

NEUROEPIDEMIOLOGY

Epidemiology of the epilepsies

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Methodological issues**DIAGNOSTIC ACCURACY AND CASE FINDING**

Accurate diagnostic and case ascertainment methods are a prerequisite for epidemiological research. In epilepsy, a common problem is diagnostic accuracy as it can be diagnosed only by taking a history of the index event or by chance observation of a seizure.¹ The diagnosis is fundamentally a discretionary judgement which depends on the skill and experience of the physician and the quality of witness information available.² Common sources of confusion are syncope or psychogenic attacks.¹⁻⁶ As many as 10%–20% of cases referred to specialised epilepsy units with seemingly intractable seizures do not have epilepsy.^{1-2,4-6} Up to 30% of patients developing epilepsy will eventually be classified as having chronic epilepsy.⁷⁻⁸ The inclusion of patients with non-epileptic attacks in the "chronic epilepsy" group may artificially inflate the proportion of chronic cases.⁸ By contrast, many patients with epilepsy have the condition for some time before the correct diagnosis is achieved.^{1,9,10} Most studies lack clear and reproducible diagnostic definitions, a recent exception being one in Ecuador.^{11,12}

Case ascertainment also poses problems in epilepsy. Some patients with seizures never seek medical attention either through concealment, denial, or ignorance.¹³⁻¹⁴ It is likely, therefore, that field studies miss patients unless sensitive screening techniques for all epileptic phenomena are included in the case ascertainment. This has not yet been achieved. It could be argued that patients not presenting to a medical agency should not be considered a problem. This may hold sway in clinical practice but in epidemiology it is important that all cases are included.¹⁵

The commonest method of case ascertainment is a retrospective review of medical notes, for seizures, antiepileptic drugs (AEDs), EEG, or a diagnostic coding.¹ There are major sources of inaccuracy and underreporting is common. The extent of this was shown by a study in Warsaw that found a prevalence rate of 5.1/1000 based on a survey of medical records alone which rose to 10.4/1000 in a sample of 0.5% of the community.¹³ Similarly, in Guam, incidence rates based on field surveys were twice as high as those based on medical records only.¹⁶

Studies employing record reviews have covered total populations,¹⁷⁻²³ a random sample,¹³⁻²⁴ or selected groups such as sick funds policy holders,²⁵ army draftees,²⁶ hospital attenders,²⁷⁻²⁸ school children,²⁹⁻³¹ government employees,³² those with learning disabilities,³³ or general practitioners' lists.³⁴⁻³⁷ A second approach has been the use of a register of cases but unless precautions are taken, these may present the same diagnostic problems as a review of existing records.^{9,38,39} An advantage of a register set up for research purposes is that the methodology may be planned in advance.¹

An epidemiological approach that does not rely on prior diagnosis is to carry out a community survey with a sensitive and specific screening questionnaire.⁴⁰ This strategy works for tonic clonic seizures and other seizures with florid clinical symptomatology. For other seizure types, however, this may not be accurate as a pragmatic screening instrument for these seizures has not yet been designed. An attempt to design such a questionnaire had to be abandoned due to the low specificity of questions relating to absence and myoclonic seizures.⁴⁰

Community surveys using a screening questionnaire have been carried out in various locations.^{12,13,41-66} Entire populations, random samples, or subgroups have been selected. Such surveys depend crucially on the adequacy of the screening methods and these are difficult to design. It is important to reach a balance between sensitivity and specificity, which has not yet been satisfactorily achieved.⁴⁰ A screening questionnaire and its validation are not easily transferable between different populations due to cultural and social influences and must in all cases be piloted and validated for each population.

CLASSIFICATION

Current classifications of epilepsy are unsatisfactory for epidemiological purposes. Cases are categorised according to seizure type and broad aetiological categories. The agreed seizure type classification incorporates EEG data in a way which is inadequately defined.⁶⁷ Even when presented with extensive EEG recordings and clinical data, specialists often fail to agree on classification⁶⁸ and disagreements concerning seizure classification are often voiced.^{69,70} The use of EEG in field sur-

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veys is often impractical, in which case the seizure type classification is inapplicable.⁷¹ Many published studies, however, have reported the use of this system, without using EEG data and others have used modified versions of the scheme which do not require EEG data.¹¹

Epileptic seizures may be a manifestation of many disease entities and an aetiological classification is of great interest. The relative frequency of different causes may vary in different locations. Cysticercosis is, for instance, the commonest identified cause of epilepsy in parts of Latin America,⁷²⁻⁷⁴ but is virtually unknown in Europe. Most studies that have attempted to classify aetiologies have done so in broad aetiological groupings (symptomatic and cryptogenic or idiopathic). Few cross sectional studies have attempted to classify patients in terms of more strictly defined aetiologies. Reasons for this may be logistical as in many locations complex investigations are impractical. The use of the terms idiopathic epilepsy and cryptogenic epilepsy is a particular source of confusion. Idiopathic epilepsy is used by some authors to refer to the primary generalised epilepsies which have a genetic component with strictly defined clinical and EEG findings,⁷⁵ but by others to refer to any case in which aetiology has not been established. This may make comparisons impossible, as most of the cryptogenic epilepsies differ in many respects from primary generalised epilepsy.

