the OPCS.

2.1.15 Confidentiality and ethical considerations

The information gathered was held at the Linkage office and details of the patients and their conditions were kept in accord with the Data Protection Act (Medical Research Council, 1994; Bressman *et al.*, 1997). Diagnoses were coded using the *International Classification of Disease*, 10th edition (ICD-10NA) (World Health Organization, 1992). The researcher had access to patients' records at all the practices, so that all available data were examined to ensure accuracy of diagnosis and their date.

The study was approved by the ethics committee at the NHNN.

2.2 Prognosis of epilepsy

2.2.1 Background to The National General Practice Study of Epilepsy

The prognosis for seizure remission is one of a patient's key concerns when a diagnosis of a seizure is made. To establish the remission rates and factors that allow prognosis to be made early in the course of the condition, a cohort of newly diagnosed patients with seizure disorders was identified between 1984 and 1987. These individuals were the basis of the NGPSE. The study was designed to enable an incident cohort to be identified and followed. The early identification at a community level of all definite and possible cases was important to include patients who would die shortly after diagnosis, and to identify mild cases. This section lays out the methodology of the study of prognosis in the groups with epilepsy and febrile convulsions.

2.2.1.1 The identification of the incident cohort

2.2.1.1.1 Community base

This nationwide study was publicised in the medical press and by personal contacts of the investigators. Two hundred and seventy-five general practitioners volunteered to notify the study of every patient on their list newly presenting with epilepsy, or in whom the diagnosis was suspected. GPs who agreed to participate in the study were registered for subsequent communications.

2.2.1.1.2 Study design and registration

2.2.1.1.2.1 Inclusion criteria

Any patient who had experienced a possible seizure of any type and who presented to a doctor was eligible. All ages and suspected aetiologies were to be included. The seizure-provoking registration was called the "index seizure". This was not always the first seizure because patients do not always present to medical agencies until they have had a number of seizures.

2.2.1.1.2.2 Exclusion criteria

Patients with a previous diagnosis of epilepsy were excluded and neonatal seizures were also excluded.

2.2.1.2 Initial registration

Active recruitment went on from June 1984 to October 1987. To maintain a high

profile and to minimise selection bias, the registered GPs were mailed twice a month with reminders to ensure as complete a recruitment as possible.

2.2.1.3 The prevention of bias

2.2.1.3.1 Random selection

GPs were recruited from all over the UK from rural and urban practices. As patients do not choose their GP because of a future seizure, choice of GP does not bias the study.

2.2.1.3.2 Completeness of ascertainment

In the instructions given to the GPs, it was emphasised that all patients with symptoms that might be attributable to a seizure could be recruited. This ensured that the milder or more obscure cases would not be under-represented in the cohort. This raised the sensitivity, but meant that some specificity was lost at the recruitment phase.

2.2.1.4 Data collection on registration

Demographic and clinical details were collected, together with characteristics of the index seizure.

The patient registration forms filled by the GP were coded and stored in the study office and a database entry was started. A study registration card was sent back to the GP to put in the patient's notes. This had two purposes: first, to reduce double registration at the GP level and, second, to remain in the patient's notes if the patient changed GP.

Each patient was flagged at the NHS Central Register. This allows the tracing of any patient who changes GP, and the study is automatically informed of any deaths in the cohort, together with a copy of the death certificate.

2.2.1.5 Further follow-up

At 6 months, further follow-up details were collected from the GP through a detailed questionnaire on details of seizures, treatment, and neurological, medical and psychological developments. If no reply was received within 3 months, a follow-up letter and further questionnaire were sent; if this produced no response, the GP was telephoned by the study coordinator and the questionnaire filled out.

2.2.1.6 Hospital enquiry

Details of those patients referred to a hospital clinic were requested from the supervising consultant, using a different questionnaire 6 months after registration. This was to confirm the diagnosis of epilepsy, seizure type, aetiology and results of investigations. If no response was obtained from this or a follow-up letter at 3 months, the hospital notes were requested. If this failed, then copies of all the relevant hospital correspondence were requested from the GP.

2.2.1.7 Patients changing GP

When patients changed GPs, the new GP would be alerted to their involvement in the study by the card that had been put into the patient's notes at registration. The card asked that the new GP inform the study of the patient's new general practice. If this failed to occur, the patient could be traced using the individual's NHS number, via the NHSCR and the Family Health Service Authority. Follow-up forms were then sent to the new GP.

2.2.1.8 Patient classification

All the information gathered from the registration forms, the 6-month follow-up and the hospital enquiry were used by the study panel to classify the patient.

2.2.1.9 Study panel

The study was coordinated by a panel based at the Chalfont Centre for Epilepsy. This reflected the appropriate specialties to the community study of epilepsy comprising three neurologists, a paediatrician with an interest in epilepsy, two general practitioners and a statistician.

2.2.1.10 Seizure classification

Seizures and epilepsy were classified by the panel on the basis of all the information available at 6 months after the index seizure, first into four groups: definite epilepsy, probable/possible epilepsy, febrile convulsions and non-epileptic episodes. The probable/possible group comprised those cases in which, even at 6 months, the diagnosis could not be excluded or confirmed but remained in question; often the differential diagnosis was syncope or non-epileptic seizures.

Children aged between 1 month and 6 years, who experienced a first seizure during an

episode of fever but not in the context of CNS infection, were identified as having had a febrile convulsion.

Seizure classification was based on the International Classification of Seizures (1981) with adaptation for the fact that not all cases had had an EEG.

2.2.1.11 Aetiological classification

The cases were further classified into the following groups:

- cryptogenic – no identified underlying cause or idiopathic; remote symptomatic postnatal CNS lesions;
- acute symptomatic – seizures starting within 3 months of an CNS insult;
- seizures associated with congenital or perinatal neurological abnormality.

This classification is similar to that used in other large community-based studies, which allows comparison (Hauser *et al.*, 1982). The study classification predated the ILAE's aetiological classification of the epilepsies. Those cases classified as symptomatic were further divided into aetiological groups:

- vascular – where there was clear evidence of vascular or embolic disease;
- tumour – either radiological or a clear clinical picture consistent with an expanding lesion;
- trauma – if a definite history of head injury with loss of consciousness lasting more than an hour within the previous year;
- alcohol related – when seizures occurred on withdrawal or during a period of excessive intake;
- post-infective – during or in the aftermath of a confirmed episode of encephalitis, bacterial meningitis or cerebral abscess;
- a cryptogenic group (not necessarily identical to the cryptogenic above because it includes congenital neurodevelopmental deficits that are not caused by birth injury).

2.2.1.12 Definitions

Epilepsy is defined according to ILEA guidelines as repeated (two or more) unprovoked epileptic seizures more than 24 h apart (Commission on Epidemiology and Prognosis, 1993).

A simple FC is defined as a convulsion in which there are none of the following features: focal signs at onset or post-ictally; repeated episodes during the same episode of febrile illness; or duration of seizure longer than 15 min. The presence of any one of these features renders a FC complex (National Institutes of Health Consensus Statement, 1980).

2.2.1.13 Sample size

A sample size of 1,200 was chosen in order to achieve 700 cases of probable and definite epileptic seizures (Parmer *et al.*, 1995).

2.2.1.14 Further follow-up

2.2.1.14.1 Patient follow-up from first seizure

Regular active surveillance was chosen as the method to follow up patients. This ensures that data collection is carried out at reasonable lapses of time, so that information is not lost. It puts the responsibility for data collection on the central study office, removing as much of that responsibility from the GPs as possible. Active surveillance is far more likely to be accurate than systems that rely on passive reporting and is one of the great strengths of the NGPSE.

Each year, the GP was sent a form to fill in details about the patient's epilepsy, medication and medical developments.

In 1993, a second hospital follow-up was carried out.

2.2.1.14.2 Follow-up of the FC cohort

For those cases classified as FCs, certain details were specifically requested. These were: "complexity" of further FCs; treatment with AEDs at the time of the FC or subsequently; and any neurodevelopmental problems.

2.2.1.15 Remission of epilepsy

Remission was defined as a seizure-free interval occurring any time after the index seizure – whether the patient was taking AEDs or not. Terminal remission was defined as seizure freedom at the time of last follow-up. Remission was calculated for 1, 2, 3 and 5 years.

Remission was examined both separately and in combination for patients with definite

epilepsy and probable epilepsy. Years in remission were calculated up to the end of 9 years of follow-up, both from index seizure and from first seizure if that was within 6 months of the index seizure.

Analysis of remission for groups stratified according to classification, aetiology and age band was also carried out.

2.3.1 Statistical analysis

All data were coded and analysed in collaboration with the Medical Research Council Biostatistics Unit at Cambridge. Data were entered on DataEase software, and analysed on both SPSS and BMDP.

The outcome for patients with definite or probable seizures at the 6-month classification was analysed, using the Cox proportional hazards regression model (Parmer *et al.*, 1995) to identify factors associated with periods of 1-, 2-, 3- and 5-year remission (i.e. complete seizure freedom irrespective of treatment status). Deaths were considered as recurrences if associated with a seizure, and otherwise as censored observations, on the principle that any model that includes an interaction must also contain lower-order interactions. To illustrate this: in a hypothetical model in which there is interaction between age, sex and another factor on the development of a subsequent illness, there must also be interactions between age and sex, age and the factor, sex and the factor, as well as the effects of the three main variables themselves. The are three different types of variable: (1) continuous variables; (2) binary variables; and (3) categorical variables. All of these need to be treated differently to ensure validity.

In this analysis, having prospectively defined the start of follow-up as 6 months after the index seizure, the classification of seizures was not confounded by follow-up. Moreover, the seizure count examined was counted prospectively not retrospectively. This contrasts with previous remission analyses. Follow-up extended to 31/12/1993, death or loss to follow-up, whichever was the earliest.

Twenty-eight candidate variables were identified to test for prognostic importance: 23 (numbers 1–5, 9–11, 14–28) binary (yes/no) and five (numbers 6–8, 12, 13) continuous (see Table 50 and Table 51 on page 149). Age at first seizure was

categorised into five groups to allow the hazard for remission to vary non-linearly with age. (In particular, poor prognosis in those whose epilepsy starts very young is well known.) The actual number of seizures was coded as the exact number from zero to nine, and then ten or above; truncation was implemented to avoid difficulties of precise estimation in patients with large numbers of seizures. In addition, three binary variables to indicate more than ten seizures before the index one, during the 6-month assessment period or during both these periods were also considered; their inclusion allows a jump in the hazard induced by the truncation. Logarithmic transformation of some continuous variables was chosen because exploratory analysis indicated that they exerted a non-linear effect on the hazard. (Although the reciprocal transformation has been used in other studies [Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993a] we opted for logarithms that provided more parsimonious models, which were easier to interpret.) For each end-point (1-, 2-, 3- and 5-year remission), separate univariate analyses were performed for each co-variate, as well as multivariable analyses incorporating most of the set. In addition, stepwise selection techniques were used to identify a subset of variables that influenced remission (p = 0.05 for inclusion and p = 0.10 for removal). Patients with probable seizures are included in the analysis, along with those with definite seizures, to quantify associations with remission as precisely as possible; their exclusion would reduce the sample by 30%. To allow for different risks of remission, this grouping was included as a possible prognostic factor in the analysis and was also investigated in an analysis of interactions with other factors. Similar arguments apply to omission of patients with single seizures (i.e. index seizure only) or acute symptomatic seizures; exclusion of both of these would reduce the sample by more than one-third. Some analyses performed on the full dataset were repeated on three restricted subsets (patients with definite seizures only, the full dataset excluding single seizures, the full dataset excluding acute symptomatic seizures). Finally, we made a limited investigation of the effect of treatment, during the 6 months post-index, after controlling for the number of seizures during this period and the occurrence of secondarily generalised seizures.

2.3.2 Statistical analysis of FC cohort

For the FC cohort odds ratios (ORs) and 95% confidence limits (95%CLs) were calculated using logistic regression for various factors that might affect neurological

prognosis. The interval from the first FC to the development of epilepsy (defined as at least two unprovoked seizures at least 24 h apart), or to the last follow-up date, whichever was earlier, was calculated and summarised by actuarial (Kaplan–Meier) techniques. The Cox proportional hazards regression model was used to assess the prognostic importance of baseline factors for the development of epilepsy. An extended version of this model with time-dependent co-variates was used to investigate changes in the hazard for development of epilepsy associated with the occurrence of further FCs.

To increase the sensitivity of OR calculations, it is possible to pool the figures from different sources (Nelson *et al.*, 1976, 1978a; Annegers *et al.*, 1979b; Verity *et al.*, 1985b; Annegers *et al.*, 1987; Verity *et al.*, 1991; Forsgren *et al.*, 1997).

2.4 Confidentiality and ethical considerations

Confidentiality and data security were maintained throughout the study. It was only possible to identify patients by separate, unlinked files; this complies with the Data Protection Act. The study was approved by The National Hospital of Neurology and Neurosurgery and Institute of Neurology Joint Ethics Committee, and was recommended to its members by the Royal College of General Practitioners. The study is registered with the Office of Population Census and Surveys and the Data Protection Registrar (Dyck *et al.*, 1981; Medical Research Council, 1994).

Results

3.1 General Practice – NHNN Linkage Study

3.1.2 Practices

Thirteen general practices in London and a practice in Tonbridge were recruited into the study. During the course of the study, one practice withdrew when the single-handed GP retired and the GPs replacing him did not wish to take part in the study. Information for this practice was discarded. All the practices in London qualified for deprivation scores (see page 17) which are shown as percentages of the practice population in Table 21. The percentages given are multiplied by the practice population size to determine additional payments.

Table 21. The percentage of each general practice's population qualifying for deprivation payments

	Jarman deprivation score (% practice)		
Practice	**High (I)**	**Medium (II)**	**Low (III)**
A	0	0	0
B	0	0.002	3
C	0	0.001	10
D	0	0	37
E	0	24	0.003
F	0	4	35
G	0	14	30
H	0	34	10
I	0.01	1	72
J	0.004	2	86
K	8	29	53
L	18	52	7
M	35	32	28
TOTAL	**3**	**13**	**26**

A, D & J were the practices used to survey prevalence

A-M anonymised practices

Population

The total practice population on 1/1/1995 was 95,891; on 1/7/1996 it was 100,230. As there were 14,551 new patients and 9,711 people left the practices, with 818 deaths, there is a discrepancy of 378 people – a 0.004% error.

The three practices that constituted the population for the prevalence study had a population of 27,658 on 1/7/1996.

The incidence population is broadly comparable with the UK population, showing a slight excess of adults from age 30 to 54 and a compensatory reduction in the older age groups, over-65s accounting for 16% of the UK population and 13% of the linkage population. This is shown in Table 22.

Table 22. Linkage population

Age bands (years)	Linkage Population (%)	UK population in 1991 census (%)
0-9	11	13
10-19	9	11
20-29	14	16
30-39	26	20
40-49	16	14
50-59	11	9
60-69	8	8
70-79	6	7
>80	3	4

Economically, the population appears relatively prosperous compared with that of the UK as a whole. Among those working, there is a higher rate of professional class and less unemployment (Table 23).

The qualification of some of the practices for deprivation payments (see Table 21) reflects that this is not the whole picture. There are higher numbers of people who do not qualify for unemployment benefit in these areas, including refugees and those receiving long-term sickness benefit. It may be that this reflects a wider socioeconomic divide within small areas than is usual in the UK as a whole.

Table 23. Demographic data from the Linkage study compared with the UK population, 1991

Ethnic group	Linkage population (%)	UK population (%)	Economic group	Linkage population (%)	UK population (%)
White	80	94	Professional	9	6
Irish	7	2	Managerial and Technical	36	26
Black	7	1	Skilled Non-Manual	14	10
Indian and Pakistani	3	2	Skilled Manual	17	24
Chinese and Other	4	1	Partly Skilled	10	12
			Unskilled	6	4
			Unemployed	8	18

Ethnic minorities constitute a greater part of the population than in the UK population as a whole (Table 23).

