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THE EPIDEMIOLOGY OF MORTALITY AND TREATMENT OF PEOPLE WITH EPILEPSY

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Abstract

The UK National General Practice Study of Epilepsy (NGPSE) is a prospective, population based study of newly diagnosed epilepsy including acute symptomatic seizures and single seizures. Patients were followed for 11,400 person years (median follow-up [25th, 75th centiles] is 11.8 years [10.6-12.7]). Out of 564 patients with definite and 228 with probable epilepsy, 149 and 50 deaths respectively were analysed. Long-term mortality was twice that of the general population (standardized mortality ratio [SMR] 2.1 [95% Confidence interval (CI)=1.8,2.4]). Multivariate Cox regression and time dependent co-variate analyses were utilised for the first time in a study of mortality in epilepsy. Patients with generalised tonic clonic seizures had an increased risk of mortality (hazard ratio or HR 6.2 [95%CI=1.4,27.7; p=0.049]). Time dependent co-variate analysis examined the influence of ongoing factors on mortality. Seizure recurrence (HR 1.30 [95%CI=0.84,2.01]) and AED treatment (HR 0.97 [95%CI=0.67,1.38]) did not influence mortality.

Treatment patterns in 564 patients with definite epilepsy were followed prospectively for 11-14 years. Treatment was started in 433 (77%) patients. Only 15% of single seizure (index seizure = first seizure) cases had any medication prescribed initially. Due to subsequent seizure recurrence, more than 70% of these patients ultimately received antiepileptic medication. 209/564 patients (37%) were on treatment for epilepsy at last follow-up. 98/209 (47%) of those on treatment were in 5-year terminal remission.

Figures from this study suggest that of 30,000 patients newly diagnosed with epilepsy every year in the United Kingdom, approximately 6000 have inadequate seizure control in the long term. A third of the patients in this group have one or more seizures monthly. Only 2/3rds of these patients with frequent seizures had switched medication in order to try and achieve better seizure control. There is probably still considerable room for improvement in prescribing practice in the UK.

PUBLICATIONS ARISING FROM THIS THESIS

1. **Lhatoo SD,** Sander JWAS, Shorvon SD. The dynamics of drug treatment in epilepsy: an observational study in an unselected population based cohort with newly diagnosed epilepsy followed prospectively over 11-14 years.
   J Neuro Neurosurg Psychiatry 2001;71: 632-637

2. **Lhatoo SD,** Johnson AL, MacDonald BK, Goodridge DM, Sander JWAS, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort.
   Ann Neurol. 2001; 49: 336-44.

3. **Lhatoo SD,** Solomon JK, McEvoy AW; Kitchen ND, Shorvon SD, Sander JWAS. A prospective study of the requirement for and the provision of epilepsy surgery in the United Kingdom.
   Epilepsia 2003; 44: 673-6

4. **Lhatoo SD**, Langan Y, MacDonald BK, Zeidan S, Sander JWAS. Sudden unexpected death: a rare event in a large community based prospective cohort with newly diagnosed epilepsy and high remission rates.
   J Neuro Neurosurg Psychiatry 1999; 66: 692

5. **Lhatoo SD**, Sander JW. The prognosis of epilepsy in the National General Practice of Epilepsy. In; Prognosis of Epilepsies 2003. Ed Jallon P; John Libbey Eurotext.

AWARDS ARISING FROM THIS THESIS

Lhatoo SD, Johnson AL, MacDonald BK, Goodridge DM, Sander JWAS, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort.

Young Investigator Award. American Epilepsy Society 2000.

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My parents, who taught me that there are Everests to be climbed beyond the Himalayas, will be proud of the small contributions these studies make to modern epilepsy practice. My thanks to my wife Sonam, and my children Karchen and Rigzin for their generosity with the time that this thesis took to completion!

AUTHORS CONTRIBUTION

The National General Practice Study of Epilepsy was conceived of and started by Professors SD Shorvon and JWAS Sander of the Department of Clinical and Experimental Epilepsy in the Institute of Neurology, Queen Square London in 1984. This study has reported previously on the prognosis and mortality of epilepsy in this cohort.

This author was solely responsible for the running of this study from January 1998 until January 2000. He was responsible for the maintenance of the database software. During this period, this author collected data from 275 collaborating general practices and was responsible for the collation, data entry statistical analysis and interpretation of accumulated information.