An international classification of epilepsies and epileptic syndromes has been proposed by the International League Against Epilepsy (ILAE).⁷⁶ This scheme, which is perhaps appropriate for use in tertiary referral centres, is difficult to apply in a field study or in retrospective surveys. Probably as a result of this it has seldom been used in any large population study.⁷⁷ The Commission of Epidemiology and Prognosis of the ILAE in their recent guidelines for epidemiological studies on epilepsy offers a simplified version of the scheme and its use should be encouraged (see appendix).⁷⁸ These guidelines define idiopathic epilepsies as being partial or generalised epileptic syndromes with particular clinical and EEG characteristics and a genetic component. The term cryptogenic epilepsies should be reserved for unprovoked partial or generalised seizures in which no factor associated with an increased risk of seizures has been identified and the term symptomatic for seizures associated with a known risk factor.⁷⁸

Further difficulties arise concerning the definition of "epilepsy". The inclusion of single seizures, neonatal seizures, febrile seizures, acute symptomatic seizures, and inactive seizures may vary from study to study, and this may alter any rate by twofold or threefold. Another source of difficulty in prevalence studies is the patient with inactive epilepsy. It is now clear that in most people with epilepsy the seizures cease^{8,35,79} but there is no agreement as to what duration of remission should occur before a patient is no longer designated as an active case. Some influential investiga-

tors have taken the view that "once an epileptic always an epileptic",⁸⁰ others have defined epilepsy as a condition in which a seizure has occurred in the preceding year, two years, or five years. Some investigators have taken treatment status into account, with patients in remission included if they are still taking drugs. Most reports have not considered this problem and it is often difficult to determine if reported rates, particularly of prevalence, are for the active condition or lifetime rates. In recognition of this problem the Commission's guidelines have also defined epilepsy in terms of activity.⁷⁸ An active case is defined as a person with epilepsy who has had at least one seizure in the previous five years regardless of treatment. Inactive cases are defined as remission with treatment (a person with epilepsy with no seizures for more than five years and receiving treatment at the time of ascertainment) or remission without treatment (a person with epilepsy with no seizures for more than five years and not receiving treatment at the time of ascertainment).

Geographic distribution

INCIDENCE

Most of the incidence studies have been retrospective and carried out in the developed world. To date no prospective general population based study of the incidence of epileptic syndromes has been reported. There have, however, been a few clinic based studies of the incidence rates of specific syndromes—for instance, photosensitive epilepsy.⁸¹

Case ascertainment has usually been carried out from medical records or from the hospital clinic, as, for instance, in the studies from Nigata City, Japan,⁸² Iceland,¹⁷ Guam,¹⁶ Warsaw,¹³ Copparo, and Italy,²¹ but some have covered the whole population of an area, as in Umea, Sweden.⁸³ Some investigations were augmented by a medical re-examination.^{13,17,84} In the Guam¹⁶ and Warsaw studies,¹³ a representative household sample was also included. The studies from Rochester, Minnesota and Aarhus, Denmark, have used a retrospective research register.^{9,38,39} In five studies from the developing world a community based house to house survey was used and incidence rates derived from patients whose seizures started in the year before the survey. Two of these studies were in Ecuador^{12,55} and the others were in China,⁵⁸ Chile,⁶³ and Tanzania.⁶⁴ Studies from groups of general practitioners have been carried out in the United Kingdom^{34,37,85} and they have used the number of patients registered in each practice as denominators instead of the more usual census figures. A particular problem in these investigations is the wide variation from practice to practice, suggesting that some general practitioners may have been more assiduous in their registration than others.

The annual incidence rates reported vary between 11/100 000 in Norway¹⁸ to 230/100 000 in Ecuador,⁵⁵ although most lie between 40 and 70/100 000 (table 1). The highest figures are from populations in developing countries^{12,55,63} and this has been a con-

Table 1 Published incidence and prevalence rates of epilepsy in the general population in different countries

Country	Annual incidence /100 000	Prevalence /1000
Brazil ⁹⁷	NA	13*
Colombia ⁴⁶	NA	19.5*
Chile ⁶³	113	11.5-17.7
China ²⁸	35	4.4
Ecuador ^{12 54 55}	122-190	6.7-8.0 ¹² 7.1-17.0 ⁵⁴
	230	9.3 ⁵⁵
Ethiopia ⁶²	NA	5.2
Faroes ³⁶	42	7.6
Guatemala ⁶⁶	NA	5.8
Iceland ¹⁷	26	5.2
Italy ²¹	33	6.2
India ^{60 98}	NA	3.6 ⁶⁰ 2.5 ⁹⁸
	NA	2.3
Libya ²⁸	NA	2.3
Nigeria ⁵¹	NA	5.3
Norway ²⁰	33	3.5
Pakistan ⁶⁵	NA	7.4-14.8
United Kingdom ^{85 35 36}	63 52 48	4.2 ⁸⁵ 5.3 ³⁵ 4.3 ³⁶
United States ^{9 95}	NA 54	6.8 ⁹⁵ 5.7 ⁹
Tanzania ⁶⁴	73-140	5.1-37.0