3.1.2.1 Comprehensive notes search

Table 24. Percentage of notes audited by age band

Age (years)	percentage in audit (%)
0-4	92
5-9	99
10-14	91
15-19	96
20-24	100
25-29	101
30-34	100
35-39	98
40-44	96
45-49	102
50-54	95
55-59	93
60-64	94
65-69	91
70-74	90
75-79	93
80-84	92
85-89	86
>90	84

In all, 97% of the notes of all the patients registered on 1/7/1996 were examined. The audit rates for different age groups show that older patients were less likely to be audited (Table 24).

For all disorders, 70% had been picked up in the prospective collection of data; a further 31% of cases were found at the time of the comprehensive audit in 1996 (percentages rounded to whole numbers). When certain conditions that are not traditionally referred to neurologists were excluded (dementia, back conditions without myelopathy, shingles, diabetic

polyneuropathy and febrile convulsions), the percentage identified prospectively rose to 79%.

3.1.3. Incidence and lifetime prevalence rates

Overall, the onset of 625 neurological disorders was observed per 100,000 population p.a. (including all the diagnoses tabulated except shingles); 6% of the population in whom lifetime prevalence was surveyed had had a neurological disorder.

The neurological disorders ascertained are tabulated, giving age- and sex-adjusted incidence rates per 100,000 p.a. (common conditions are shown in Table 25, intermediate conditions in Table 26, unusual conditions in Table 27, a breakdown of serious CNS infections in Table 28 and single incident diagnoses in Table 29). Lifetime prevalence per 1,000 persons is also given (common diagnoses in Table 30, less frequent diagnoses of the CNS in Table 31 and of the peripheral nervous system [PNS] in Table 32).

Table 25. The age and sex adjusted incidence rates for common neurological conditions compared to previously reported rates

Conditions	NHNN-Linkage age & sex Adjusted IR (with 95% confidence intervals)/100,000 per year	Previously reported incidence rates/100,000 per year	
Stroke			
First cerebrovascular episode	205 (183, 230)	200	Bamford *et al.*, 1988
Second cerebrovascular episode	42 (33, 55)	28-35	Sorensen *et al.*, 1982
			Walker *et al.*, 1985
Intracranial haemorrhage	10 (5, 17)		5% of stroke i.e. 10
Seizure disorders			
Epilepsy	46 (36, 60)	24-53	Brewis *et al.*, 1966
			Hauser *et al.*, 1993
Single seizures	11 (7, 18)	20	Kurtzke, 1984
Tumours			
Primary CNS tumours (benign and malignant)	10 (5, 18)	7	Brewis *et al.*, 1966
			Walker *et al.*, 1985
		15	Counsell *et al.*, 1996
Parkinson's disease	19 (12, 27)	12-18	Brewis *et al.*, 1966
			Rajput *et al.*, 1984b
Compressive mononeuropathies -all except CTS*	49 (39, 61)	40	Kurtzke, 1984
Arm - all excluding CTS*	24 (17, 33)		
Leg - all	20 (14, 29)		
Polyneuropathies		40	Kurtzke, 1984
Diabetic polyneuropathy	54 (33, 83)	11	Cockerell *et al.*, 1996
All, excluding diabetic and alcoholic	15 (9, 23)		
Shingles	140 (104, 184)	71	Cockerell *et al.*, 1996
		131	Ragozzino *et al.*, 1982
		400	Kurtzke, 1984
		480	Schoenberg *et al.*, 1993
Post-herpetic neuralgia	11 (6, 17)	13	Ragozzino *et al.*, 1982
		34	Cockerell *et al.*, 1996
		9% of shingles,	Schoenberg *al.*, 1993

*CTS, carpal tunnel syndrome, was an excluded diagnosis.

Table 26. Incidence rates of conditions of intermediate frequency

Condition	Age and sex adjusted IR/100,00 per year	Previously reported IR/100,000 per year	
Bacterial CNS infection (overall)	7 (4, 13)	10	Brewis *et al.*, 1966
		11	Fraser *et al.*, 1973b
Essential tremor	8 (4, 14)	24	Rajput *et al.*, 1984a
Trigeminal neuralgia	8 (4, 13)	2	Brewis *et al.*, 1966
		4	Kurtzke, 1984
Benign CNS tumour	7 (3, 13)	10	Kurtzke, 1984
Multiple sclerosis	7 (4, 11)	2-8	Brewis *et al.*, 1966
			Shepherd *et al.*, 1980
			Kurtzke, 1984
Severe head injury	7 (3, 12)	4-6	Langton Hewer, 1993
Subarachnoid haemorrhage	7 (3, 12)	10-15)	Brewis *et al.*, 1966
			Kurtzke, 1984
Subdural haemorrhage	6 (3, 12)		
Cluster headache	6 (3, 10)	10(6-14)	Swanson *et al.*, 1994
Cranial nerve disorder (excluding II, III, IV, VI, Bell's palsy or trigeminal neuralgia)	6 (2, 12)		
Disorders of II, III, IV, VI, including pupillary abnormalities but not optic neuritis	6 (3, 11)		
Aseptic meningitis	5 (2, 9)	1	Brewis *et al.*, 1966
		11 (10,12)	Beghi *et al.*, 1984
Metastatic CNS tumour	4 (1, 9)	15	Kurtzke, 1984
		14 (12,16)	Counsell *et al.*, 1996
Presenile dementia	4 (2, 9)		
Cerebral palsy	3 (1, 8)	1.5	Brewis *et al.*, 1966
		9	Kurtzke, 1984
		2.7	Rosen *et al.*, 1992
Neonatal encephalopathy or stroke	3 (1, 8)		
Other congenital CNS abnormalities	3 (1, 8)	7	Kurtzke, 1984
Brachial neuritis	3 (1, 7)	2	Beghi *et al.*, 1985
Guillain-Barré syndrome	3 (1, 6)	1-2	Kurtzke, 1984
Myasthenia gravis	3 (0.8, 7)	0.25-0.8	Aiello *et al.*, 1997
		1	Robertson *et al.*, 1998
Primary malignant CNS tumour	3 (0.7, 7)	5	5 Kurtzke, 1984
		5(F) 6(M)	Ryan *et al.*, 1992
Transient global amnesia	3 (0.5, 7)		
Spinal cord injury	3 (0.9, 7)	5	Kraus *et al.*, 1975
		1.3-4	Kurtzke, 1984
			el Masry *et al.*, 1997

Table 27. The incidence rates for conditions where three or fewer were affected

Condition	Age and sex adjusted IR/100,00 per year	Previously reported IR/100,000 per year	
Acute cervical myelopathy related to disc	2 (0.2, 6)		
Cranial nerve injury	2 (0.5, 5)		
Demyelination disorders not limited to optic nerve or fulfilling criteria for MS	2 (0.4, 5)	1.2	Kurtzke, 1984
HIV encephalopathy	2 (0.8, 5)		
Idiopathic myelopathy	2 (0.4, 6)		
Motor neuron disease	2 (0.3, 5)	1-2	Brewis *et al.*, 1966
			Kurtzke, 1984
Chronic spondylitic myelopathy	2 (0.5, 6)		
Truncal mononeuropathy	2 (0.6, 6)		
Diabetic amyotrophy	1 (0.1, 4)		
Focal dystonia	1 (0.1, 4)	2.2	Nutt *et al.*, 1988
Non-cervical disc-related cord or cauda damage (i.e. Other disc or anatomical anomalies)	1 (0.1, 3)		
Optic neuritis	1 (0.2, 3)	1.6	Brewis *et al.*, 1966
		3	Kurtzke, 1984
Spinal malformation	1 (0.1, 2)	3.3	Brewis *et al.*, 1966

Table 28. Breakdown of different CNS infections

CNS bacterial and other infections	*n*
Tuberculosis	3
Meningococcal meningitis	3
Syphilis	2
Streptococcal meningitis	1
Streptococcus pneumoniae brain abscess	1
Listeria	1
Cryptococcus	1
Ventriculitis in a man dying of reticulosis	1

Table 29. Conditions in which only a single incident case occurred

Four patients with cerebellar degenerations with additional features (not related to alcohol).
Three patients with degenerative conditions, the main feature of which was dementia (but not attributable to Alzheimer's or vascular disease).
Aqueduct stenosis
Arnold-Chiari malformation
Cerebral cyst
Communicating hydrocephalus
Frontal dementia with anterior horn cell disease
Idiopathic isolated neurogenic bladder
Myositis
Myotonic dystrophy
Neurofibromatosis
Neurosarcoid with cord involvement
Lupus encephalopathy
Syringomyelia
Tonsillar herniation with Chiari malformation
Tuberous sclerosis

Table 30. The lifetime prevalence of common neurological diagnoses

Conditions	lifetime prevalence/1,000 population (95% CL)	Previously reported point prevalence (*PP*) rates or estimated lifetime prevalence /1000	
Stroke	9 (8, 11)	5	Langton Hewer, 1993
Transient ischaemic attack	5 (4, 6)	2	Sorensen *et al.*, 1982, Langton Hewer, 1993
		6	McGeddes *et al.*, 1996
Active epilepsy	4 (4, 5)	5	The Research Committee of RCGP, 1960
			Pond *et al.*, 1960, Langton Hewer, 1993)
Congenital neurological deficit	3 (3, 4)	overall 3; 2/1,000 between 7-10y; CNS malformation: 0.7; Downs: 0.5	Kurtzke, 1984
Parkinson's disease	2 (1, 3)	1 (PP)	Kurtzke, 1984
		2	Brewis *et al.*, 1966; Langton Hewer, 1993
			Mutch *et al.*, 1986; Chio *et al.*, 1998
Multiple sclerosis	2 (2, 3)	1	Shepherd *et al.*, 1980; Langton Hewer, 1993;
		2	Rice Oxley *et al.*, 1995, McDonnell *et al.*, 1998
Diabetic polyneuropathy	2 (1, 3)	3	Savettieri *et al.*, 1993
Compressive mononeuropathies[1]	2 (2, 3)	0.4 (PP)	Kurtzke, 1984
Subarachnoid haemorrhage	1 (0.8, 2)	0.5	Phillips *et al.*, 1980; Kurtzke, 1984
Polyneuropathy (excluding diabetic and alcoholic)	1 (0.8, 2)	0.4 (PP)	Kurtzke, 1984
Single seizures	1 (0.9, 2)		
Bacterial meningitis	1 (0.8, 2)	Abscess 0.02 (PP); meningitis 0.05 (PP)	Kurtzke, 1984

[1] Not including carpal tunnel syndrome

Table 31. The lifetime prevalence of less common CNS disorders

Conditions	NHNN-Linkage Lifetime PR (with 95%CL)/1,000	Previous Reported prevalence rates/1,000	
Meningitis or encephalitis (CNS infections)	1 (1, 1)		
Aseptic meningitis	0.9 (0.6, 1)		
Essential tremor	0.8 (0.5, 1)	3 (1)	Langton Hewer, 1993
Polio	0.7 (0.42, 1)		
Severe head injury	0.6 (0.4, 1)	2	Langton Hewer, 1993
Optic neuritis	0.6 (0.3, 1)	0.1	Kurtzke, 1984
Benign CNS tumours	0.5 (0.3, 1)	0.6, in brain, 0.1 in cord	Kurtzke, 1984
Intracranial haemorrhage	0.5 (0.2, 0.8)		
Other movement disorders	0.4 (0.2, 0.7)	Hereditary ataxia 0.08	Kurtzke, 1984
Viral encephalitis	0.4 (0.2, 0.7)	0.1	Kurtzke, 1984
Spondylitic and compressive myelopathy	0.4 (0.2, 0.7)		
Cluster headache	0.3 (0.2, 0.6)	0.3(F), 1(M)	Ekbom *et al.*, 1978, D'Alessandro *et al.*, 1986
Subdural haemorrhage	0.3 (0.2, 0.6)		
Malignant CNS tumours	0.2 (0.06, 0.4)	Primary malignant 0.05/ metastatic in brain 0.15/ metastatic cord 0.05	Kurtzke, 1984
Nerve or plexus injury	0.2 (0.05, 0.4)	0.3	Kurtzke, 1984
Demyelinating conditions not fulfilling criteria for multiple sclerosis	0.1 (0.04, 0.3)		
Cauda equina lesion	0.1 (0.02, 0.4)		
Dystonia primary	0.1 (0.02, 0.4)	0.3	Nutt *et al.*, 1988
secondary	0.1 (0.03, 0.3)		
Idiopathic intracranial hypertension	0.1 (0.02, 0.3)		
Intrinsic myelopathy	0.1 (0.02, 0.3)	0.06	Foster, 1980
		Syrinx 0.07	Kurtzke, 1984
Spinal cord injury	0.1 (0.02, 0.3)	0.8	cit. in Kraus *et al.*, 1975 & 1978
		0.5	Kurtzke, 1984
Narcolepsy	0.1 (0.02, 0.3)		
Motor neuron disease	0.1 (0.01, 0.3)	0.04-0.1	Kurtzke, 1984
		0.06	Langton Hewer, 1993
Aqueduct stenosis and hydrocephalus in adults	0.1 (0.01, 0.3)		
HTLV-1 myelopathy	0.04 (0, 0.2)		
Transient global amnesia	0.04 (0, 0.2)		

Table 32. The lifetime prevalence of less common PNS disorders

Conditions	NHNN-Linkage lifetime PR (with 95%CL)/1,000	Previous reported prevalence rates/1,000	
Leg mononeuropathy - all	1 (0.8, 2)		
Arm mononeuropathy - all excluding carpal tunnel syndrome	0.7 (0.5, 1)		
Trigeminal neuralgia	0.7 (0.4, 1)	0.4	Kurtzke, 1984; Langton Hewer, 1993
Post-herpetic neuralgia	0.7 (0.4, 1)		
Muscular dystrophies	0.4 (0.2, 0.7)	0.02-0.05	Langton Hewer, 1993
		0.6	Kurtzke, 1984
Myasthenia gravis	0.4 (0.2, 0.7)	0.04 - 0.1	Kurtzke, 1984; Langton Hewer, 1993
		0.08	Christensen *et al.*, 1993
		0.1 (0.08, 0.2)	Aiello *et al.*, 1997
		0.4	Kurtzke, 1978
Eye movement disorders	0.3 (0.2, 0.7)		
Brachial neuritis	0.3 (0.1, 0.6)		
Guillain-Barré syndrome	0.2 (0.08, 0.5)	0.08	Langton Hewer, 1993
Horner's syndrome	0.2 (0.04, 0.4)		
Other mononeuropathy	0.1 (0.04, 0.3)		
Pupillary abnormalities	0.08 (0.01, 0.3)		
Sacral plexitis / plexopathy	0.04 (0, 0.2)		

The age- and sex-specific incidence rates for first cerebrovascular episode are given below with age-specific incidence rates for epilepsy, single seizures and Parkinson's disease (Table 33).

No correlation between socio-economic deprivation at a practice level (using Jarman score) and incidence or prevalence of commonn neurological conditions was significant.

3.1.4 Quality control

During the complete notes search carried out with the medical students (see page 106), 97% of the general practice Lloyd George notes were examined. The check for false negatives, after a search of the complete notes uncovered three missed cases among 1,655 notes searched, gave a false-negative rate of 0.2%. The check for false negatives in the lifetime prevalence subpopulation uncovered six missed cases in the search of the complete notes, among 719 notes searched; this gave a false-negative rate of 0.8%.

Table 33. Age-specific incidence rates for stroke, epilepsy and Parkinson's disease

Incidence Rates /100,000 per annum by age band adjusted to UK population					
Age band	**First stroke**		**Epilepsy**	**Single seizures**	**Parkinson's disease**
(years)	Men	Women	M&F	M&F	M&F
0-4			86	32	
5-9			46	12	
10-14			94		
15-19			52		
20-24			33	16	
25-29			19	19	
30-34			24	5	
35-39			54	14	
40-44	35	82	18	9	
45-49	194		50	10	20
50-54	240	167	50		
55-59	560	203	31	15	
60-64	1051	629	34	34	50
65-69	817	940	37		37
70-74	850	926	142		222
75-79	972	1271	50	25	100
80-84	806	890	32		
85-89	299	757	29	29	116
>90					
>40	467	446			

3.2 NGPSE - the prognosis of febrile convulsions

3.2.1 Demographics and features of FCs

Of patients with FCs, 220 were recruited: 13 (6%) were lost to follow-up before 1990, six because of emigration; another five (2%) were lost in 1994 or 1995; and the remaining 202 were followed to 1996 or beyond. Median follow-up was 11.2 years (25th, 75th centiles: 10.3, 11.9). None of those remaining in the UK died during the follow-up period. Median age at first FC was 1.6 years (25th, 75th centiles: 1.2, 2.4 years). There was an excess of boys (60%). Of the 220 children, six (3%) had identified pre-existing neurological problems, and a further 20 (9%) developed problems after their first FC. The distribution and features of the FCs are shown in Table 34 and Table 35.