In collaboration with Dr A Johnson from the Cambridge MRC Biostatistics Unit, this author used statistical methods novel to the analyses of data in the mortality of epilepsy. This included Cox model multi-variate analysis as well as time dependent co-variate analysis of data. He was solely responsible for interpreting analysed data and the writing up of all the publications that arose in the course of the preparation of this thesis.

The section on the dynamics of the treatment of epilepsy was entirely conceived of by this author. This included the epidemiological model of the long-term treatment of epilepsy in the United Kingdom based on the sub-sections on observations made, including treatment of first seizures, numbers continuing treatment and treatment changes.

INTRODUCTION

Epidemiology is the study of the natural history of disease, which includes its frequency, severity and course as well as the identification of the risk factors that influence these aspects. Thus, neuroepidemiology is the branch of epidemiology that deals with the disease processes or conditions that afflict the nervous system. The natural history of any disease is best studied in population based cohorts where the disease spectrum is seen in its entirety rather than in hospital based groups where there is an inherent bias towards patients who have more severe disease and are likely to seek specialist medical help. This is particularly true of the epilepsies where age, demographics, disease aetiology, remission, recurrence and severity vary widely.

Apart from the population-based reports from the Mayo Clinic in Rochester, there were no large-scale epidemiological studies of epilepsy until the National General Practice Study of Epilepsy, which is unique in its representation of the epilepsies in a modern, industrialised nation context. It is particularly attractive as a resource in the study of epilepsy because of its design as a prospective study that, through comprehensive and regular data collection, provides accurate information on its long-term prognosis including seizure remission, recurrence and mortality. This study has already reported on the short and intermediate term mortality of epilepsy, analysed prospectively. We undertook to further explore the long-term aspects of mortality in epilepsy in this same cohort.

Through its observational, non-interventional nature, this study provides valuable insights into the treatment of the epilepsies, which for both doctors and patients, involves a long-term commitment to various drugs and drug regimens. Increasingly, modern epilepsy treatment moves towards standardisation and rationalisation of therapies and without specialist intervention or supervision, many patients are at risk of inadequate or inappropriate treatments. The National General Practice Study of Epilepsy is invaluable in its potential to reflect current practices

and provides an accurate representation of the dynamics of treatment changes in the long term. There is particularly interesting information on 20-30% of patients with treatment resistant epilepsy who are most likely to require ongoing treatment intervention.

The purpose of the studies detailed in this thesis was to analyse and describe mortality in the long term and its various aspects, in a community based population with epilepsy; further, it was to describe in a longitudinal and observational fashion, the modern day treatment of epilepsy in the United Kingdom.

The study on mortality confirms in a prospective fashion what large-scale retrospective studies have suggested; that the mortality of epilepsy is elevated in the long-term even in community based populations with epilepsy. The multivariate analysis and the time dependent co-variate analysis are novel analyses. The Cox model multivariate analysis confirms what uni-variate analyses in previous studies have shown; that older age at diagnosis, cerebrovascular disease, alcohol, tumours and congenital neurological deficits are associated with increased mortality. The time dependent co-variate analysis examining dynamic variables shows that seizure recurrence and drug treatment in epilepsy do not influence mortality in a community based cohort with epilepsy.

The study on treatment makes observations on antiepileptic drug therapy in a community-based cohort in the UK for the first time. It reveals that a substantial proportion of patients do not have their medication changed despite continuing seizures, suggesting room for improvement in the management of epilepsy in the community. It also confirms the observation that lack of response to initial medication due to lack of efficacy can predict poor response to further medication changes although the significance of this finding in this purely observational, non-interventional study is limited.

AIMS OF THE STUDIES

MORTALITY

The aim of the study of mortality was:-

- To determine whether mortality in patients with epilepsy is elevated in the long term
- To determine mortality rates according to age, aetiological classification, cause, seizure type, time since diagnosis and seizure frequency before index seizure
- To perform a Cox proportional hazards model multi-variate analysis of mortality using baseline variables
- To perform a time dependent co-variate analysis of mortality using baseline and dynamic variables

TREATMENT

The aim of the study of treatment was:-

- To determine the number of patients that receive treatment for newly diagnosed epilepsy in the general population
- To make observations on treatment patterns and the dynamics of the treatment of epilepsy over time
- To determine current trends in the community treatment of epilepsy in the United Kingdom.