*Lifetime prevalence.

sistent finding: almost all studies coming from such countries have reported incidence rates of over 100/100 000 whereas those from the developed world were usually between 40 and 70/100 000. In the developed world the classic studies of incidence are those from Rochester, Minnesota based on the Mayo Clinic linkage system.^{9 38} These have assessed incidence from 1935 to 1984. Age adjusted annual incidence rates varied between 40 and 50/100 000 and few changes were seen in overall rates although over time the incidence decreased in children and increased in elderly people. In the developing world a study from semirural Ecuador where meticulous care was taken with methodological issues, an annual incidence rate between 122 and 190/100 000 was reported.¹²

PREVALENCE RATES

As cross sectional data are more easily obtained there are many more studies of the prevalence of epileptic seizures than of incidence; studies have been carried out in more than 25 countries in all five continents.^{9 13 16-21 31-32 34-36 42-52 54-57 60 63-66 82 86-102} Most studies giving data on incidence also report prevalence, and there are additional investigations, some of which have been restricted to selected populations such as army draftees,²⁶ sick fund policy holders,²⁵ mine workers,¹⁰³ school children,^{48 90 104} elderly people,¹⁰⁵ and birth cohorts of children.^{84 106}

As with incidence rates, reported prevalence rates are also very variable and rates as high as 57/1000 and as low as 1.5/1000 have been given for active epilepsy (table 1). The average lifetime prevalence rates reported in these studies is 18.5/1000 (range 2.8-44/1000) for children only and 10.3/1000 (range 1.5-57/1000) for all ages. The problems of case ascertainment have been largely ignored in some of these studies, and no doubt this is partially responsible for the 30-fold range in prevalence rates. The importance of definition can be illustrated by the study of 6000 patients from

one general practice in southern England, where a lifetime prevalence of 20.3/1000 was found for all cases (including single, recurrent, active, and inactive cases but excluding febrile seizures) and 17.0 for those with recurrent seizures only, 10.5 for those with active epilepsy (defined as a seizure in the previous two years) or on treatment, and 5.3/100 000 for those with active epilepsy only.³⁵

In relatively unselected populations, most studies in both the developing and the developed world have found the point prevalence of active epilepsy to lie between 4 and 10/1000.^{9 12 13 17 21 22 24 31 35-36 51 60 62 65 66 85 95 96} For prevalence studies, case finding methods may be usefully combined, and the population investigated at both community and hospital levels by screening questionnaire and medical examination. Many investigations may have underestimated the prevalence of epilepsy, and even if single seizures, febrile convulsions, seizures with acute illnesses, neonatal seizures, and inactive epilepsy are excluded, rates for chronic epilepsy of around 5 to 10/1000 are probably applicable to all general populations in both the developed and developing world.

There have been studies originating in developing countries which reported high prevalence rates for epilepsy. These were from Tanzania,^{87 107} Nigeria,⁵⁰ Liberia,⁹³ Chile,⁶³ Brazil,¹⁰⁸ and Panama.¹⁰⁹ The last study reported the highest recorded prevalence rate, of 57/1000; this was a study of 337 tribesmen with a concomitant high incidence of febrile convulsion. One problem with these studies, however, is that they were mostly on a small scale and were of selected or isolated populations which may have had high rates of genetic or rare degenerative diseases or a high prevalence of parasitic diseases.⁸

Most large scale studies of populations in the developing world have reported overall prevalence rates for active epilepsy around or below 10/1000.^{12 51 58 60 62 65 66}; some of these studies have, however, reported differential rates for urban and rural areas, usually with higher rates in the rural areas.^{12 65} This is clearly illustrated in a study from southern Pakistan where a prevalence rate for active epilepsy of 9.9/1000 for the area as a whole was reported; in the rural areas this was 15/1000 by contrast with 7.4/1000 in the urban population.⁶⁵ Similarly, in Ecuador a minimum lifetime prevalence of 14.3/1000 was reported for an Andean region; corresponding values for the urban and rural areas were respectively 9/1000 and 15.4/1000.¹² In this study the area surveyed was divided into two distinct subregions: an upper region situated 2500-3200 m above sea level and inhabited primarily by people of Amerindian background and the other a temperate region situated at 1500-2000 m above sea level and with a population of African extraction. The lifetime prevalence of epilepsy was much lower in the higher area than in the lower region (11.2/1000 *v* 24.8/1000). Other studies have also reported differing prevalence rates from within study areas. In Tanzania, an overall prevalence rate of 10/1000 was reported for a rural district consisting of 11 villages;

rates varied among the villages and a prevalence range of 5 to 37/1000 was found.⁶⁴ The differences reported in these studies from Pakistan, Ecuador, and Tanzania seem unlikely to be attributable to differential case ascertainment between the region as each study used identical methods, study design, and diagnostic confirmation in each area. No clear aetiological reason for these variations in prevalence in contiguous geographic areas were identified. These differences are of great potential importance, for herein may lie a clue to aetiology and indeed they possibly provide the basis for the prevention of epilepsy in rural areas. Future epidemiological work should be carried out to identify the reasons for these pronounced differences, including studies of the prevalence and case-control studies of neurocysticercosis and other parasitic diseases in rural areas of developing countries.