Table 34. Distribution of FCs

number of FCs	Patients *n*	%
1	132	60
2	30	14
3	30	14
4	9	4
5-9	14	6
≥10	5	2

Table 35. Features of first and subsequent FCs

First FC	Subsequent FCs				Total
	None	Simple	Prolonged	Repeated	
Simple	122(1)	48(9)	4(1)	3	177(11)
Focal	1				1
Prolonged	8(1)	9(6)			17(7)
Repeated		17(3)		2(1)	19(4)
Combination	1	5(2)			6(2)
Total	132(2)	79(20)	4(1)	5(1)	220(24)

Number treated with AEDs in parentheses.

3.2.2 Sequelae of FC

Twelve (6%) developed epilepsy and two others had seizures (one of whom is currently under investigation for possible epilepsy; the other had two seizures over 24 h on stopping the sodium valproate given for FC). Of the 12 who developed epilepsy,

five had focal and three generalised epilepsy; four remain unclassified. Of those 14 cases who developed unprovoked seizures, five occurred in the 43 children who had had a complex FC. Of the 12 who developed epilepsy, three had other problems: two children with learning difficulties and one with cerebral palsy had focal epilepsy.

Twenty children subsequently developed neurodevelopmental delay or abnormalities; ten developed a clear neurological deficit: five learning difficulties, one moderate dyspraxia, one clumsiness with abnormal behaviour, one mild cerebral palsy, one severe general delay and one mild delay. Six were referred to psychologists for behavioural disturbance and four for speech therapy. Of those developing learning difficulties, two subsequently returned to "normal" schooling after special education. Of 43 who had had complex features, 10 required special education compared with 10 of 177 who had only simple FCs.

Twenty-four (11%) received regular antiepileptic medication. Sodium valproate was the drug most frequently prescribed – to 17 children; phenobarbital was prescribed to five children and phenytoin to two; one child received first sodium valproate then phenobarbital. No child who was prescribed an AED and did not subsequently develop epilepsy is still on that treatment.

Twelve children were diagnosed with epilepsy during follow-up, giving cumulative percentages (95%CL) of 1.4% (0, 2.9) by 2 years, 3.3% (0.9, 5.7) by 5 years and 5.2% (2.2, 8.3) by 10 years. The percentage at maximum follow-up (12.9 years) was 5.9% (2.6, 9.2). ORs for the development of neurological abnormalities after the first FC, and hazard ratios (HRs) for the development of epilepsy estimated from univariate analysis, are reported together with frequencies for several demographic characteristics and clinical features (Table 36 - see over).

Totals of 22 children with new neurological abnormalities, and only 12 with epilepsy, mean that confidence intervals for summary statistics are wide, and consequently it is possible to reach only limited conclusions. A complex first FC was associated with subsequent neurological abnormality ($F = 11$, d.f. = 1, 218, $p < 0.001$).

Table 36. Odds (OR) and hazards ratios (HR) for the development of neurological deficit or epilepsy after febrile convulsion

Characteristics	Neurological deficit			Epilepsy		
	number		OR	number		HR
	No	Yes		No	Yes	
Sex						
Boys	118	15	1.0	127	6	1.0
Girls	82	5	0.48 (0.16, 1.38)	81	6	1.49 (0.48, 4.62)
Age at 1st FC						
<18 months	91	8	1.0	93	6	1.0
>18 months	109	12	1.25 (0.49, 3.21)	115	6	0.82 (0.26, 2.54)
<3y	168	18		175	11	1.0
>3y	32	2	0.58 (0.13, 2.66)	33	1	0.52 (0.07, 4.01)
Neurological abnormality prior to 1st FC						
No	194	20		203	11	1.0
Yes	6	0		5	1	3.48 (0.45, 27.0)
1st FC						
Simple	167	10	1.0	167	10	1.0
Complex	33	10	5.1 (1.9, 13.2)	41	2	0.82 (0.18, 3.75)

Figures in parentheses are 95% CL.

Two distinct cut-off points for age, at 18 months and 3 years respectively, were examined (Table 36). An alternative analysis with age (logarithmically transformed) treated as a continuous variable did not yield a significant result. A multivariate model including age and the other three features shown in Table 37 confirmed the association between complex first FC and subsequent neurological abnormality (OR = 6.8). A multivariate model, including age, sex and type of first FC, confirmed the association between complex first FC and subsequent neurological abnormality (OR = 4.6 (1.7, 12.2).

Actuarial analyses for the development of epilepsy using the Cox model were also undertaken with time-dependent co-variates, to assess the effect of subsequent FCs (after the first). By contrast to analyses that use baseline (or fixed) co-variates, which remain static throughout the follow-up period, those with time-dependent co-variates allow for changes during follow-up. Although they provide an estimate of the effect of subsequent FCs on the risk of epilepsy, they are more difficult to use for predictive purposes than the standard Cox model with fixed co-variates, because of uncertainty in predicting changes to the time-dependent co-variates themselves.

Table 37. Odds ratios (OR, 95%CL in parentheses) for the development of epilepsy after febrile convulsions with specific features and associations between these features and neurological deficit

Epilepsy: Features of FC	Yes	No	OR (95%CL)	*p*
Focal ever*	0	6	1.3 (0.05, 31)	0.89
Repeated ever	2	23	1.6 (0.3, 10.1)	0.61
Prolonged ever	1	25	0.7 (0.1, 4.0)	0.66
Any complex feature	3	47	1.1 (0.3, 4.6)	0.85
Two or more complex features*	0	6	1.3 (0.05, 31)	0.89
Complex features with >1 FC	2	1	41.4 (0.2, 6252)	0.15
Abnormal prior to FC	1	5	3.7 (0.1, 132)	0.47
Four or more fcs	6	20	9.4 (1.5, 57)	0.015
Neurological deficit:	**Yes**	**No**		
Focal ever	2	4	5.4 (0.3, 92)	0.24
Repeated ever	6	19	4.1 (0.9, 18)	0.057
Prolonged ever	7	19	5.1 (1.2, 22)	0.024
Any complex feature	11	39	5.1 (1.7, 15)	0.0038
Two or more complex features	3	3	11.6 (0.7, 19.5)	0.089
Complex features with >1 FC	1	2	5.2 (0.1, 274)	0.41
Four or more FCs	6	20	3.9 (0.9, 161)	0.063

*0.5 added to each cell for calculation of odds ratio to eliminate zero count.

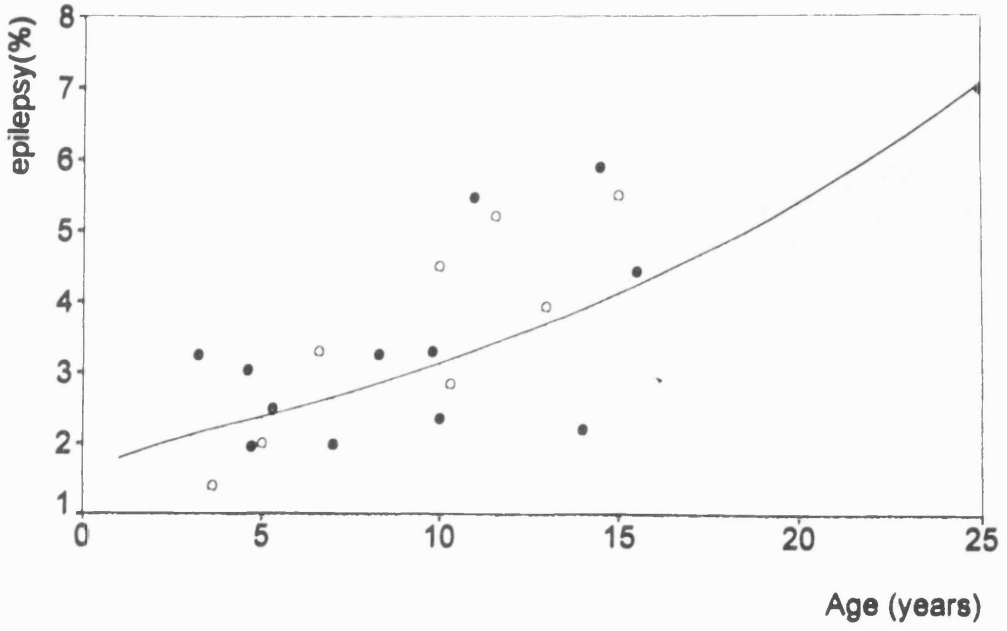
One time-dependent co-variate set to zero from the start of follow-up, with an increment of one at the time of a second FC, suggested an increased risk of epilepsy (hazard ratio, HR = 19.2 [2.48, 148.8]) after recurrence. An alternative analysis with the time-dependent co-variate increased by one with each subsequent FC (up to a maximum of 4) supported this (HR = 2.48 [1.68, 3.65]; the inclusion of a second, squared term suggested that the risk attenuated after 5 FCs. However, as this represents extrapolation beyond those included in the analysis (up to the fourth FC), and because the number of patients experiencing more than three FCs is small, this conclusion must be interpreted cautiously. Inclusion of the four baseline co-variates (age at first FC, sex, prior neurological abnormality, complex first seizure) with the time-dependent ones gave a slight emphasis to the effect of the latter. The addition of a further time-dependent co-variate to code for treatment with AEDs (increased from zero to one on starting, and the reverse on stopping) slightly reduced the effect.

3.2.3 Analysis of studies examining chance of developing epilepsy post-FC

Altogether we identified 17 cohort studies (including the NGPSE), we excluded four because of uncertainty about inclusion (particularly whether those who had experienced afebrile seizures before the first FC were excluded), recruitment (whether first FC only, and whether hospital or community based) or duration of follow-up (Faxén, 1935; Millichap, 1968; Livingston, 1972; Stanhope *et al.*, 1972). For the remaining 13 studies, the figure shows the percentage that developed for epilepsy plotted against mean (or median) age at last available follow-up (using asterisks) (Herlitz, 1941; Friderichsen *et al.*, 1954; Frantzen *et al.*, 1968; van den Berg *et al.*, 1969; Nelson *et al.*, 1976; Heijbel *et al.*, 1980; Ross *et al.*, 1980; Annegers *et al.*, 1987; Verity *et al.*, 1991; Berg *et al.*, 1996b; Knudsen *et al.*, 1996; Forsgren *et al.*, 1997). The last available follow-up was determined either as reported or by summing the reported mean age of onset of the first FC and the mean period of follow-up. The curve determined by logistic regression, fitted to these points, is also shown. Further estimates reported in some studies (Friderichsen *et al.*, 1954; Annegers *et al.*, 1987) are shown by open circles. The figure shows a dearth of results between the ages of 15 and 25 years; it also shows variation between studies (expected from variation between important factors) and, as expected, an increase with age, suggesting overall percentages of 2.4, 3.1, 4.1, 5.4 and 7.1% with epilepsy by 5, 10, 15, 20 and 25 years of age respectively. (As shown in Figure 1).

A further overview, pooling data from six studies that report the type of first FC, is shown in Figure 2. The NGPSE is the only study with a point estimate of the OR of less than one for epilepsy after a complex, as opposed to a simple, first FC. However, there is no evidence of heterogeneity between studies ($\chi^2 = 5.15$, d.f. = 5, $p = 0.40$), and the overall OR (random effects model) of 3.4 (CL = 2.1, 5.4) suggests a substantial increase in the risk of epilepsy after a complex first FC.

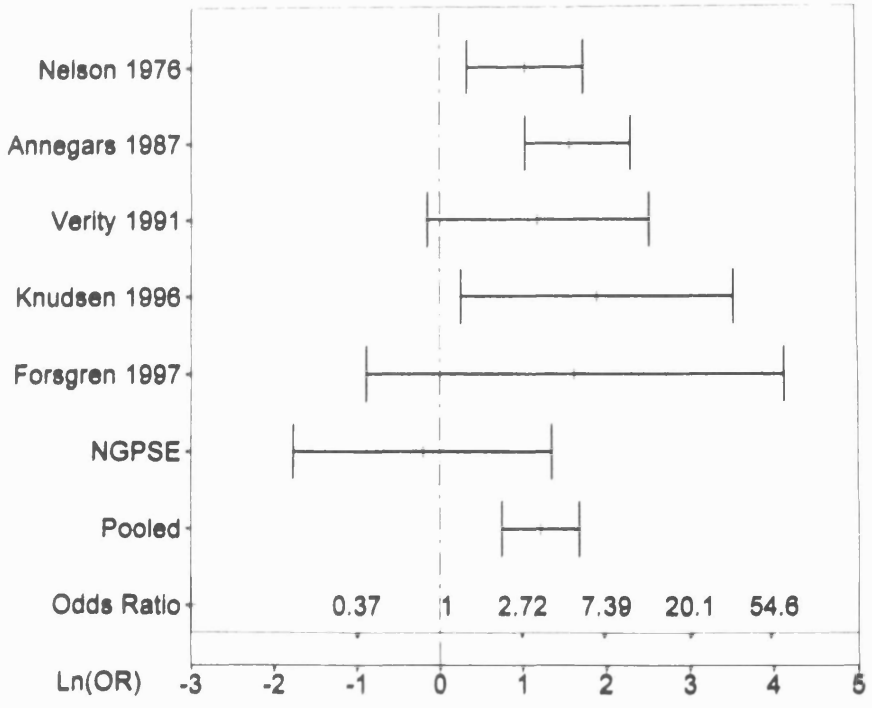
Figure 1 The percentage of children developing epilepsy against age attained in 17 studies.



●: latest available estimate with fitted logistic regression.

o: intermediate estimates

Figure 2. Odds ratios and 95%CL for development of epilepsy after a first complex vs a simple febrile convulsion.



3.3 NGPSE:- Results of remission analysis and Cox analysis of factors affecting the long-term prognosis for remission in definite and probable epilepsy

Seven hundred and ninety-two patients with definite or probable epilepsy were recruited: 70, among whom there were 66 deaths, were followed for less than one year from index seizure; 29 (of whom 24 deaths) for 1–2 years; 39 (of whom 17 deaths) and 21 (of whom 17 deaths) for 3–4 years; 12 (of whom 10 deaths) for 4–5 years; 33 (of whom 8 deaths) for 5–6 years; 159 (of whom 4 deaths) for 6–7 years; 180 (of whom 2 deaths) for 7–8 years; and 249 (of whom 2 deaths) for longer. Only 33 patients were completely lost to follow-up during this period.

The rate of patients entering cumulative remission or in terminal remission is given for patients with definite and probable epilepsy in Table 38, Table 39, Table 40 and Table 41.

These remission rates are also given after exclusion of single and acute symptomatic seizures (Table 42). Tables of remission for patients with definite epilepsy are given according to a broad aetiology (excluding congenital abnormality in which the numbers were too small for meaningful analysis) and by age band (Table 43, Table 44 and Table 45, respectively).