A CRITICAL REVIEW OF THE LITERATURE

1.1 METHODOLOGICAL CONSIDERATIONS

Methodology is an important issue and requires proper attention in all epidemiological studies. As with many other disease conditions, lack of standardisation in many studies of epilepsy renders their interpretation difficult.

1.1.1 The definition of epilepsy

The diagnosis of epilepsy, by definition, is made only after a two or more unprovoked epileptic seizures, although it is becoming increasingly evident that the majority of patients with single seizures go on to have more. "Epilepsy" encompasses a wide range of conditions in which seizures are a manifestation. The use of the term "epilepsies" is therefore, preferable to "epilepsy" (Sander JWAS 1993). Single, acute symptomatic seizures and childhood febrile convulsions are not considered to be epilepsy in most studies. (Acute symptomatic seizures have been variably defined as seizures occurring within a week [Hauser, and others 1982], to three months [Sander, and others 1990] of a causative insult)

The study of the prognosis of epilepsy is rendered difficult by the diversity of underlying diagnoses of which epilepsy is a symptom. Potential aetiologies range from those well known to those that are unknown (cryptogenic).

1.1.2 Diagnostic difficulties

Diagnosing epilepsy can be a complex task, especially since a good witnessed account of the seizure is crucial. For a variety of reasons, this is often difficult to obtain. Seizures may be nocturnal or occur in the early

morning and thus may be un-witnessed; some, such as minor complex partial seizures and absence attacks, may be brief, and may not appear as abnormal to the unpractised eye. Poor observation in describing the seizure, and inaccuracy of second-hand accounts are common sources of error. Some, such as the elderly, those with learning difficulties, and those with infrequent seizures may not be able to provide an eloquent account of events. There may also be significant variability in the way clinicians interpret information. In some reports up to 26% of patients referred to specialist epilepsy clinics are diagnosed as not having epilepsy (Betts 1983; Lesser R 1996; Scheepers 1998; Smith 1999). Inter- observer reliability has been found to be as low as a kappa value of 0.58 in one study (van-Donselaar, and others 1991). 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 and Kurland 1975). This lag time means that, when studies exclude patients without a definite diagnosis, considerable bias may occur. Most studies, apart from the NGPSE, do not address this important clinical issue (Annegers, and others 1986; Blom S, and others 1978; Cleland PG, and others 1981; Goodridge and Shorvon 1983b).

There is no single test or set of investigations that is definitive in the diagnosis of seizure disorders. Thus, adding to the difficulty of diagnosis are other paroxysmal conditions, the presentation of which may be confused with epileptic seizures, such as syncope, vertigo, panic disorder, hyperventilation syndrome, night terrors, sleep-walking, benign sleep myoclonus, cardiac dysrhythmias, transient ischaemic attacks, non-epileptic seizures, panic attacks, hypoglycaemia, hypoxia, confusional migraine and cataplexy (Commission on Classification and Terminology of the International League against Epilepsy 1989).

Acute symptomatic seizures, such as those that occur during a metabolic disturbance or an acute illness, are not considered epilepsy. This is because they are deemed to be caused by transient pathological processes, which when removed, cannot provoke further seizures, and a continuing tendency to seizure activity does not occur. The distinction is, however,

conventional and not the result of a clear-cut physiological demarcation. For example, alcohol can provoke seizures, both when taken in excess as well as during withdrawal in alcohol dependence; it can also however, precipitate seizures in juvenile myoclonic epilepsy for example and thus it would be incorrect putatively to label all seizures associated with alcohol as being acute symptomatic in aetiology.

It is important that studies take the issue of diagnosis seriously, so that there is a necessary level of standardisation that renders the outcome of such studies meaningful and useful.

1.1.3 Limitations of the classification of epilepsy

A comprehensive syndromic classification was commissioned by the ILAE (Commission on Classification and Terminology of the International League against Epilepsy 1989) with the stated intention of having a reliable clinical tool for the classification of epilepsy and to allow comparison between studies. Unfortunately, it has its limitations and substantial numbers of patients are unclassifiable (Manford, and others 1992).

Whilst this classification incorporates EEG and, in certain cases, MRI findings, it does not make allowances for the recent advent of the genetics of the epilepsies, advances that will undoubtedly hasten the reclassification of seizure syndromes (Everitt and Sander 1999; Johnson and Sander 2001).