LIFETIME PREVALENCE

Cumulative incidence or lifetime prevalence rates are much higher than the incidence or the prevalence of active epilepsy, and on the basis of available figures it is generally agreed that between 1.5% to 5% of any population will have non-febrile seizures at some time.^{8 9 12 17 35 36 38 39 83 85 108} This finding applies to patients in both the developed and the developing world where the incidence seems to be higher and where treatment with antiepileptic drugs is not usually available. From the difference between lifetime prevalence and the point prevalence of active epilepsy it is obvious that most patients developing epilepsy will cease to have seizures or will die. It is likely that in most patients with seizure disorders the condition remits: however, it is known that the epilepsies are associated with an increased mortality, particularly but not exclusively with symptomatic cases.¹¹⁰⁻¹¹³ Patients with chronic epilepsy seem to be particularly at risk but the impact of mortality on the prevalence of epilepsy and the extent to which the difference in lifetime and point prevalence rates is due to mortality has not yet been fully appraised.¹¹⁴⁻¹¹⁵

In the developed world the overall good prognosis for seizure control is now attributed mainly to the widespread and early use of antiepileptic drugs.^{8 112} The suggestion has been made, however, that a significant number of patients developing an epileptic syndrome will enter a permanent remission regardless of treatment with drugs.⁸ Support for this proposition has come from analysis of epidemiological data arising from the developing world where despite the lack of antiepileptic drugs a significant number of patients enter long term remission.¹¹⁶ In addition, it is well recognised that a number of epileptic syndromes—for instance, benign rolandic epilepsy and benign familial neonatal convulsions—have an excellent outcome which is independent of drug treatment.¹¹² This is an area that requires further work, because if this lack of effect of antiepileptic drugs on prognosis is true on a wider basis, a change in the routine management of epilepsy may be necessary. If patients with an inherently good prognosis for their

epileptic syndrome could be identified at the onset of their condition, the option of no treatment or only very short courses (to avoid seizure related accidents and morbidity) could become clear alternatives. If by the same token inherently bad prognosis syndromes could be identified earlier, more aggressive management may limit the “progression” of the disorder.

Demographic and secular trends

Little attention has been directed to changes in epidemiological rates over time. In most studies, age specific incidence rates are bimodally distributed with the highest peak in the first decade, and within this decade in the first year of life. The rates fall in the second decade and remain low in early and mid-adult life only to increase in late life when the second peak occurs. This, however, might be changing as some interesting shifts have been seen recently.¹¹⁷ In south east England, the incidence of epilepsy in children declined from 152/100 000 in the period of 1974 to 1983 to 61/100 000 in the years from 1984 to 1993 while increasing in elderly people over the same period.³⁶ Similarly, in Rochester, Minnesota, the incidence of seizure disorders has decreased in children over time whereas it increased in elderly people to a point that the highest peak is now seen in people over the age of 75.³⁸ In Sweden, it has recently been reported that the highest incidence of epileptic seizures is now in people over the age of 65 (139/100 000 *v* overall incidence rate for epilepsy of 56/100 000⁸³). The United Kingdom National General Practice study of epilepsy, a study of incident cases, found that only a quarter of all cases recruited were under age 15 when over 40% of new cases in this age range would be expected if previous age specific incidence data are correct. In this study over a quarter of the patients identified were aged 60 years or over.^{10 118} One other study has also recently reported changes in the prevalence of epilepsy in the same population over time: the prevalence of active epilepsy declined from 5.3/1000 in 1983 to 4.3/1000 10 years later.³⁶ No clear explanation for these changes has yet been advanced. In children speculation has centred on the role of improved prenatal care and the adoption of healthier lifestyles by expectant mothers, leading to a decrease in defects in neuronal migration and to a reduction in the incidence of birth hypoxia.¹¹² In elderly people it is presumed that an increase in life expectancy allied to cerebrovascular diseases is responsible for the increase. This seems paradoxical, however, as the incidence of cerebrovascular diseases has decreased in the community over the past two decades.³⁸

Clinical characteristics

Many studies have reported that most patients have generalised seizures and proportions as high as 88% have been reported.⁵⁸ This is, however, likely to be due to such methodological problems as described above. In studies in

which particular care was taken with seizure classification and EEG was used, most patients had partial seizures with or without secondarily generalisation and this is also the experience of most tertiary referral centres. In Rochester, Minnesota 66% of the patients had partial seizures⁹ and in the Warsaw field study 65% of patients were reported to have had partial seizures.¹³ In the large population-based Ecuadorian study, seizures were classified without the use of EEG, and half of the patients were reported to have had partial seizures.^{12,13} In the United Kingdom National General Practice study of epilepsy, in which routine investigations were applied, 52% of patients had partial seizures, 39% generalised seizures, and the remaining were unclassifiable.¹⁰