Table 38. Years of cumulative remission from index seizure for patients with definite epilepsy

	Follow-up from index seizure (years)								
Remission of epilepsy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1 year									
Percentage remission (CI)	54 (49, 58)	79 (75, 83)	86 (83, 90)	90 (87, 93)	92 (89, 95)	94 (91, 96)	94 (92, 97)	95 (92, 97)	95 (93, 98)
No at risk	564	238	101	62	44	34	27	18	13
2 years									
Percentage remission (CI)		47 (43, 52)	68 (64, 73)	78 (73, 82)	82 (78, 86)	86 (82, 92)	88 (85, 92)	91 (87, 94)	93(89, 97)
No at risk		564	259	149	102	79	58	39	25
3 years									
Percentage remission (CI)			44 (39, 49)	61 (57, 66)	68 (64, 73)	74 (69, 78)	78 (74, 83)	83 (79, 87)	86 (81, 91)
No at risk			564	265	177	141	111	73	39
5 years									
Percentage remission (CI)					40 (35, 40)	54 (49, 59)	60 (55, 65)	63 (58, 69)	68 (61, 75)
No at risk					564	271	195	125	65

Table 39. Years of cumulative remission from index seizure for definite and probable epilepsy

	Follow-up from index seizure (years)								
Remission of epilepsy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1 year									
Percentage remission (CI)	58 (54, 62)	82 (79, 85)	88 (84, 89)	91 (91, 95)	93 (91, 95)	94 (91, 96)	95 (93, 97)	95 (93, 98)	96 (94, 98)
No at risk	792	302	123	75	54	44	37	22	15
2 years									
Percentage remission (CI)		53 (48, 56)	71 (67, 75)	88 (77, 83)	84 (81, 87)	87 (84, 90)	89 (86, 92)	91 (88, 93)	93 (90, 96)
No at risk		792	328	188	128	101	75	50	29
3 years									
Percentage remission (CI)			49 (45, 53)	65 (61, 69)	72 (68, 75)	77 (73, 80)	81 (77, 84)	85 (81, 88)	87 (83, 91)
No at risk			792	334	223	176	137	87	44
5 years									
Percentage remission (CI)					44 (40, 48)	57 (53, 62)	62 (58, 67)	66 (61, 70)	71 (65, 77)
No at risk					792	348	250	157	80

Table 40. Terminal remission rates for one to five years from index seizure for definite epilepsy

	Follow-up from index seizure (years)								
Remission of epilepsy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1 year									
Percentage remission (CI)	54 (49, 58)	70 (66, 74)	73 (69, 77)	76 (72, 80)	79 (74, 83)	84 (80, 87)	80 (76, 85)	83 (78, 88)	84 (77, 91)
No at risk	544	505	486	470	456	441	377	255	127
2 years									
Percentage remission (CI)		47 43(52,)	63 (58, 67)	66 (61, 71)	68 (63, 73)	75 (71, 80)	74 (69, 79)	73 (68, 79)	76 (69, 82)
No at risk		541	499	481	465	447	394	324	203
3 years									
Percentage remission (CI)			44 (39, 49)	58 (53, 62)	61 (56, 66)	65 (61, 70)	66 (61, 71)	68 (62, 73)	68 (62, 74)
No at risk			537	496	478	458	405	343	280
5 years									
Percentage remission (CI)					40 (35, 45)	53 (48, 58)	53 (48, 58)	53 (47, 58)	54 (48, 60)
No at risk					533	487	438	381	320

Table 41. Years of cumulative remission from first seizure for definite epilepsy

	Follow-up from index seizure (years)								
Remission of epilepsy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1 year									
Percentage remission (CI)	41 (37, 46)	74 (77, 78)	82 (79, 86)	87 (84, 90)	90 (87, 93)	92 (89, 94)	92 (90, 95)	94 (92, 96)	95 (92, 97)
No at risk	564	303	125	83	60	45	37	29	18
2 years									
Percentage remission (CI)		34 (29, 38)	61 (56, 65)	73 (68, 77)	79 (74, 82)	83 (79, 87)	85 (82, 89)	87 (84, 90)	90 (86, 93)
No at risk		564	328	192	129	97	75	54	40
3 years									
Percentage remission (CI)			30 (26, 35)	53 (48, 58)	63 (58, 67)	70 (66, 77)	76 (71, 80)	80 (76, 84)	83 (78, 87)
No at risk			564	338	222	169	132	88	54
5 years									
Percentage remission (CI)					26 (22, 30)	44 (39, 49)	53 (48, 58)	59 (54, 64)	64 (59, 70)
No at risk					564	339	252	173	112

Table 42. One- to five-year cumulative remission from index seizure for patients with definite epilepsy excluding single seizures and acute symptomatic seizures

	Follow-up from index seizure (years)								
Remission of epilepsy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1 year									
Percentage remission (CI)	40 (35, 45)	73 (68, 78)	83 (78, 87)	88 (84, 91)	90 (86, 94)	92 (89, 96)	93 (89, 96)	93 (90, 96)	93 (90, 96)
No at risk	397	223	95	57	40	32	25	15	15
2 years									
Percentage remission (CI)		33 (27, 38)	60 (54, 65)	72 (66, 77)	78 (73, 83)	82 (78, 87)	85 (81, 90)	88 (84, 92)	91 (87, 96)
No at risk		397	242	138	93	71	53	35	23
3 years									
Percentage remission (CI)			29 (24, 34)	51 (45, 56)	60 (54, 65)	67 (61, 72)	72 (67, 77)	78 (72, 83)	82 (76, 87)
No at risk			397	246	164	130	102	67	38
5 years									
Percentage remission (CI)					24 (19, 29)	42 (37, 48)	49 (43, 55)	54 (47, 60)	60 (52, 68)
No at risk					397	251	180	115	64

Table 43. Cumulative remission from index seizure for patients with definite epilepsy stratified by broad aetiology

	Follow-up from index seizure (years)						
Three-year remission	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Idiopathic							
Percentage remission (CI)	41 (36, 47)	61 (55, 67)	68 (63, 74)	75 (62, 79)	78 (73, 83)	83 (78, 88)	86 (81, 92)
No at risk	345	190	124	100	79	51	29
Remote symptomatic							
Percentage remission (CI)	38 (26, 49)	48 (36, 60)	59 (47, 71)	66 (54, 78)	69 (57, 80)	75 (62, 87)	75 (62, 87)
No at risk	119	45	34	23	19	14	14
Acute symptomatic							
Percentage remission (CI)	70 (59, 82)	78 (68, 89)	83 (73, 92)	86 (77, 95)	91 (83, 98)	93 (85, 100)	93 (85, 100)
No at risk	83	19	13	11	9	6	3
Five- year remission							
Idiopathic							
Percentage remission (CI)			37 (31, 42)	53 (47, 59)	58 (52, 64)	62 (56, 68)	69 (60, 77)
No at risk			346	200	142	90	50
Remote symptomatic							
Percentage remission (CI)			34 (21, 46)	46 (33, 59)	54 (40, 67)	61 (46, 75)	61 (46, 75)
No at risk			119	39	31	22	10
Acute symptomatic							
Percentage remission (CI)			68 (56, 80)	74 (63, 86)	78 (67, 89)	78 (67, 89)	78 (67, 89)
No at risk			83	20	15	11	11

Table 44. Cumulative three-year remission from index seizure for patients with definite epilepsy stratified by age at index

	Follow-up from index seizure (years)						
Age (years)	**3**	**4**	**5**	**6**	**7**	**8**	**9**
<16							
Percentage remission (CI)	35 (26, 43)	53 (44, 62)	64 (56, 72)	70 (62, 78)	73 (65, 80)	82 (74, 89)	85 (77, 93)
No at risk	148	95	68	51	43	33	18
16-39							
Percentage remission (CI)	47 (39, 55)	64 (57, 71)	68 (61, 75)	73 (66, 80)	79 (73, 86)	81 (74, 87)	82 (75, 89)
No at risk	193	97	65	58	46	28	18
40-59							
Percentage remission (CI)	64 (52, 75)	77 (66, 87)	81 (72, 90)	84 (75, 93)	87 (78, 96)	90 (81, 99)	90 (81, 99)
No at risk	87	25	16	13	11	5	3
60+							
Percentage remission (CI)	38 (27, 50)	57 (45, 68)	66 (55, 78)	75 (64, 86)	80 (69, 90)	85 (73, 97)	92 (80, 100)
No at risk	136	48	29	19	13	9	3

Table 45. Cumulative five-year remission from index seizure for patients with definite epilepsy stratified by age at index seizure

Age (years)	Follow-up from index seizure (years)				
	5	6	7	8	9
<16					
Percentage remission (CI)	30 (22, 37)	45 (37, 54)	53 (44, 62)	57 (48, 66)	57 (48, 66)
No at risk	148	100	75	50	34
16-39					
Percentage remission (CI)	43 (35, 50)	57 (49, 65)	61 (53, 69)	63 (55, 71)	73 (61, 84)
No at risk	193	104	74	52	28
40-59					
Percentage remission (CI)	53 (40, 65)	66 (54, 78)	71 (59, 83)	75 (52, 88)	83 (67, 99)
No at risk	87	31	21	11	6
60+					
Percentage remission (CI)	40 (27, 52)	55 (42, 68)	61 (48, 74)	67 (51, 83)	67 (51, 83)
No at risk	136	36	26	20	5

Of the 792 patients with definite or possible epileptic seizures who were recruited (Table 46), 45 were censored[4], either because they died or were lost to follow-up within the first 6 months; they are excluded from this analysis. Of the 747 remaining, 107 died, 2 were censored within 1 year, and 46 within the next 4 years of follow-up; 527 patients were followed up to at least 1993. The 747 in this analysis have been followed prospectively for up to 9.5 years [median (25th, 75th centiles); 6.6 (5.6, 7.6) years] from the 6-month assessment. Further details of the patients are shown (see Table 46 to Table 49).

Table 46. Cases in the NGPSE

	Definite	Probable	Total
Total	564	228	792
Died within 6m of index	34	9	43
Lost within 6m of index	0	2	2
Available for analysis 6m post index	530	217	747
Died within the next year	29	9	38
Censored within the next year	1	1	2
At least 1-year further follow-up	500	207	707
Died within the next 4 years	42	13	55
Censored within the next 4 years	18	28	46
At least 5-year follow-up	440	166	606
Died before 31/12/93	9	5	14
Censored in 1991/92	3	1	4
Censored in 1992	43	18	61
Censored in 1993	377	139	516
Followed beyond 1993	8	3	11

[4] "Censored" is the technical term used in Cox analysis to describe data from patients whose follow-up ended before the event of interest (in this case remission) and the end of the study.

Table 47. Characteristics of patients with definite and probable epilepsy in remission analysis

Characteristic	Classification at 6 months post-index seizure		
	Definite	Probable	Total
Sex - M	275	91	366
F	255	126	381
Age at first seizure (years)			
<1	14	12	26
1-4	35	27	62
5-9	50	11	61
10-14	53	24	77
15-19	63	23	86
20-29	66	26	92
30-39	58	16	74
40-49	40	15	55
50-59	47	17	64
60-69	46	16	62
70-79	38	16	54
80-	20	14	34
Median (25th, 75th)	26 (13, 54)	25 (11, 55)	26 (12, 54)
Age at index seizure (years)			
<1	8	9	17
1-4	31	26	57
5-9	51	12	63
10-14	48	23	71
15-19	65	20	85
20-29	72	27	99
30-39	61	21	82
40-49	34	12	46
50-59	47	17	64
60-69	53	15	68
70-79	36	18	54
80-89	19	14	33
90-	5	3	8
Median (25th, 75th)	28 (14, 56)	27 (12, 56)	27 (14, 56)

Table 48. Characteristics of patients with definite or probable epilepsy in remission analysis - numbers of seizures

Number of seizures before index seizure	Classification at six months post-index seizure		
	Definite	**Probable**	**Total**
0	228	103	331
1	133	43	176
2	48	19	67
3	27	9	36
4	15	5	20
5	11	4	15
6	8	4	12
7	1	2	3
8	2	3	5
9	5	-	5
10	11	5	16
>10	41	20	61
Number of seizures from index to 6 months post-index seizure			
1	329	163	492
2	69	11	80
3	33	11	44
4	20	5	25
5	8	2	10
6	8	1	9
7	10	6	16
8	2	1	3
9	1	2	3
10	4	4	8
>10	46	11	57
Total number of seizures before 6 months post-index seizure			
1	164	82	246
2	107	41	148
3	61	20	81
4	35	13	48
5	24	6	30
6	19	4	23
7	11	6	17
8	8	2	10
9	5	6	11
10	5	3	8
>10 (but <11 both before and after index)	16	7	23
>10 before index and <11 after	29	16	45
<11 before index and >10 after	34	7	41
>10 both before and after index	12	4	16

Table 49. Characteristics of patients with definite or probable epilepsy in remission analysis - interval from first to index seizure

Interval from first seizure to index	Classification at 6 months post-index seizure		
(weeks)	**Definite**	**Probable**	**Total**
0 (index = first)	228	103	331
< 1	6	1	7
1-4	32	13	45
5-12	57	15	72
13-25	57	13	70
26-51	38	20	58
(years)			
1-2	35	18	53
2-5	42	20	62
5-10	20	6	26
10-20	12	6	18
>20	3	2	5
Median in weeks (25th, 75th) - excluding index = first seizure	26 (10,104)	47 (12,126)	32 (10,104)

Those whose follow-up from the index seizure is less than 18 months (5.5 years) contribute to the analysis, but are censored before they could have entered into 1-year (5-year) remission. Hazard ratios and 95% confidence limits for achievement of 1- and 5-year remission using univariate and multivariate analysis are shown in Table 50 and Table 51; hazard ratios of less than 1.0 imply a reduced chance of achieving remission. Results for 2- and 3-year remission were similar but are not shown for the sake of clarity.

Table 50. Variables and hazards ratios for 1- and 5-year remission using univariate and multivariate analysis

Characteristic	Number (%) at index[a]	Percent completing 1 year [b]	Hazards ratios (95%CL) For achieving 1-year remission Univariate[b]	Multivariate[b]	completing 5 years	For achieving 5-year remission Univariate[b]	Multivariate[b]
No. available for analysis	747	707			606		
1.Female sex	381(51)	(52)	0.96(0.81,1.12)	1.00(0.84,1.19)	(51)	1.13(0.91,1.40)	1.26(1.00,1.57)*
Age at first seizure (years)							
2. 0 - <4	75 (10)	(11)			(11)		
3. 4 - <16	165(22)	(23)	1.05(0.87,1.27)	1.13(0.90,1.40)	(25)	0.89(0.69,1.14)	0.94(0.71,1.25)
4. 40 - <50	55(7)	(8)	1.06(0.79,1.42)	1.10(0.80,1.50)	(7)	1.07(0.73,1.55)	0.97(0.65,1.44)
5. >50	214(29)	(25)	1.09(0.91,1.30)	1.22(0.97,1.53)	(21)	1.12(0.88,1.44)	1.07(0.78,1.45)
Number of seizures							
6. Before index (log)			0.71(0.56,0.90)**	0.82(0.53,1.28)		0.69(0.49,0.95)*	0.62(0.32,1.18)
7. From index to 6 months (log)			0.33(0.25,0.44)***	0.40(0.27,0.57)***		0.29(0.19,0.45)***	0.22(0.12,0.40)***
8. Total (log)			0.53(0.43,0.66)***			0.48(0.36,0.64)***	
9. >10 before index	61(8.2)	(8.1)	0.93(0.69,1.26)	1.24(0.80,1.91)	(7.6)	1.14(0.77,1.68)	1.92(1.06,3.47)*
10. >10 from index to 6 months	57(7.6)	(7.6)	0.36(0.24,0.53)***	0.64(0.37,1.10)	(7.6)	0.49(0.29,0.82)**	1.67(0.74,3.76)
11. Both >10 before index and>10 from index to 6 months	16(2.1)	(2.1)	0.58(0.29,1.17)	1.42(0.58,3.47)	(2.1)	0.68(0.25,1.83)	0.99(0.29,3.41)
12. Weeks from 1st seizure to 6 months (log)			0.93(0.84,1.02)	1.01(0.88,1.15)		0.89(0.79,1.01)	0.98(0.81,1.18)
13. Seizures /week before index (log)			1.04(0.92,1.17)			1.11(0.95,1.29)	

a number (and percentage) of patients in group at 6 months, 1-year and 5-y,ears where relevant.
b Hazard ratios from analysis restricted to subjects with onset at age 5 years or over.

* $p< 0.05$; ** $p< 0.01$; *** $p<0.001$

Table 51. continuation of Table 49 Variables and hazards ratios for 1- and 5-year remission using univariate and multivariate analysis

Characteristic	Number (%) at index[a]	Percent completing 1 year [b]	Hazards ratios (95%CL) For achieving 1-year remission Univariate[b]	Multivariate[b]	completing 5 years	For achieving 5-year remission Univariate[b]	Multivariate[b]
Aetiology (definite & probable epilepsy)							
14. Cryptogenic	489(65)	(68)	0.97(0.81,1.16)	0.89(0.65,1.21)	(72)	0.88(0.69,1.10)	0.75(0.47,1.18)
15. Vascular	92(12)	(10)	0.95(0.74,1.23)	0.71(0.43,1.17)	(7.8)	1.11(0.77,1.60)	0.84(0.43,1.62)
16. Alcohol	38(5.1)	(5.4)	1.05(0.75,1.48)	0.73(0.44,1.22)	(5.9)	1.14(0.76,1.71)	0.73(0.39,1.34)
17. Tumor	22(3.0)	(1.6)	0.73(0.38,1.41)	0.63(0.27,1.43)	(1.2)	0.54(0.17,1.68)	0.51(0.13,1.90)
18. Post-traumatic/ infection	28(3.8)	(4.0)	1.08(0.71,1.64)	0.76(0.43,1.37)	(4.3)	0.96(0.55,1.67)	0.57(0.27,1.19)
Classification (pre-ILAE)							
19. No identified etiology	342(46)	(48)	0.93(0.79,1.10)	1.36(0.49,3.76)	(51)	0.87(0.70,1.08)	4.33(0.57,32.9)
20. Remote symptomatic	98(13)	(11)	0.86(0.67,1.11)	1.47(0.49,4.37)	(9.7)	0.84(0.59,1.21)	3.70(0.46,29.5)
21. Acute symptomatic	74(9.9)	(9.8)	1.24(0.96,1.61)	1.70(0.57,5.03)	(9.9)	1.45(1.06,1.98)*	5.34(0.69,41.3)
22. Perinatal neurological dysfunction	16(2.1)	(2.3)	0.65(0.24,1.75)		(2.0)	0.31(0.04,2.22)	
23. Probable not definite epilepsy	217(29)	(29)	1.09(0.91,1.31)	1.19(0.41,3.43)	(29)	1.10(0.86,1.41)	3.31(0.41,26.2)
Seizure type at index							
24. Primary tonic-clonic	195(26)	(26)	1.11(0.92,1.33)	0.85(0.60,1.19)	(28)	1.00(0.79,1.26)	0.74(0.49,1.12)
25. Any partial	264(35)	(35)	0.88(0.74,1.04)		(34)	0.90(0.71,1.12)	
26. Pure partial only	73(9.8)	(9.8)	0.94(0.72,1.23)	0.89(0.60,1.32)	(9.1)	0.92(0.63,1.34)	0.90(0.53,1.51)
27. Secondarily generalised	191(26)	(25)	0.88(0.73,1.06)	0.85(0.60,1.18)	(25)	0.91(0.71,1.16)	0.84(0.55,1.28)
28. Primary or secondarily generalised	386(52)	(51)	0.99(0.83,1.16)		(54)	0.93(0.75,1.15)	

a number (and percentage) of patients in group at 6 months, 1-year and 5-y,ears where relevant.
b Hazard ratios from analysis restricted to subjects with onset at age 5 years or over.

* $p< 0.05$; ** $p< 0.01$; *** $p<0.001$

Initial exploratory analyses identified complex interactions between age of onset below 4 years, number of seizures from index seizure to 6 months, and classification into definite and probable epilepsy (variables 2, 7 and 23 in Table 50 and Table 51) for 1-year ($p = 0.023$), 2-year ($p = 0.040$) and 3-year ($p = 0.004$) remission. For 3-year remission, there was an additional interaction ($p = 0.006$) between age of onset below 4 years, number of seizures from index to 6 months and the occurrence of secondarily generalised seizures (variables 2, 7 and 27 in Table 50 and

Table 51). For 5-year remission, a less powerful end-point as a result of fewer "events", the only interactions ($p = 0.029$) involved age at onset below 4 years and the occurrence of secondarily generalised seizures (variables 2 and 27). [These results suggested reduced chances of achieving remission in patients with definite epilepsy who have onset before the age of 4 years, but enhanced achievement of remission in those with only possible epilepsy with onset before 4 years by comparison with other groups. The most careful solution to the problem of these interactions, all of which involved onset below 4 years, was simply to exclude this group.] Accordingly, to ensure elimination of the heterogeneity associated with this young-onset group, further analyses were restricted to those with age of onset at 5 years and over. In practice, this restriction has comparatively little influence on the results presented, other than widening the confidence intervals on the hazard ratios. Restriction of the analysis to those with onset at age 5 and over eliminated all interactions that were significant at $p = 0.05$.

A separate limited analysis was performed in the group with age of onset at less than 5 years. Hazard ratios and 95% confidence limits for achievement of 1- and 5-year remission using univariate and multivariable analysis are shown in Table 50 and Table 51; hazard ratios less than 1.0 imply a reduced chance of achieving remission. Results for 2- and 3-year remission (not shown) were similar. The graph of the Cox model is given in Figure 3 and the values tabulated in Table 52.

Figure 3. The percentage achieving remission for patients with onset at age 5 years or over who had experienced one, two, five and ten seizures from index seizure to 6 months

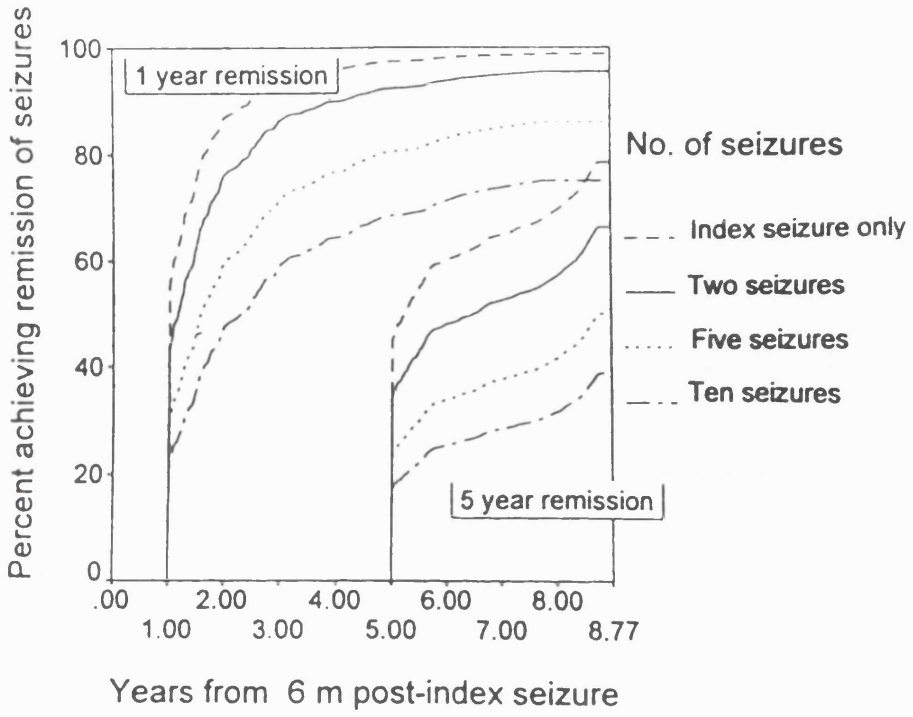


Table 52. The chances of achieving 1- or 5-year remission over time as a function of the number of seizures between index and six months

Number of seizures between index and 6 months	Percentage achieving one year remission				Percentage achieving five year remission			
	Index only	2 or 3	4 to 9	≥10	Index only	2 or 3	4 to 9	≥10
Years from index seizure								
1	56	44	31	24				
2	87	77	61	50				
3	94	87	74	62				
4	96	91	79	67				
5	97	93	82	71	46	35	23	16
6	98	94	85	74	61	48	33	24
7					65	52	36	27
8					70	56	40	30
9					80	67	49	38

Discussion

4.1 The incidence and lifetime prevalence of neurological disorders in the general population

In the general population, 0.6% have had a neurological condition diagnosed in the last year and 6% have had a neurological condition in their lifetime. The incidence and lifetime prevalence rates for an urban community have been described (see Table 25 to Table 33 on pages 122 to 129). This is the first time that such a description has been attempted in the UK in over 30 years. The epidemiology of many of these neurological disorders has not been reported previously.

4.1.1 Previous studies and estimates of neurological conditions in the community

This is the first large prospective study measuring the frequency of all serious neurological conditions in the community in the UK since the Carlisle study was carried out (Brewis *et al.*, 1966). There have been major advances in investigation and diagnosis of neurological disorders since then. Moreover, there has been significant demographic change in these three decades. Carlisle had a mainly white indigenous population, with a younger age profile – differing from current demography (Perkin, 1997). Much recent community-based neuroepidemiological work has been carried out at the Mayo Clinic, Rochester, USA. Studies such as the Rochester study, although useful, describe a population whose ethnicity and lifestyle do not necessarily reflect those of the UK (Glista *et al.*, 1977).

Current estimates of numbers of neurological patients and their needs come from routine statistics and OPCS based disability studies. Studies based in specialist clinics or from abroad are also used.

The routine statistics generated in primary care are unlikely to be accurate. Generalists report diagnostic uncertainty in neurology (Newsom-Davis *et al.*, 1997). GP computer systems are set up for clinical work; because they are not designed specifically for epidemiology, they often fall short of the necessary standards for data collection as a result of poor validity and completeness. The UK national morbidity surveys (Ebrahim, 1995) have attempted to address the frequency of complaints in general practice; a major limitation is that conditions with low incidence and relatively chronic courses

may give false incidence rates because patients in this system will count as "new" when they change practice and see a participating GP for the first time (Newrick *et al.*, 1996).

Population-based estimates from the USA report point prevalences of neurological conditions (excluding headache, back pain and disc disease, mental handicap, psychosis, non-neurological visual and hearing loss, and nervous system trauma) of 3.6 per 100 (Kurtzke, 1982). In the UK, disease of the nervous system accounted for 7.6% of all GP consultations between 1981 and 1982; this higher rate may reflect superior case ascertainment (Royal College of General Practitioners, 1986), although the latter figure includes headache and diseases of the ears and eyes, and is a period rather than a point prevalence.

The Harris report looked at all disabilities in private households among those aged over 16 years in the UK. Disabilities were divided into groups and, taking those relevant to neurology (CNS disorders, muscular dystrophies, congenital malformations of the spine and hydrocephalus, cerebral birth injury, senility as a cause of cognitive disability), 78/1,000 were disabled to some extent by these disorders (Harris, 1971). The OPCS survey of disability 16 years later graded disability according to severity, as well as overall frequency. The prevalence of complaints relevant to neurology were 13% for "CNS disorders", 2% each for dementia and mental handicap, and 6% for back complaints. In a later study, "CNS complaints" accounted for 7% of disability overall, but 16% of conditions with a high severity score (9 or 10/10) (Martin *et al.*, 1988). These figures do not tell us anything about the underlying disease, the likely duration of patients disability nor do they help us know how many patients there are whose symptoms are treatable.

4.1.2 Problems of neuroepidemiology

One of the central problems in the measurement of neurological disorders is that only "the tip of the iceberg" is known to health-care professionals. Some disease is subclinical, some symptomatic disorders are not "medicalised" (they may never be brought to a doctor's attention), and some conditions may be presented to a doctor but not diagnosed. Frequent conditions such as migraine may never be brought to the attention of a doctor. Mild neuropathy may not bother the patient because it is either

asymptomatic or of such insidious onset that it is never thought of as a medical condition. Dementing illnesses and parkinsonism may be ascribed to normal ageing. Certain conditions with social implications, such as epilepsy, may be denied by the patient.

Case-finding methods need to be tailored to the disease's spectrum of severity and frequency. Our study did not use door-to-door techniques or population sampling, and relied on patients presenting their symptoms to a doctor. This means that some conditions are under-ascertained. Nevertheless the frequency of diagnosed cases is of importance to plan medical services and this information can be used in conjunction with clinical and epidemiological data from both clinic based and door-to-door studies to refine estimates.

There is variation in case definition between different studies. We identified the most robust and clinically relevant definitions that were available. As there is variation in the choice of definitions, it is not always possible to compare studies performed by different groups. In some studies, notably of Parkinson's disease, the rates are reported according to the different criteria; given the number of conditions that we were dealing with, we did not use this form of analysis.

Case ascertainment and the statistical corrections (such as cluster analysis) for error resulting from lost cases vary between studies. We have used multiple case-finding techniques to ensure completeness. Neurology has the highest number of conditions listed in the *International Classification of Diseases*. The high numbers of different uncommon diseases mean that exhaustive methods of case ascertainment and audit are most appropriate because sampling error increases with rarer events. The complete notes search formed an important method for completing this study; without it, we would have failed to identify one in five cases. Clearly, this has repercussions for resourcing such studies in the future because it is labour intensive. We did not use cluster analysis to estimate lost cases because this would have to be done separately for each condition as a result of variation in the likelihood of their being reported; given the low numbers in many conditions, the confidence limits of such estimates would have been high.

4.1.3 Advantages of neuroepidemiology in the UK

The NHS of the UK is an ideal system to study epidemiology because health care is free at the point of access, which means that one of the blocks to seeking medical care has been removed. Each patient can be traced through the system, allowing complete long-term follow-up which has proved difficult elsewhere. Of all registered patients, 78% consult their GP each year and 13% of all consultations are for conditions of the nervous system – including eye and ear complaints (Ebrahim, 1995). In addition, GPs have a duty to see their elderly patients and screen for occult disease, which encourages patients to discuss symptoms for which they may otherwise not have sought medical care. These factors reduce the error of "non-presentation".

It should not be forgotten that this survey will not include the small number of patients who are in long-stay hospitals for severe neurological problems.

4.1.4 Practices and populations

The large population studied reflects urban Britain. The demographic features of the NHNN-GP Linkage population are shown in Table 22 and Table 23. The age/sex distribution shows lower numbers at the extremes of age, with a compensatory excess of young adults (between 30 and 54 years), compared with the whole population of England and Wales (OPCS). Taken as a whole, the linkage population's ethnicity differs from that of England and Wales, and shows a higher proportion of non-white British people than for the population as a whole, as would be expected for this urban population. Despite social class and unemployment rates being "better" than for the UK as a whole, all the general practices except one (whose population on 1/7/1996 was 13,220 people) qualified for deprivation payments according to the Jarman index.

There are problems with the Registrar General's coding of social class, particularly the exclusion of housewives, carers, students, and unemployed, long-term ill and elderly people, who constitute over a third of the population (39% overall of the population in England and Wales in 1991). Socioeconomic class is a surrogate marker of affluence when used to describe a community rather than individuals. This to some extent explains the paradox between higher socioeconomic class in the measured part of our population, and the high rates of deprivation payment among the practices.

Unlike some large-scale community studies, we used the GPs' register as the population base. This is more accurate than estimates based on census data which, particularly in urban areas, underestimate the population by up to 10% (Soni Raleigh *et al.*, 1999).

No neuroepidemiological study based in a developed country attempts to address the problem of migration within long-term studies. Given the current population mobility of up to 20% p.a., this is clearly a methodological failing. We calculated migration into our estimates; by monitoring the population changes over time (see page 108).

4.1.5 Quality control of case ascertainment in the Linkage study

The thoroughness of notes searches and active surveillance was unusual. The percentage of patients identified prospectively was good, but was better for those diagnoses for which GPs traditionally seek a neurological opinion instead of managing the patient themselves. There was a difference across the practices in terms of percentage of cases identified prospectively. This seems to be partly related to the completeness of the computer entry of diagnoses, which allowed the researcher to access information about the patient in that manner, rather than relying on the GPs to register cases. The two practices with the highest number of prospectively identified cases also ran efficient systems to notify cases. One kept a neurology book very stringently; the other kept all letters pertaining to neurological diagnoses separately and had a high rate of entry on the computer system.

4.1.6 Incidence with respect to certain conditions

4.1.6.1 Conditions in which this study concurs with previous reports

The common conditions were all found to have incidence rates in accordance with previous reports (see Table 25, Table 26 and Table 27 on page 122): first and subsequent stroke, intracerebral haemorrhage, subarachnoid haemorrhage, epilepsy, bacterial infection of the CNS, aseptic meningitis, multiple sclerosis, optic neuritis, primary malignant tumours of the CNS, benign CNS tumours, severe head and spinal cord trauma, cerebral palsy, congenital abnormalities, motor neuron disease, Parkinson's disease, cluster headache and Guillain–Barré syndrome. For lifetime prevalence rates, the following agreed with previously reported prevalence data (see

Table 30, Table 31 and Table 32 on page 126): transient ischaemic attacks, active epilepsy, Parkinson's disease, benign and malignant brain tumour, motor neuron disease and diabetic polyneuropathy.