In most studies, only two seizure types were common: tonic clonic convulsions and partial seizures with or without secondarily generalisation. Other seizure types—that is, generalised absence, tonic and atonic seizures, and myoclonic seizures—are uncommon. Generalised absence, for instance, is usually reported in less than 2% of patients.¹⁵ Although this is a seizure type known to all medical students and practitioners, it is rare in population terms. The patient presenting with an absence is much more likely to have partial seizures than true generalised absence attacks, although these are often confused. For the diagnosis of true generalised absence seizures, an EEG recording showing three per second spike and waves discharges is necessary. Some studies that have reported the presence of generalised absences did not include EEG as part of the methodology.¹⁵

The present scheme for seizure classification is unsatisfactory and not suitable for field studies, in which the use of EEG is not practical. The categorisation of seizure type is often difficult, and there seems to be little doubt that partial seizures are often underreported. Many so-called generalised seizures are secondarily generalised, and should be categorised as partial, and the detection of a partial onset may depend on the skill of the investigator or the extent of investigation. The studies showing the highest proportion of partial seizures are those in which medical services are the most complex. Thus although this classification has often been said to have been used in large scale surveys, the reported seizure classification should be viewed with caution. Another point to note is the almost complete absence of unclassified convulsions in published reports which purport to have used the international classification. In hospital practice about one third of cases are unclassifiable.¹

Only a few population based studies have reported frequency and severity of seizures. Indeed, very often it is difficult to ascertain, from study reports, how many cases have qualified as cases only due to the use of antiepileptic drugs. In one large study on the use of antiepileptic drugs on prevalent cases in a developed country when this information was provided, 46% of patients were reported to have been seizure free in the previous year, 33% had between one and 12 seizures a year, and the remaining more than one seizure a month, 8% of whom had more than 50 seizures a year.¹¹⁹ In a prevalent population in a developing country where treatment with antiepileptic drugs was not generally available and only 15% of patients were using drugs at the time of the survey, 45% of patients were reported to have had less than 10 seizures before the survey, 14% between 10 and 100 seizures, and the remaining 26% more than 100 seizures.¹¹⁶

Table 2 gives the frequency of epilepsy in a population of 100 000 in a developed country based on the figures discussed above.

Risk factors, aetiologies, and the heterogeneity of the epilepsies

RISK FACTORS AND AETIOLOGY

From hospital and clinic studies it is well known that the range of aetiologies in the epilepsies varies in different age groups and also according to geographic location. Congenital, developmental, and genetic conditions are associated with epilepsy in childhood, adolescence, and in young adults. In elderly people, cerebrovascular disease is common. Head trauma, sporadic CNS infection, and tumours may occur at any age although tumours are more likely over the age of 40. In certain areas endemic infections that are associated with epileptic seizures are common. The aetiology of epilepsy may be multifactorial and an acquired condition may be more likely to occur if an inherited predisposition is present.² The relative contributions of each of these potential causes for the aetiology of the epilepsies in the general population have, however, not yet been formally ascertained.

In most field investigations, a putative aetiology for the epilepsy was found in only about a quarter or a third of cases. In the Rochester study,⁹ 5% were due to head trauma, 5% to cerebrovascular diseases, 4% to brain tumour, 4% to congenital or genetic abnormalities, and 3% to infectious diseases, whereas in the study from Copparo (which has one of the highest percentages of cases with known aetiology) 20% were said to be secondary to perinatal injuries, 7% to head trauma, 5% to infective diseases, 4% to cerebrovascular diseases, and 2% to brain tumour; in 61% no cause was found.²¹ In Ecuador, no putative cause for the seizures was identified in at least 73% of the patients.¹² Likely aetiologies were estimated in the remaining 27% of patients and these included birth trauma (9%), head injury (7%), neurocysticercosis (3%), and cerebrovascular diseases (3%). In the United Kingdom

Table 2 The frequency of epilepsy in a population of 100 000 in a developed country

New cases of epilepsy each year (incidence)	40–70
Cases of active epilepsy (prevalence)	500–1000
Cases who ever had epilepsy	2100–5000
Seizure frequency for those with active epilepsy:	
No seizures for more than 12 months	230–460
Between 1 and 12 seizures/year	165–330
Between 12–50 seizures/year	65–130
More than 50 seizures/year	40–80

National General Practitioners' study of epilepsy, seizures were classified as idiopathic or cryptogenic in 72%, remote symptomatic in 25%, and the remaining 3% were associated with neurological deficits present at birth.¹⁰ The commonest putative aetiology in this study was cerebrovascular disease. Overall 16% of all patients had this as the cause of their epilepsy but it rose to 49% in the group older than 60. A similar finding has been reported from Sweden: cerebrovascular diseases were responsible for 30% of all cases of epilepsy in adults, but this increased to 46% in those aged 60 or over.⁸³

It is self evident that the more extensive the investigation, the more likely are aetiological factors to be identified. To what extent this would modify the findings of a large scale epidemiological investigation is uncertain. Brain MRI identifies a very much higher rate of positive causes in hospital based surveys but in field surveys or in retrospective record reviews it is inapplicable.¹²⁰ Indeed no population based study of epilepsy with modern neuroimaging as part of the study design has yet been reported. Because of this, the true incidence of symptomatic epilepsies in the general populations is unknown, and is likely to be much higher than that found in the epidemiological studies cited above. As yet, no epidemiological based study accurately describes the range of aetiologies of epilepsy. This deficiency urgently needs to be corrected and is a vital prerequisite to sensitive case-control investigations of relative risk.