4.1.6.2 Conditions with higher rates than previously reported

Some conditions had higher rates in this study than in previous reports, with confidence limits that did not overlap. As we used 95% confidence limits and compared the incidence rates for 30 conditions, we would expect one figure to be higher and another lower just by chance. Only diabetic polyneuropathy had a higher incidence than reported previously. Among the 33 lifetime prevalence rates, the conditions with higher prevalence rates were completed stroke, subarachnoid haemorrhage, compressive mononeuropathies and polyneuropathies not caused by alcohol or diabetes. The prevalence rates quoted for the following conditions were from previous point prevalences and so are not directly comparable: CNS infections, optic neuritis and Guillain– Barré syndrome.

4.1.6.3 Conditions with lower rates than previously reported

Incidence rates for the following conditions were lower in this study than previously reported: metastatic brain tumours, spinal malformation, essential tremor and neurosurgical operations. For lifetime prevalence rates, the following conditions were found to have lower rates: spinal cord injury, cerebral palsy and essential tremor.

No cases of IIH or viral encephalitis were identified in the incidence study.

4.1.6.4 Previously unreported conditions

The incidence rates have not previously been reported for the following conditions: subdural haemorrhage, HIV encephalopathy and non-bacterial CNS infections, demyelinating disease not fulfilling the criteria for MS, cranial nerve injury, neonatal encephalopathy or stroke, transient global amnesia, myelopathy, spinal stenosis, cranial nerve palsy, mononeuropathies, polyneuropathies, diabetic amyotrophy and plexopathy. In terms of lifetime prevalence, the numbers of individuals who have had the following conditions has not been reported for a community: intracranial haemorrhage, subdural haemorrhage, intracranial infections, demyelination (other than MS), optic neuritis, congenital CNS disorders as a whole, aqueduct stenosis,

narcolepsy, transient global amnesia, myelopathy, spinal canal stenosis, mononeuropathies, plexopathies, postherpetic neuralgia and neurological eye disorders.

4.1.7 Discussion of individual conditions (in alphabetical order)

4.1.7.1 Brain tumours

Our incidence rates for benign [7 (3, 13)/100,000 p.a.] and malignant brain tumour [primary 3 (0.7, 7)/100,000 p.a.; metastatic 4 (1, 9)/100,000 p.a.] agree with most studies of their incidence, except the recent report from Lothian which gave a crude rate that was twice that expected for primary intracranial tumours. The use of crude rates is open to question because Scotland's demographic structure and health outcome measures are unlike those for the rest of the UK and Europe. The lifetime prevalence of benign [0.5 (0.3, 0.9)/1,000] and malignant intracranial tumours [0.2 (0.06, 0.4)/1,000] concurs with the previous prevalence estimate (Kurtzke, 1984).

4.1.7.2 *Cluster headache*

The incidence rate of cluster headache was similar to that in a previous study, despite using a different case definition (Swanson *et al.*, 1994). However, the lifetime prevalence rate may be slightly lower [0.33 (0.15, 0.63)/1,000] compared with previously reported prevalence rates of 0.28/1,000 for women and 1.09/1,000 for men (D'Alessandro *et al.*, 1986); if these were averaged to give a rough rate for the population of 0.69/1,000, it would remain higher than the upper confidence limit of our lifetime prevalence rates.

This condition is probably under-diagnosed in general practice, because it has not figured in undergraduate medical textbooks. This will affect community-based studies that rely on diagnosis but not "door-to-door"-type surveys.

4.1.7.3 *Congenital brain and spinal cord abnormalities "major infantile neurological damage"*

Despite increasing capacity to monitor pregnancy and fetal outcome, the only congenital problems that are falling are spinal malformations and hydrocephalus, probably as a result of folate prophylaxis and termination of pregnancy for identified structural abnormalities. Cerebral palsy, perinatal asphyxia and stroke still cause

significant morbidity, which is contributed to by the increased survival of very small and very pre-term babies. The prevalence of these disorders exceeds that of demyelinating disorders or Parkinson's disease. Patients with these disorders will often have multiple handicaps, and many will need lifelong care for aspects of daily life; many will also experience neurological complications such as epilepsy.

There is scope for continued well-designed studies of causality in CP, which has already been the subject of many studies; neonatal stroke is less well researched. Rigorous investigation of patients to identify the heterogeneous underlying causes is vital.

4.1.7.4 *Dystonia*

The only reported incidence of focal dystonia was 2 (1.6–3.4)/100,000 p.a. (Nutt *et al.*, 1988), with which our study concurs [1 (0.1, 4)/100,000 p.a.].

The prevalence of focal dystonia in Rochester, USA was reported as 0.30 (0.17, 0.48)/1,000. In our study, focal dystonia was found, which was divided into primary [0.12 (0.02, 0.35)/1,000] and secondary [0.12 (0.03, 0.31)/1,000]; these lifetime prevalences accord with the prevalence rates from Rochester (Nutt *et al.*, 1988).

The epidemiological study of these conditions is limited, their underlying cause is unknown and it seems that further investigations might be useful

4.1.7.5 *Epilepsy*

The incidence rates of epilepsy and single seizures agree with previous studies and we found a lifetime prevalence rate of active epilepsy of 0.4 (0.4, 0.5)/1,000, also in close concurrence with previous reports. The rate for ever having a seizure was somewhat low at 1.2%, which may reflect the lack of case finding by techniques such as door-to-door surveys in this study. The age-specific incidence rates are highest below the age of 14 years and in the range 70–74 years; the highest single seizure incidences are for younger than 4 years and 60–64 years.

4.1.7.6 *Essential tremor*

The incidence [8 (4–14)/100,000 p.a.] and lifetime prevalence [0.80 (0.48, 1.24)/1,000] of essential tremor in this study are low. Many studies have been

conducted in areas known for high rates and, as this condition has a large heritable component, the difference from foreign studies is not surprising. There are no previous community-based estimates from the UK.

If further investigation of this condition were deemed necessary, it would be important to have very clearly defined and objective criteria for case identification.

4.1.7.7 *Head and other serious neurological injury*

This report of the incidence of poor neurological outcome after head injury agrees with a previous working estimate (Langton Hewer, 1993); this pertains for cord injury as well (Kurtzke, 1984; el Masry *et al.*, 1997). However, the lifetime prevalence rates for cord and severe head trauma are lower than previous estimates of prevalence. This may reflect that these estimates were made for the population as a whole, including patients in institutions; such people were not in this community-based study.

Head and spinal cord injury are a source of low incidence of severe neurological handicap in all age groups.

The long-term outcome, and hence complications, of neurological injury are not fully described (Eisenberg *et al.*, 1985).

4.1.7.8 *Idiopathic intracranial hypertension (IIH)*

We found no incident cases of IIH in our study. Given the reported low frequency of 1–2/100,000 p.a. (Radhakrishnan *et al.*, 1993), this is not totally unexpected. The lifetime prevalence was found to be 0.1 (0.02, 0.29)/1,000.

4.1.7.9 *Infection*

The incidence of bacterial CNS infection correlates with the figures from the Carlisle study of 30 years ago, despite immunisation for *Haemophilus* B and prophylaxis for outbreaks of meningitis caused by *Neisseria* sp. The results for aseptic meningitis overlapped with the confidence intervals from the Rochester study. The only previously reported prevalences for infectious diseases gave point prevalences. Our lifetime prevalence study shows that a large group of individuals have been affected by these conditions; however, it was beyond the scope of the study to examine these individuals for sequelae and the notes at general practice are all too frequently unclear

on this point.

The frequency of these conditions is fairly well described, but associations with poor neurological outcome are largely unknown.

Viral encephalitis can be difficult to separate from other encephalopathic illnesses. Mild forms may never be diagnosed. No cases of acute viral encephalitis were identified in the incidence study, compared with 7/100,000 p.a. in the Rochester study and the Carlisle study (Brewis *et al.*, 1966; Beghi *et al.*, 1984).

This is a fairly problematic area because the clear-cut case definition disguises a clinical dilemma: when, on the one hand, to investigate fairly non-specific symptoms that merge in a spectrum with the relatively clear-cut cases of aseptic meningitis and, on the other, to investigate encephalitis. Viral encephalitis may be a devastating illness despite modern antiviral treatments, and in many cases the viral agent remains unidentified. Given our limited knowledge of this disorder, it seems to be ideal for epidemiologically based research.

4.1.7.10 *Motor neuron disease*

The incidence rate we found agrees with the accepted rate of between 1 and 2/100,000 p.a. (Brewis *et al.*, 1966; Juergens *et al.*, 1980). Reported prevalence figures vary considerably, with a range of 0.036–0.11/1,000 (Kondo, 1978). Our lifetime prevalence rate is in accordance with the upper end of previous prevalence rates [0.09 (0.01, 0.31)/1,000].

4.1.7.11 *Multiple sclerosis*

The incidences of multiple sclerosis and optic neuritis agree with those of previous reports. Other demyelinating disorders that do not fall into this category have not been reported previously. The lifetime prevalence of a diagnosis of multiple sclerosis was high compared with older studies at 2 (1.6, 2.6)/1,000 rather than 1.20/1,000 (Langton Hewer, 1993) or 0.80–1.40/1,000 (Shepherd *et al.*, 1980; Rice-Oxley *et al.*, 1996), although it agrees with more recent surveys (McDonnell and Hawkins, 1998). In addition, optic neuritis had a lifetime prevalence of 0.6 (0.3, 1)/1,000, and other demyelinating disorders of 0.1 (0.04, 0.3)/1,000. Demyelination accounts for a significant number of neurological diagnoses in the community and such high figures

have important repercussions for funding services and potential new treatments.

4.1.7.12 *Myasthenia gravis*

The incidence and prevalence rates for myasthenia agree with the recent report from Cambridge (Robertson *et al.*, 1998). Earlier studies reported lower rates [0.38 (CL = 0.17, 0.71)/1,000] compared with 0.04–0.11/1,000 (Kurtzke, 1984; Langton Hewer, 1993; Aiello *et al.*, 1997). This may be the result of improved diagnosis and survival, a real increase or a regional variation with higher rates in England.

4.1.7.13 *Parkinson's disease*

The incidence and lifetime prevalence rates agree with those of previous reports. They are towards the upper end of the range of the previous figures reported. This may part correcting the crude rates to an increasingly elderly population may appear to make the rates rise. The incidence rate rises sharply with age (see Table 33 on page 129).

4.1.7.14 *Peripheral neuropathy*

4.1.7.14.1 Polyneuropathy

There is no previous report of the incidence of peripheral neuropathy in the community. We found an incidence of 16 (9, 24)/100,000 p.a. when alcoholic and diabetic neuropathy were excluded. The lifetime prevalence is in keeping with this at 1.13 (0.76, 1.63)/1,000, which reflects a condition that is often of long duration but may be associated with conditions that shorten life.

There is a need for a basic descriptive epidemiology of the neuropathies. Given the significant number that are cryptogenic, and the fact that toxins may play an important role in neuropathy, it would not be unreasonable to hope that analytical epidemiology may identify additional factors.

4.1.7.14.2 Diabetic polyneuropathy

The prevalence of diabetic neuropathy can be estimated from the Rochester study (Dyck *et al.*, 1993), in which 1.3% of the population had diabetes: 26.8% had type 1, of whom 54% had polyneuropathy; and 73.2% had type 2, of whom 29% had polyneuropathy. This gives an estimated community rate of diabetic polyneuropathy of 4.65/1,000. However, they observed that only 15% of patients with type 1 diabetes

and 13% of patients with type 2 diabetes had symptomatic polyneuropathy, from which a prevalence rate of 1.86/1,000 for symptomatic diabetic neuropathy can be estimated. A rough calculation of the point prevalence of diabetic polyneuropathy gives 2 (CL = 1.86, 2.99)/1,000 (Neil *et al.*, 1989). Our result of 1.9 (1.4, 2.6)/1,000 falls within the ranges of these results.

A case definition would have to be chosen taking into consideration whether causal factors were being sought; if this were the case, it seems inevitable that better information would be gained from presymptomatic diagnosis, which is inherently likely to require more resources (Melton *et al.*, 1987).

Controls have to be used because there is a background rate of neuropathy from other causes in the community. Some instruments for the quantification of sensory testing have established normal ranges, which may help (Bloom *et al.*, 1984).

4.1.7.14.3 Inflammatory neuropathy and Guillain–Barré syndrome

The incidence is around 1.5 (1.3–1.8)/100,000 p.a. (Rees *et al.*, 1998), and our study concurs with this. The lifetime prevalence in our study was 0.2 (0.08, 0.3)/1,000, which seems to be on the low side allowing for mortality.

4.1.7.15 *Plexitis/Plexopathy*

Our incidence rate of 3 (1, 8)/100,000 p.a. confirms the only other rate from Rochester of 2/100,000 (*Beghi et al.*, 1985). The lifetime prevalence of the plexopathies confirms the clinical impression that brachial plexitis is far more common than sacral plexitis. There are no previous reports of prevalence for these conditions.

4.1.7.16 *Postherpetic neuralgia*

This is a condition that is managed largely at the community level. The patient may be referred to a number of different specialists for further management of the pain or the associated malignancy.

Previous community-based studies give divergent reports for the incidence of shingles. The range is 130–480/100,000 p.a. (Schoenberg *et al.*, 1993). It has been reported that 9% develop PHN; this would allow an estimate of 12–43/100,000 p.a. The incidence reported by us of 140 (104–184)/100,000 p.a., together with an incidence for PHN of

12 (7–19)/100,000 p.a. (incidence rate of 9% of shingles), agrees with these figures, albeit at the lower end of the confidence limits. There are no prevalence figures and the lifetime prevalence of PHN was 0.7 (0.4, 1)/1,000 population.

4.1.7.17 *Stroke*

The incidence for a first cerebrovascular episode was found to be 217 (183, 243)/100,000 p.a., a figure in close accordance with that of other studies: 200/100,000 p.a. (Bamford *et al.*, 1988). This does not support the notion that the incidence of stroke is falling, although it agrees with the finding that, in the north-west of England, rates for rural areas were falling and those for urban areas were higher than in rural areas and also static. That report gave an overall age- and sex-adjusted incidence rate of 160 (150,170)/100,000 p.a.; towns had rates of 163–205/100,000 p.a. compared with a rural rate of 118/100,000 p.a. (Du *et al.*, 1997). The age-adjusted rates in our study show an increased rate of stroke in younger age groups and a lower rate in the oldest age groups, compared with most other studies.

The number of individuals having subsequent episodes of stroke in this study [45 (33, 58)/100,000 p.a.] was at the higher end of confidence intervals of previous reports [28–35/100,000 p.a. (Sorensen *et al.*, 1982; Walker *et al.*, 1985)]. Likewise the lifetime prevalence figures give high rates for stroke at 9 (8, 11)/1,000 versus 5/1,000, which has been used as a working estimate in the UK (Langton Hewer, 1993). Transient ischaemic attacks (without stroke) have been variously reported in the past at 1.5/1,000 (Langton Hewer, 1993), 5.18/1,000 (Sorensen *et al.*, 1982) and 6/1,000 (Walker *et al.*, 1985); our rate, at 4.68 (3.90, 5.61)/1,000, is in agreement with the higher values.

The incidence rate for intracerebral haemorrhage is as expected and our lifetime prevalence rate (which is the first reported) is only four times higher – not unexpected given the high case fatality in this condition.

Subdural haematoma has not been reported elsewhere. The lower lifetime prevalence rate in relation to IR probably reflects that the population at risk of subdural haematomas have other pathologies or are in older age groups.

4.1.7.18 *Subarachnoid haemorrhage*

Our subarachnoid incidence rate agrees with previous estimates. However, we found more individuals who had ever had an SAH in our population than was reported from the Rochester study (Kurtzke, 1984): 1.2 (0.8, 1.7)/1,000 versus 0.5/1,000.

4.1.7.19 *Syringomyelia*

Two studies have looked at the epidemiology of this condition in the north of England. In the Carlisle study, the prevalence was found to be 0.09/1,000 (Brewis *et al.*, 1966). A more recent study in Newcastle upon Tyne found an incidence (retrospective) of 0.4/100,000 p.a. and a prevalence of 0.06/1,000 (Foster, 1980).

Intrinsic spinal cord defects were not identified in our incidence study, but a value of 0.10 (0.02, 0.3)/1,000 was identified in the lifetime prevalence study.

4.1.7.21 *Trigeminal neuralgia*

Our study found an incidence rate of 8 (4–14)/100,000 compared with lower rates in the studies in Rochester and Carlisle. The lifetime prevalence of 0.7 (0.4, 1)/100,000 is higher than in previous reports.

4.1.7.22 *The provision of neurosurgery*

In Rochester, USA, the annual rate for surgical procedures for spinal disorders was 42/100,000 p.a. lumbar discectomies and 6/100,000 p.a. cervical discectomies (Glista *et al.*, 1977).

During the incidence period there was a significant neurosurgical intervention in 29 (20–38)/100,000 p.a. (Carpal tunnel release, nerve biopsy and repeat operations for the same condition were excluded.)

4.1.8 Summary

We have reported on the incidence and lifetime prevalence rates of neurological disorders in a community in the UK. This is the first study that attempts to describe such a wide range of conditions in the UK in the past 30 years.

As the review of the literature of neuroepidemiology makes clear, there are still

methodological flaws in many studies. The data on which resourcing has been based are probably inaccurate and need to be updated. Our study provides the incidence and lifetime prevalence rates for neurological disorders in the UK; we have paid close attention to the factors which are likely to have resulted in underestimation in previous studies.

We have demonstrated that there is a considerable burden of neurological disease. Methodologically, the thoroughness of the search contributed to the quality of the study and, despite the labour-intensive nature of this method, the exhaustive methods used seem to have an important role in studying these disorders (as explained on page 106). The use of GP registers and correcting for migration ensured that calculations were based on appropriately accurate population figures.

Future studies might address a number of key questions:

- the continued observation of incident cases to narrow the confidence intervals
- the identification of trends in incidence rates of the commoner disorders
- the assessment of all individuals with a history of neurological diseases in a community to gain a perspective of prevalent disability, its causes and its potential for improved management
- the importance of socioeconomic factors in the development of neurological disease
- the effect of neurological disease on patients lives over time (in various ways - physical, social and economic)

Such studies might allow appropriate resources to be allocated to the neurological and disabilities sectors of health care and address some important implications of such diagnoses for patients.

4.2 The outcome of febrile convulsions

The outcome for this community-based cohort of 220 patients followed prospectively from first presentation with a FC was, in general, favourable. However, almost 6% have developed epilepsy by the age of 13 years. This is a greater proportion than in children from the general population, among whom the cumulative incidence rate of unprovoked seizures for ages 2–25 years is 1.4% (Annegers *et al.*, 1987). Our finding is similar to that of other, large-scale, community-based, prospective cohorts (see page 135). The NGPSE cohort resembles these studies demographically and clinically. There is an excess of boys (60%) in the usual range from 53% to 59% (Nelson *et al.*, 1978a; Knudsen, 1985a; Annegers *et al.*, 1987; Noah *et al.*, 1988; Tsuboi *et al.*, 1991; Offringa *et al.*, 1992; Berg *et al.*, 1996b), with typical numbers of complex features (20%) (Verity *et al.*, 1985a; Offringa *et al.*, 1994) and recurrences (33%) (Berg *et al.*, 1990; Offringa *et al.*, 1994).

We identified 17 cohort studies (including the NGPSE) via Medline search and referenced articles (Faxén, 1935; Herlitz, 1941; Friderichsen *et al.*, 1954; Frantzen *et al.*, 1968; Millichap, 1968; van den Berg *et al.*, 1969; Livingston, 1972; Stanhope *et al.*, 1972; Nelson *et al.*, 1976; Heijbel *et al.*, 1980; Ross *et al.*, 1980; Annegers *et al.*, 1987; Verity *et al.*, 1991; Berg *et al.*, 1996b; Knudsen *et al.*, 1996; Forsgren *et al.*, 1997). We excluded four of these (Faxén, 1935; Millichap, 1968; Livingston, 1972; Stanhope *et al.*, 1972) because of uncertainty about inclusion, recruitment or duration of follow-up. For the remaining 13 studies, the figure (see page 135) shows the percentage that developed epilepsy plotted against the mean (or median) age at last available follow-up. Given the variation in reporting age at last available follow-up, this is either as reported or estimated by summing the reported mean age of onset of the first FC and the mean period of follow-up. The curve determined by logistic regression was fitted to the study end-points. There is a dearth of results between 15 and 25 years. An increase of epilepsy with age is shown, giving overall percentages of 2.4, 3.1, 4.1, 5.4 and 7.1% with epilepsy by 5, 10, 15, 20 and 25 years of age. The presence of important prognostic factors in study definitions (e.g. FCs in neurologically abnormal children may have a higher recurrence rate) will influence findings substantially (Verity *et al.*, 1985a, 1991).

We show a significant association between further FCs after the first FC and the development of subsequent epilepsy, using hazards ratios (with 95%CLs), which are an appropriate method for quantifying the strength of an association between a risk factor and the outcome in longitudinal studies. Studies of FC, using significance testing (Annegers *et al.*, 1987; Verity *et al.*, 1991), have ascribed differing levels of risk for epilepsy and other neurological sequelae to the presence of complex FCs, numbers of FCs, family history of FC or epilepsy, and prior or subsequent neurological deficit. Odds ratios have been used in two studies: a small cohort had non-significant findings as a result of wide confidence intervals (Forsgren *et al.*, 1997); the other (Berg *et al.*, 1996b) has to date limited follow-up, but demonstrates an increased rate of unprovoked seizures at 2 years in those who had experienced more FCs [OR = 4.2 (1.9, 6.6); 20.4 (4.4, 36.4)] for children with one or four FCs respectively. These children were analysed after assignment to high- and low-risk (of FC recurrence) groups (stratified by family history, age at first FC and temperature at first FC) in a multivariate model for risk of unprovoked seizures after FC. Those at low risk of FC recurrence increased their relative risk of subsequent unprovoked seizures if subsequent FCs occurred, but children at high risk did not increase their risk of unprovoked seizures by having further FCs (Berg *et al.*, 1996b).

In carrying out an actuarial analysis of the development of epilepsy using the Cox model, time-dependent co-variates were used to assess the effect of FCs after the first FC. By contrast, with analyses that use baseline (or fixed) co-variates, which remain static (e.g. sex) or predetermined (e.g. age) throughout the follow-up period, those with time-dependent co-variates allow for changes during follow-up. Although they provide an estimate of the effect of subsequent FCs on the risk of epilepsy, they are more difficult to use for prediction than the standard Cox model with fixed co-variates, because of uncertainty in predicting changes to the time-dependent co-variates themselves.

Complex features of FCs have been proposed as key prognostic features, although in our study they were not associated with the development of epilepsy; the wide confidence limits (see Table 36 and Table 37) restrict interpretation. We pooled data from all studies which give sufficient information about complexity of first FCs with

long-term follow-up to get a further overview (Nelson *et al.*, 1976; Annegers *et al.*, 1987; Verity *et al.*, 1991; Knudsen *et al.*, 1996; Forsgren *et al.*, 1997).This is shown on page 135. The NGPSE is the only study with a point estimate of the odds ratio of less than one for epilepsy after a complex FC compared with a simple first FC. However, there is no evidence of heterogeneity between studies (5.15, d.f. = 5, p = 0.40), and the overall odds ratio (random effects model) of 3.4 (CL = 2.1, 5.4) suggests a substantial increase in the risk of epilepsy after a complex first FC.

For many years, FCs have been treated on the basis that this will lower the risk of recurrence and subsequent epilepsy. However, our study and others show that this risk is small. Furthermore, although both daily phenobarbital and diazepam with fever have been shown to reduce the chances of recurrent FC (Wolf *et al.*, 1989; Tsuboi *et al.*, 1991; Knudsen, 1996), studies have not demonstrated a reduction in the incidence of subsequent epilepsy (Knudsen, 1985b; Wolf *et al.*, 1989; Offering *et al.*, 1991; Knudsen *et al.*, 1996). Moreover, prolonged prophylactic treatment has adverse effects (Wolf *et al.*, 1978; Farwell *et al.*, 1990; Hirtz *et al.*, 1993; van Esch *et al.*, 1994). Some authorities advise AEDs for FCs only for "frequent recurrences" (Joint Working Group of the Royal College of Physicians and the British Paediatric Association, 1991; Valman, 1993), or for prolonged FCs (> 20 min), or if they occur before 9 months of age, or after a third recurrence (Rylance, 1990). Others advise AEDs for FCs with complex features, or in children with neurological deficit. In this cohort, 11% of children were treated with long-term AEDs, including eight patients with uncomplicated FCs – inappropriate treatment according to modern protocols. Two other community-based studies mention treatment rates of 0.5% in Sweden (Forsgren *et al.*, 1997) and 13.7% in the UK (Verity *et al.*, 1991). There is little evidence of benefit with AED therapy in FCs and clear evidence of harm; it can be advocated only under rare circumstances.

The definition of neurodevelopmental sequelae is not straightforward. FCs occur in young children in whom the neurological diagnosis of development delay is notoriously difficult. Five per cent of our cohort were noted to have at least moderate learning difficulty or other new neurological deficits at some time after their first FC, and a further 5% required psychological or speech therapy, which may constitute "deficit"

but is less well defined. In a study of 413 children who had had FCs but no subsequent unprovoked seizures, and who were tested psychologically and neurologically at 7 years of age, there were no differences when compared with siblings who had not experienced FCs. This lends no support to the argument that subtle intellectual deficits are missed in children who have had FCs (Ellenberg *et al.*, 1978).

In this cohort, there is a 6% rate of epilepsy for a follow-up of 12.9 years. If it is assumed that at least 2.2% of all children experience FCs and that the lifetime prevalence of epilepsy by 25 years is 14/1,000 (Annegers *et al.*, 1987), then a minimum of 1 in 11 cases of patients presenting with epilepsy by age 25 years will have had a FC. Although it cannot be inferred that this is a causal relationship, further investigation of the link might lead to the identification of preventable predisposing factors. Various factors, such as maternal alcohol and tobacco use in pregnancy, are associated with FCs or complex features; however, their elimination would not have an appreciable effect on the incidence of FCs (Cassano *et al.*, 1990; Nelson *et al.*, 1990).

The lumping of all seizures fulfilling the criteria for FC should be abandonned. For example those children belonging to the identified genetic syndromes should be looked at separately to answer questions about prognosis in a more homogeneous group. Likewise children who have FCs on a background of developmental delay also seem to form a clinically distinct group and need to be studied separately from "all FCs". No doubt this will leave a group of children who have FCs and who do not have delay or an identifiable genetic disorder;to this group warrant further study. By making the groups studied for prognosis for epilepsy more homogeneous it may be possible to see if hippocampal sclerosis is a sequel - an association which is often postulated but remains unproven.

Further study is needed of preventable or treatable conditions in childhood that may be associated with FCs, such as childhood iron deficiency anaemia (Pisacane *et al.*, 1996), toxocariasis (Arpino *et al.*, 1990), toxoplasmosis (Critchley *et al.*, 1982) and human herpes virus-6 infection (Rantala *et al.*, 1990; Hall *et al.*, 1994; Barone *et al.*, 1995; Rantala *et al.*, 1995).

The further follow-up of this cohort will help determine if FCs continue to be associated with an increased risk of epilepsy throughout life.

4.3 Prognosis for epilepsy

In the NGPSE cohort, over a third of patients were aged under 20 years and a quarter over 60 years at presentation. The cohort is representative of newly diagnosed patients in the community.

4.3.1 Actuarial analysis of remission

The overall chance of entering a period of remission by 9 years from presentation was high, with 95% of patients entering 1-year remission and 68% entering 5-year remission during this time period. This confirms the findings from other population-based cohorts that, in general, epilepsy is a relatively benign condition.

The chance of going into remission increases during the first 5 years and then plateaus between 5 and 7 years. This suggests that epilepsy that does not remit early is unlikely to improve with time.

One of the key strengths of the NGPSE study has been the inclusion of individuals with probable or possible epilepsy, as well as those with definite epilepsy. This avoids the bias of only ascertaining certain types of seizures or more recurrent episodes, and is more likely to represent the true range of the epilepsies than studies that exclude these cases. When the remission data of individuals with probable epilepsy were compared with those from patients with definite epilepsy, there is a slightly better prognosis for remission among the probable epilepsy group. This may be a result of the inclusion of less severely affected patients, as well as of some who turned out not to have epilepsy.

Often patients with single seizures and provoked seizures are excluded from studies of the long-term remission of epilepsy. The diagnosis of these patients is always retrospective, however, because, without observing these patients for a period of time, it is not possible to be certain that the seizure was single or was provoked by a putative factor. The last point is especially important because it is well known that factors that provoke seizures in patients not diagnosed with epilepsy also provoke seizures in people with epilepsy in a similar fashion– the classic example being alcohol. When these patients were excluded from the analysis, the remission rates were slightly lower – 82% for 1-year and 60% for 5-year remission.

Neither aetiological classification nor seizure type had much effect on remission rates.

There were exceptions, and patients with congenital neurological deficits had lower remission rates, as did those with underlying structural abnormalities. The last finding was not robust, however, only achieving statistical significance for 3-year remission. Part of this effect may have been the high mortality rate in those with symptomatic epilepsy – 67 died in the first 8 years. This means that they contributed less to the overall remission data.

In this study, terminal remission rates were 10% lower than cumulative remission rates. This is higher than the 4–6% difference reported in the Rochester study of epilepsy (Annegers *et al.*, 1979a). This may be the result of the regularity with which we ascertained seizure recurrence using active surveillance rather than passive reporting. It may also result from lower loss to follow-up.

4.3.2 Multivariate analysis of prognosis from first presentation

In the Cox model of the demographic and clinical factors affecting the long-term prognosis for remission of epilepsy, the most important finding was that only one clinical factor appeared to predict prognosis – this was the number of seizures occurring in the 6 months after presentation. Other factors (e.g. seizure type and aetiology) are unimportant, or turn out to be variables associated with this single important prognostic factor. All variables that measured early seizure numbers showed a correlation between increased seizures and poorer outcome. This is a finding of great clinical importance, because it will allow the physician who sees a patient early after first presentation to make an accurate assessment of the chance of future long-term remission. Thus, for example, if a patient has 10 seizures in the first 6-month assessment period, there is a 51% chance of achieving a 1-year remission by 2 years, compared with 78% if the patient has experienced only two seizures in the same interval; similarly, for 5-year remission, the chances are 30% and 55% at 8 years (see Figure 3, page 152).

One great advantage of this study was that, because prognosis was taken from six months after the index seizure, seizure counts during this period were prospective. Moreover, this meant that classification was not confounded by follow-up. We found no significant difference for chances of remission among primary generalised tonic–clonic seizures, partial seizures only, any partial seizures, and secondarily generalised

or any generalised tonic–clonic seizure. The lack of correlation with focal-onset seizures accords with the similar lack of correlation with underlying pathology. Potentially, a confounding factor is the differential mortality for patients with severe underlying pathology who were followed for shorter periods, because death supervened, but this contributed little to the remission data.

An important strength of the study is the identification of patients at a population level, so that the inherent bias of hospital studies (particularly those confined to one specialty) was avoided. The study showed that newly diagnosed patients have a good chance of entering long-term seizure remission, as outlined elsewhere (Hart *et al.*, 1990; Cockerell *et al.*, 1995). Thus, 9 years after the index seizure, 84% (77–91%) of those with definite epileptic seizures are in 1-year remission and 54% (48–60%) in 5-year terminal remission; 95% (93–98%) had had a 1-year remission and 68% (61–75%) a 5-year remission at some point in their follow-up (Cockerell *et al.*, 1995). Mortality in the early years was also high (Cockerell *et al.*, 1994, 1995). At the time of this analysis, 150 (19%) of the 792 patients had died.