Sex

Most reports show slightly higher rates in males than in females.¹ The suggestion that this is due to a higher incidence of head trauma has never been formally confirmed, and the low overall incidence of post-traumatic epilepsy makes this unlikely.^{121 122} Syncope and psychogenic attacks are much more common in females than in males, and the potential for misdiagnosis in epilepsy in females is greater.⁴ Consultation rates from general practices in the United Kingdom, for instance, show that females consult their general practitioner for episodes of disturbed consciousness of any sort twice as often as males.¹²³

Race and socioeconomic status

There are several small scale reports showing high rates in black African populations.^{50 86 87 93} In Ecuador, the prevalence of seizures was much higher in a population predominantly of African descent than in a neighbouring population made up mostly by Amerindians.¹² A higher prevalence rate for Afroamericans than for white subjects was reported in two studies of American school children.^{27 124} A similar finding was reported in adults from a census of neurological diseases in a biracial population of Copiah County in the south of the United States.⁹⁵ Similarly, United States mortality data suggest that the prevalence of epilepsy in non-white subjects is twice that of white subjects in America.¹²⁵ A lower standard of perinatal care might be relevant, and the infant

mortality rates among the black population in America is twice that of the white population.^{27 126} Data from other developed countries and also from developing countries suggest higher prevalence rates in the lower socioeconomic classes^{17 34 46 63 127} but no definitive evidence for this suggestion has yet been unveiled. Case-control studies to consider this issue are also needed.

THE HETEROGENEITY OF THE EPILEPSIES

A fundamental issue, often glossed over in the epidemiological literature, is that of the heterogeneity of the epilepsies.⁸ Many different conditions, with differing causes and outcomes, may express themselves solely by the occurrence of recurrent epileptic seizures. Epilepsy is a collection of syndromes and conditions rather than a single disease, but most studies have reported on "epilepsy" as a whole or according to seizure type rather than by any more meaningful classification. An analogy can be drawn with the anaemias.¹²⁸ If the epidemiology of anaemia were studied as if it were a single disorder, it is unlikely that useful aetiological data would ever arise.

The syndromes of idiopathic epilepsy

Even the "idiopathic" epilepsies, which are often considered homogeneous, include conditions with differing incidence and outcome.¹¹² Thus generalised absence epilepsy, epilepsy with generalised tonic clonic convulsions on awakening, and juvenile myoclonic epilepsy are all well recognised syndromes under the rubric of the generalised idiopathic epilepsies. These conditions probably have different genetic mechanisms and may have different natural histories. A 24-fold difference in the cumulative incidence of generalised absence epilepsy has been reported between populations in Sweden and Japan, perhaps due to genetic differences.¹⁵ These aetiologically important factors would be obscured by epidemiological studies that categorised them all under idiopathic epilepsy.

It is self evident but often overlooked that classification by seizure type alone is not sufficient to allow a classification by syndrome. Generalised tonic-clonic seizures are characteristic of many epileptic syndromes. Such seizures can occur in acute symptomatic epilepsy, generalised epilepsy, whether idiopathic or symptomatic, and in all forms of localisation related epilepsy. The clinical characteristics of partial seizures also disclose little of aetiological or prognostic value. Seizures represent an expression of an underlying pathology, the cause of which is not disclosed in the phenomenology of the symptom. Epidemiological studies have, however, typically relied heavily on seizure characteristics as the key epilepsy variable.

Many epilepsy syndromes can only be diagnosed with the benefit of several years of follow up. Cross sectional studies will inevitably misclassify a significant number of cases. Studies done before access to modern investigation techniques do not reflect current thinking about the aetiology of epilepsy. The same

also applies to field studies, particularly in developing countries, in which even EEG is often not practical.

The need for case-control studies to investigate aetiology

Studies have suggested that there are geographic differences in the incidence of epilepsy, with a higher incidence in the developing world. It is often implied that infections of the CNS are partly responsible for this increased incidence and this might well be true as many agents that infect the CNS are associated with both acute symptomatic seizures and seizures in the aftermath of infection.^{129 130} Often, studies from the developing world link a high prevalence of some local infectious disease with epilepsy but most of these studies lack sufficient controls to confirm conclusively that the infections are the underlying cause. In Ecuador, Peru, Brazil, and Mexico for instance, neurocysticercosis is prevalent in attenders of neurological clinics, many of whom may have epilepsy.^{73 74 129-134} Post-mortem and other studies suggest that asymptomatic cysticercosis is also common.^{129 135} What is unknown, however, is the prevalence of epilepsy in all people who harbour cysticerci in their brain. No adequate large scale study of neurocysticercosis, on a population basis, has ever been carried out to ascertain attributable risk. Other parasitic disorders such as malaria,^{129 130 136 137} schistosomiasis,¹³⁸ paragonimiasis,^{129 130 136} or American trypanosomiasis^{63 129 139} have also been implicated as risk factors for subsequent epilepsy, but again this has not yet been substantiated. Another possible explanation for the finding of high prevalence rates in geographically isolated clusters, would be that this is due to genetically determined syndromes,⁸ but this also lacks confirmation.

Another important area of uncertainty is the role of neuronal migration disorders and other developmental abnormalities of the cerebral cortex in the aetiology of the epilepsies in the general population in both developed and developing countries. These are now well established as associated with chronic epilepsy in hospital attenders.^{140 141} It is, however, not known what the prevalence of these conditions is in the population at large to enable an estimation of relative risk. By the same token, the finding of hippocampal sclerosis in patients with chronic partial epilepsy is associated with a history of febrile convulsion between the ages of 3 months and 5 years in over two thirds of the cases.¹⁴² Epilepsy, however, develops in less than 3% of children who experience a febrile convulsion with no previous neurological abnormalities and the risk factors for this are known.^{124 142} It is still not known how common hippocampal sclerosis is in the general population or even among those who as youngsters experienced febrile convulsions but did not subsequently develop chronic epilepsy.

Syndromic classification

Two difficulties can be foreseen with a "syndromic approach" to the neuroepidemiology

of the epilepsies. Firstly, the present syndromic classification is provisional. Recent advances in neuroimaging and neurogenetics are likely to identify further syndromes. For example, familial autosomal dominant frontal lobe epilepsy recently became characterised clinically, and shortly thereafter was linked to a specific genetic cause in some families.¹⁴³ Other new disorders include the milder forms of neuronal migration disorders associated with epilepsy.^{140 141} Secondly, there are questions that epidemiology in its present form cannot answer. For example, the reason why, in pathologically defined conditions, the response to treatment and final outcome is not always the same. This seems to indicate that factors other than gross pathology influence outcome. Cavernous angiomas, for instance, cause epilepsy in less than 70% of patients identified.¹⁴⁴ Why do some patients with lesions in similar locations develop epilepsy and others do not? Furthermore, some who develop seizures respond to drug treatment, whereas others develop intractable epilepsy. The risk of epilepsy after severe non-penetrating head injury is about 20% at five years; some respond to drug treatment whereas others develop intractable epilepsy.¹²¹ There is anecdotal evidence that some people with epilepsy of temporal lobe type associated with hippocampal sclerosis respond favourably to certain antiepileptic drugs whereas others fail to respond to any drug. Thus presently "aetiologies" are not the sole determinant of outcome and response to treatment and unknown factors must exist. Current epidemiological studies are likely to fail to define completely the epileptic substrate. Further research at a neurobiological level is required before progress can be made. For any future research to have an impact it must also take into account the advances in neurogenetics and neuroimaging that so far have not been used to any extent in epidemiological work on the epilepsies.

Conclusion

Little is known about the true epidemiology of the different epileptic syndromes in the general population, as definitive studies are lacking. However, data based on seizure types suggest that the epilepsies are common, with an incidence between 40 and 200/100 000 depending on geographic location. Despite this high incidence the overall prevalence lies between 0.5%–1% of the general population. It may be more common in specific age groups—that is, children and elderly people—and in particular, geographic locations for genetic or environmental reasons. Changes in the age-specific incidence may be occurring with a shift to the older age groups. Those who develop epilepsy, not complicated by an underlying neurological disorder, have a good prognosis for full seizure control, although the full impact of mortality on the outcome of the epilepsies in the general population has not yet been fully assessed.

To extend our knowledge in this area future studies need to be large scale, general popula-

tion based prospective incidence studies of the different epileptic syndromes with comprehensive case ascertainment, accurate diagnosis, and sound aetiological assignment. Cohorts of patients so identified should then be prospectively followed up to determine accurately the overall prognosis for seizure control and mortality, in tandem with analytical case-control studies to quantify aetiological risk factors. Further cross sectional studies are unlikely to be helpful. Specific questions that require investigation include the quantification of possible geographic differences in the incidence and the relative contribution of various aetiologies to the difference, the cause of possible changes in the age specific incidence, and accurate syndrome specific incidence rates. In addition, further studies to delineate the range of epileptic syndromes should be strongly encouraged.

We are grateful to Drs M F O'Donoghue, O C Cockerell, N Bharucha, and J Duncan for discussions and comments on the concepts discussed in this review.

Appendix: ILAE guidelines for epidemiological studies (adapted from⁷⁸)

(1) Definitions

EPILEPTIC SEIZURE

A clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor sensory, autonomic, or psychic events, perceived by the patient or an observer.

EPILEPSY

A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24 hour period are considered a single event. An episode of status epilepticus is considered a single event. Those who have had only febrile seizures or only neonatal seizures as herein defined are excluded from this category.

STATUS EPILEPTICUS

A single epileptic seizure > 30 minutes in duration or a series of epileptic seizures during which function is not regained between ictal events in a > 30 minute period.

"ACTIVE EPILEPSY"

A prevalent case of active epilepsy is defined as a person with epilepsy who has had at least one epileptic seizure in the previous five years, regardless of antiepileptic drug treatment. A case under treatment is someone with the diagnosis of epilepsy receiving (or having received) antiepileptic drugs on prevalence day.

EPILEPSY IN REMISSION WITH TREATMENT

A prevalent case of epilepsy with no seizures for five or more years and receiving antiepileptic drugs at the time of ascertainment.