There is debate about why some patients achieve remission and others do not. It has been suggested that the failure to control seizures early on in the illness renders the epilepsy more resistant to treatment in the future, perhaps because of secondary structural changes within the brain (Gowers, 1881; Reynolds *et al.*, 1983; Elwes *et al.*, 1984; Reynolds, 1987; Elwes *et al.*, 1990; Reynolds, 1995). However, an equally consistent explanation would be that the epilepsy in any individual patient has an inherent "treatability", and that severely affected patients will be difficult to control from very early in their condition (Keranen *et al.*, 1993; Sander, 1993; Chadwick, 1995; Shinnar *et al.*, 1996; van Donselaar *et al.*, 1997). That treatment did not have a positive impact on prognosis is a reflection of the selection (earlier treatment in patients with more severe disease) or other bias. The only way of clarifying whether early treatment has an impact on future prognosis is to carry out a randomised trial; it was recently reported that there was no improvement in long-term outcome with treatment after first, compared with later, generalised tonic–clonic seizures (Musicco *et al.*, 1997).

Aetiology has been proposed as a major determinant of prognosis for seizure

remission. This study failed to demonstrate this, although the thoroughness of the investigation was variable. Likewise, EEG data were not included. Given the design and scale of the study, information was gathered from many different sources. This meant that information, such as EEGs, would not be comparable and were not analysed for in this study. Data on family history were not sufficiently complete for useful analysis. We cannot comment on whether these factors help in the estimation of prognosis.

This group of patients includes 74 with acute symptomatic seizures. It has been argued that these patients are essentially different, and we have therefore stratified them separately from the rest of the cohort in the multivariate analysis. They seem to do better than other groups, but this improvement only achieved statistical significance in the 5-year remission data.

The finding that the sole independent predictor of seizure remission is the number of seizures in the 6 months after presentation has clear clinical relevance.

There remain questions and controversies regarding the prognosis for remission in the epilepsies; these include

- The effect of aetiology and syndromic classification on the prognosis of epilepsy. These need to be community based to avoid the severity bias of clinic-based studies.
- The effect of treatment on prognosis for remission.

Appendix 1

Definitions

Incidence

The "incidence" of a condition is the rate of occurrence of new cases in a defined population in a period of time. It is usually expressed as the number of new cases observed in a population over 1 year (incidence/100,000 p.a.). The lifetime prevalence is the accrued number of people in a defined population who have had a given disorder; it will approach the prevalence for a disorder if there is no survival disadvantage and no recovery.

Point prevalence

"Point prevalence" is the number of cases in a defined population at a particular point in time.

Period prevalence

"Period prevalence" is the number of cases present in a defined population over a specified period of time.

Lifetime prevalence

Lifetime prevalence is a period prevalence where the period is the whole of the subject's life up to the prevalence day.

Risk factor

A "risk factor" is a factor that, if present, is associated with the chance of subsequent development of a disease.

Appendix 2

Case definitions

Aseptic meningitis was defined as a benign self-limiting condition, presenting with fever and meningism, but no evidence of parenchymal brain involvement. CSF had to be sterile for bacteria, fungi and parasites, but to have a lymphocytic and mononuclear pleocytosis (Beghi *et al.*, 1984).

Benign CNS tumours included benign neoplasms within the cranium and spinal cord, and all types except those confined within the pituitary sella.

Brain tumours were defined as all space-occupying neoplastic growths within the CNS, excluding those confined to the pituitary fossa (Counsell *et al.*, 1996; Preston Martin, 1996).

Cluster headache was diagnosed in the presence at least five attacks of severe, strictly unilateral, orbital, supraorbital and/or temporal headache, lasting 15–180 min and occurring from once every other day to eight times a day, associated with sympathetic system symptoms in the face. Attacks were not classified as cluster headache if there was associated trauma, cerebrovascular disease, intracranial disorders such as raised intracranial pressure, infection or neoplasia, substance abuse or withdrawal, non-cephalic infection, or metabolic disturbance or abnormalities of the bony structure of the face, skull or neck (Headache Classification Committee of the International Headache Society, 1988).

Dystonia: Focal dystonia was defined as an abnormal movement or spasm of the eyes, oromandibular region, larynx, neck, hand or limb muscles which might be task specific; generalised dystonia was abnormal movement of one or more limb and axial trunk musculature (Nutt *et al.*, 1988). Secondary dystonia was invoked where an underlying structural lesion was so placed that it provoked the dystonia. All patients were seen by a neurologist.

Encephalitis was defined as an infection of the substance of the brain of acute or subacute onset, with neurological symptoms or signs indicative of brain parenchymal involvement – seizures, coma, focal neurological signs or impairment of mental

function – in the absence of evidence of other conditions or non-viral infections. Mild obtundation and febrile convulsions were not considered to be encephalitic (Beghi *et al.*, 1984).

Epilepsy was defined as two or more unprovoked seizures; they were further divided according to the ILAE classification of seizures when there was sufficient information. Single and acute symptomatic seizures were coded separately (Commission on Epidemiology and Prognosis, 1993). Epilepsy was considered active if a patient was taking AEDs or had had a seizure within the last year.

Essential tremor was defined as postural or action tremor predominantly in the upper half of the body, which worsened with action in a patient who gave a history of recurring or continuous tremor in the extremities and/or head – demonstrated on clinical examination – and in the absence of any systemic or neurological disorder associated with tremor. The patient could not be taking a drug known to cause tremor. A positive family history was supportive of but not essential to the diagnosis (Larsson *et al.*, 1960).

Idiopathic intracranial hypertension was defined as a raised CSF pressure (documented > 20 cmH_2O CSF pressure in non-obese and > 25 cmH_2O CSF pressure in obese patient), in an alert patient without localising signs, normal neuroimaging including venous sinuses (empty sella being accepted in the definition), and in the absence of any other cause of raised intracranial pressure. The CSF constituents had to be normal (Radhakrishnan *et al.*, 1993).

Malignant brain tumours included primary and secondary tumours within the cranial cavity and spinal cord, but excluded pituitary masses, congenital cerebral tumours and dermoids. These included those that were identified only on scan without histological confirmation, but excluded those diagnosed only clinically.

Motor neuron disease was diagnosed in the presence of a progressive pure motor syndrome according to the El Escorial criteria. All patients were seen by a neurologist and had appropriate imaging to exclude other causes and neurophysiological tests (World Federation of Neurology Research Group on Neuromuscular Diseases, 1994b).

Multiple sclerosis: We used the definition as reported by Poser *et al.* (1983), which

requires clinical and investigative results consistent with CNS demyelination disseminated in time and space; only definite and probable cases were included. All cases were seen by a neurologist and had an MRI scan consistent with the diagnosis.

Myasthenia gravis: The diagnosis was based on fluctuating fatigue of skeletal or bulbar muscles, associated with positive anti-acetylcholine receptor antibodies. If antibodies were negative, then it was necessary to have a decrement of at least 20% of the fifth summed muscle potential, compared with the first, with stimulation of 3–5 Hz. If patients had been tested with a double-blind trial of edrophonium, which was not essential for diagnosis, then the result had to be positive (Myasthenia Gravis Clinical Study Group, 1993).

Myositis is inflammatory disorder of muscle including dermatomyositis and polymyositis (categories C-2.1,2,4 in World Federation of Neurology Research Group on Neuromuscular Diseases, 1994a); cases were included where there was biopsy evidence of myositis or a neurologist had made the diagnosis in the presence of raised creatine kinase and inflammatory markers and the characteristic clinical picture.

Narcolepsy was defined as a disorder characterised by excessive daytime sleepiness associated with cataplexy, sleep paralysis and hypnagogic hallucinations (Diagnostic Classification Steering Committee, 1990; Parkes *et al.* 1995). The diagnosis had to be made by a neurologist or a physician in a sleep disorder clinic.

Parkinson's disease was defined as at least two of the cardinal signs: resting tremor, rigidity, bradykinesia and impaired postural reflexes. Atherosclerotic and neuroleptic-induced parkinsonism were excluded. All patients were seen by a neurologist (Rajput *et al.*, 1984b).

Peripheral neuropathy

1) Polyneuropathy

This was diagnosed when there were objective signs consistent with the diagnosis, in the presence of an established cause such as diabetes. Alternatively, an EMG diagnosis was required.

2) Compressive neuropathy

If the presentation was classic, it was not necessarily confirmed by EMG. Carpal tunnel syndrome was an excluded diagnosis.

Plexopathy was diagnosed when a patient presented with a consistent lower motor neuron, non-dermatomal weakness with or without sensory disturbance or deficit. This was always confirmed by nerve conduction studies or EMG. It might affect the lumbrosacral or brachial plexus (Hughes, 1995). Palsy caused by obstetric injury was not included under this heading.

Spinal stenosis was defined as spreading pain and weakness and/or numbness of the legs brought on by exertion. The presence of confirmatory clinical and radiological evidence of spinal cord encroachment at the appropriate spinal level was required (Aminoff, 1992).

Stroke was defined as a syndrome characterised by "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting at least 24 hours (transient ischaemic attacks were vascular episodes lasting less than 24 hours) or leading to death, with no apparent cause other than of vascular origin" (Hatano, 1976). "Any one or all of a group of disorders including cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage." New diagnoses of "silent cerebral infarction" were counted as incident stroke cases because these patients had all presented with neurological symptoms that required scanning for these "silent" infarcts to become apparent. Likewise, patients newly diagnosed with multi-infarct disease, atherosclerotic parkinsonism or small-vessel disease, and who had not previously been diagnosed with cerebrovascular disease, were considered as incident stroke cases. Patients who were diagnosed with subarachnoid haemorrhage and who not had subsequently had either a neurological deficit or an infarction on scan were not considered to have experienced a stroke.

Trigeminal neuralgia was defined as a painful unilateral affliction of the face, characterised by brief electric shock-like (lacinating) pains. The pain had to last seconds to 2 min, and to have four of the following characteristics: distribution confined to one or more divisions of the trigeminal nerve; a quality described as

intense, sharp, superficial, stabbing or burning, precipitating triggers on the face or in the mouth; and the absence of symptoms between attacks. Absence of neurological deficit or other causes of facial pain were also required for the definition. Multiple sclerosis and brain-stem infarction were rejected by history, examination or investigation (Headache Classification Committee of the International Headache Society, 1988).

Acknowledgements

I would like to thank many colleagues at the Institute of Neurology, the National Hospital for Neurology and Neurosurgery, the National Society for Epilepsy and in the general practices involved in the studies. I am particularly grateful to Professor Simon Shorvon who has carefully supervised all aspects of this project and the writing of the thesis. Professor Ley Sander has also been a great help to me in discussing the studies in detail. I am very grateful to Dr. Tony Johnson who has been central to the statistical analysis of the NGPSE data. I would like to thank Dr. George Harwood for his detailed comments on the text.

I want to thank the Brain Research Trust who provided a grant throughout my period of study. Additionally the National Society for Epilepsy, the National Hospital for Neurology and Neurosurgery and Action Research have supported the NGPSE.

Moreover I am grateful to all the practices and their staff whose cooperation has made this project possible and to my colleagues who have helped with aspects of the studies.

Linkage Clinic: John Duncan, Matthew Walker, Nick Moran, Yvonne Langan.

General practitioners: S. Aarons, E.S. Allen, J. Andrade, Tony Antioniou, Helen Asteriades, Margaret Bailey, Carolyn Barshall, Denise Bavin, Berry Beaumont, F. Bhatti, Susan Blake, Imogen Bloor, Margaret Brodie, Robbie Bunt, Rod Champ, John Cohen, Deborah Colvin, Kathy Connelly, J. Christophers, Fiona Cunningham, Levin David, Costas Dellaportas, K. Durrant, J.M. England, C. Evans, Chris Ford, J.M.T. Ford, Jon Fuller, Jonathon Gore, Richard Halvorsen, L. Hanson, J.M. Hawkins, AJ. Howitt, Brian Hurvitz, Steve Illiffe, Tony Inwald, Jamie Jenkins, Mark Johnson, M. Johnson, Vicky Jolliffe, K. Jolowicz, Sosie Kassab, R. Leibowitz, J.A. Leney, Miranda Leyva, Doris Lister, Pete Lovett, Jane Mansfield, A. Mitchell, Alex Moghissi, J. Moody, Michael Morris, Jonathon Munday, Elizabeth Murray, J. Orton, Helen Parkes, Taj Pradhan, Susie Ramsell, Louise Riches, I. Robinson, L. Ruckert, Alan Schamroth, Judy Sharpey-Schafer, Lionel Sherman, R. Singh, Gary Singh-Marlowe, Liam Spencer, P. Sullivan, Martin Twine, Susan Wallarton, L. Walsh, A. Warsop, Susie Waterman, M. Wiles, J. Wong.

Audit: Karen Rowe, Neil Gelatly, Dominic Heaney

Medical students: Sarah Baker, Bobby Battacharajdde, Verona Beckles, Katie Butler, Rudi Das, Sarah Donnelly, David Elliot, Toni Felix, Johannes Gerber, Perbinder Grewal, Paul Haverty, Katherine Heatley, Badrul Hussain, Zabed Hussein, Jeremy Isaacs, Mehjabeen Islam, Raj Kali, Tajali Khan, Jawad Khan, Andrew Kocen, Rebecca Leung, May Loong, Fatima Mirza, Chidi Ngwaba, Khatim Niwa, Jeya Palan, Manesh Patel, Nish Patel, Monira Rahman, Sanjay Raj, Navin Ramachandran, Julia Ring, Fiona Rose, Navdeep Sethi, Renee Sharpe, Salmah Siddiqui, Nick Silversides, Mara Sittampalam, Lucy Sperling, Shankar Sridharan, Alastair Steel, Toh Lick Tan, Joanna Tenkorang, Nicola Thorley, Fhorkan Udin, Duncan Wong.

I am indebted to and thank all the patients involved in the studies.

Glossary

AED	antiepileptic drug
AF	atrial fibrillation
BIH	benign intracranial hypertension
CI	confidence intervals
CIDP	chronic inflammatory demyelinating polyneuropathy
CL	confidence limits
CNS	central nervous system
CPS	complex partial seizures
CP	cerebral palsy
CSF	cerebrospinal fluid
CT	computed tomography
CTS	carpal tunnel syndrome
d.f.	degrees of freedom
DZ	dizygotic
EMG	electromyogram
EMIS	general practice computer system
ENT	ear, nose and throat
EURODIAB	European Diabetic Study Group
F	female
FC	febrile convulsion
FHSA	Family Health Services Agency
GBS	Guillain Barré syndrome
GPRP	The Office for National Statistics' General Practice Research Database
GP	general practitioner
GTCS	generalised tonic clonic seizure
HHV-6	human herpesvirus-6
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazards ratio
HTLV-1	human T-cell leukaemia virus I
ICD-10NA	International Classification of Diseases 10NA
IDDM	insulin-dependent diabetes mellitus / type 1 diabetes
IIH	idiopathic intracranial hypertension

ILAE	International League Against Epilepsy
LVH	left ventricular hypertrophy
M	male
MG	myasthenia gravis
MHC	major histocompatibility complex
MND	motor neuron disease
MRC	Medical Research Council
MRI	magnetic resonance imaging
MS	multiple sclerosis
MZ	monozygotic
NCPP	National Collaborative Perinatal Project
NCS	nerve conduction studies
NGPSE	National General Practice Study of Epilepsy
NHNN	National Hospital of Neurology and Neurosurgery
NHS	National Health Service
NHSCR	National Health Service Central Register
NIDDM	non-insulin-dependent diabetes mellitus / type 2 diabetes
NIH	National Institutes of Health (USA)
NINDS	National Institute of Neurological Disorders and Stroke
NOS.	not otherwise specified
OPCS	Office for Population Census and Surveys
OR	odds ratio
p.a.	per annum
PBT	primary brain tumour
PHN	postherpetic neuralgia
PNS	peripheral nervous system
PR	prevalence rate
RR	relative risk
SAH	subarachnoid haemorrhage
SEC	socioeconomic class
SLE	systemic lupus erythematosus
SMR	standardised mortality ratio
SPSS	statistical package
SUDEP	sudden unexpected death in epilepsy

TIA	transient ischaemic attack
TNF	tumour necrosis factor
UK	United Kingdom
URTI	upper respiratory tract infection
USA	United States of America
WBC	white blood cell count
WHO	World Health Organization

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