EPILEPSY IN REMISSION WITHOUT TREATMENT

A prevalent case of epilepsy with no seizures for five or more years and not receiving antiepileptic drugs at the time of ascertainment.

SINGLE OR ISOLATED SEIZURE

One or more epileptic seizures occurring in a 24 hour period.

FEBRILE SEIZURE

An epileptic seizure as herein defined, occurring in childhood after age 1 month associated with a febrile illness not caused by an infection of the CNS, without

previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures.

NEONATAL SEIZURE

An epileptic seizure as herein defined occurring in the first 4 weeks of life.

FEBRILE SEIZURE WITH NEONATAL SEIZURE

One or more neonatal seizures in a child who has also experienced one or more febrile seizures as herein defined.

NON-EPILEPTIC EVENTS

Clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of a set of neurons of the brain, including: (a) disturbances in the brain function (vertigo or dizziness, syncope, sleep and movement disorders, transient global amnesia, migraine, enuresis), and (b) pseudoseizures (non-epileptic sudden behavioural episodes presumed to be of psychogenic origin; these may coexist with true epileptic seizures).

(2) Seizure type classification

GENERALISED SEIZURES

A seizure is considered generalised when clinical symptomatology provides no indication of an anatomical localisation and no clinical evidence of focal onset. When possible, three main seizures subtypes may be categorised:

- Generalised convulsive seizures with predominantly tonic, clonic, or tonico-clonic features
- Generalised nonconvulsive seizures represented by absence seizure
- Myoclonic seizures.

In patients who have experienced several types of generalised seizure each seizure type must be categorised.

PARTIAL SEIZURES

A seizure should be classified as partial when there is evidence of a clinical partial onset, regardless of whether the seizure is secondarily generalised. The first clinical signs of a seizure ("the aura"), have a highly localising value and result from the anatomical or functional neuronal activation of part of one hemisphere.

- When alertness and ability to interact appropriately with the environment are maintained, the seizure is classified as a simple partial seizure.
- When impairment of consciousness, amnesia, or confusion during or after a seizure is reported, the seizure is classified as a complex partial seizure.
- When a seizure becomes secondarily generalised, the seizure is classified as partial seizure, secondarily generalised (simple or complex).
- When the distinction between simple and complex partial seizure cannot be made from information provided by history and medical records, the seizure is classified as partial epileptic seizure of unknown type.
- When a patient has several types of partial seizure, each should be separately categorised.

MULTIPLE SEIZURE TYPE

When both generalised and partial seizures are associated, each type must be described.

UNCLASSIFIED SEIZURES

The term unclassified seizures should be used when it is impossible to classify seizures owing to lack of adequate information.

(3) Aetiology and risk factors

Epileptic seizures and the epilepsies may be a manifestation of many cerebral or systemic diseases. The first step in categorisation of seizures should be based on the presence or absence of a presumed acute precipitating insult, which will permit distinction into provoked

or unprovoked seizures. Single or recurrent unprovoked seizures may belong to two possible categories: symptomatic seizures, or epilepsies and seizures or epilepsies of unknown cause.

SYMPTOMATIC SEIZURES OR EPILEPSIES

These are considered to be the consequence of a known or suspected cerebral dysfunction.

Provoked seizures (acute symptomatic seizures)

Seizure(s) occurring in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute CNS insult (infection, stroke, cranial trauma, intracerebral haemorrhage, or acute alcohol intoxication or withdrawal). They are often isolated epileptic events associated with acute conditions, but may also be recurrent seizures or even status epilepticus when the acute conditions recur—for example in alcohol withdrawal seizures.

Unprovoked seizures

Seizures may occur in relation to a well demonstrated antecedent condition, substantially increasing the risk for epileptic seizures. Two major subgroups may be categorised:

- Remote symptomatic unprovoked seizures owing to conditions resulting in a static encephalopathy. Such cases are patients with epilepsy subsequent to an insult of the CNS, such as infection, cerebral trauma, or cerebrovascular disease, which are generally presumed to result in a non-progressive (static) lesion.
- Symptomatic unprovoked seizures owing to progressive CNS disorders.

UNPROVOKED SEIZURES OF UNKNOWN AETIOLOGY

Cases of unprovoked seizures for which no clear antecedent aetiology can be detected. If possible, these cases can be further classified into the following sub-headings:

Idiopathic epilepsies

The term idiopathic is used here as defined by the ILAE⁷⁶ and must be reserved for certain partial or generalised epileptic syndromes with particular clinical characteristics and with specific EEG findings, and should not be used to refer to epilepsy or seizures without obvious cause.

Cryptogenic epilepsies

The term cryptogenic is used to include partial or generalised unprovoked seizures or epilepsies in which no factor associated with increased risk of seizures has been identified. This group includes patients who do not conform to the criteria for the symptomatic or idiopathic categories. Whenever possible, the Commission on Epidemiology and Prognosis encourages use of the most recent ILAE Classification of Epilepsies and Epileptic Syndromes.⁷⁶ Appropriate categorisation of individual cases may require use of state of the art technologies and procedures. In many settings in which epidemiological studies are conducted, in particular in field situations, all required information for proper classification of epileptic syndromes cannot be obtained.

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