In most reliable studies, only half of the cases are classified. In children, classification 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 with such events had a 10% chance of seizure recurrence versus 54% overall (Stroink H, and others 1998) suggesting that many may not have had epilepsy at all..

1.1.4 Demographic considerations

Population based studies are a *sine qua non* in epidemiology and are the only means of providing a comprehensive representation of the epilepsies. This is 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 and Shorvon 1995). Clinic-based studies are influenced by referral patterns, patient characteristics and seizure severity; however, many studies are clinic based (Sato S 1964; Lindsay J, and others 1979; Loiseau, and others 1983; Turnbull DM, and others 1982; Cavazutti GB, and others 1984; Camfield PR, and others 1985; Munson JF 1910; Beghi and Tognoni G 1988; Collaborative Group for the Study of Epilepsy 1992; Tinuper P, and others 1996; Sato S 1964; Hadjipanayis A, and others 1997)

The community studied will also influence findings. In Rochester, USA for example, the population is homogeneous, white, relatively affluent and of northern European descent (Hauser and Kurland 1975; Annegers, and others 1979).

1.1.5 Criteria for inclusion and exclusion

Criteria for inclusion and exclusion in epidemiological studies are central to determining standardisation. The exclusion of people with single seizures excludes those patients with a lower tendency to recur, thus apparently lowering remission rates in studies of epilepsy (Hauser and Kurland 1975; Annegers, and others 1979; Ross, and others 1980; Elwes, and others 1988). Conversely, the exclusion of patients who experience early recurrence in studies of single seizures seems likely to improve the overall prognosis. (Sander 1993) Similarly, an atypical population with more severe epilepsy 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 had an EEG are included (Shafer SQ, and others 1988). In one study, childhood febrile convulsions

were not excluded but grouped together with other seizure types (Thurston JH, and others 1982). Some studies have excluded patients with abnormal neurology before the seizure (Loiseau, and others 1983).

1.1.6 Temporal aspects

Patients should be followed from the same point in their illness – whether this is a first or second seizure presentation. If this policy is not pursued, there is a tendency to find poor outcome because of a bias towards those with ongoing seizures and more severe epilepsy (Shorvon 1984; Faxen N 1935; Sander JWAS 1993). This underlies the poor prognosis of epilepsy reported in older studies (Rodin EA 1968; Gowers WR 1885).

Most patients 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, chances of subsequent remission were only 35% (Annegers, and others 1979).

1.1.7 Definition of remission

The problem of the definition of remission, otherwise hitherto a considerable stumbling block in the interpretation of study outcomes, has been addressed to a large extent by the ILAE,. Remission has varied in description between 1-5 years (Brorson LO and Wranne L 1987; Casetta, and others 1997; Hauser and Kurland 1975; Munson JF 1910; Stroink H, and others 1998). Studies have not always clarified whether terminal remission or any period of remission is considered (Goodridge and Shorvon 1983b; Goodridge and Shorvon 1983a); and whether remission is on or off medication (Hauser and Kurland 1975; Annegers, and others 1979). Generally however, medication status is not considered part of the definition of remission, and many studies report both terminal and non-terminal remission rates.

1.1.8 Study design

Retrospective studies have considerable limitations in their design and are liable to incorporate significant bias, so that their results need to be interpreted with a degree of caution. Properly designed prospective studies avoid bias and yield appreciably better data quality although the logistical considerations inherent in such undertakings are often mammoth, and require considerable resources.

In particular in patients with seizure disorders associated with cognitive difficulties due to medication or as part of their condition, retrospective biases may be induced by inaccuracies of seizure counts, chronology of medication, reporting of adverse events and other morbidity. 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 Rochester data go back to 1935 (Annegers, and others 1979); 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 (Faxen N 1935).

1.1.9 Follow-up

Between 20 and 30% of patients with epilepsy may go on to develop a chronic disorder and thus the lengthier the follow-up period, the more meaningful a study's conclusions are likely to be. Studies of newly diagnosed patients followed for 1or 2 years find remission rates as high as 80% (Turnbull DM, and others 1982; Beghi and Tognoni G 1988; Stroink H, and others 1998). The term remission is only meaningful however, if remission periods are lengthy, thus necessitating prolonged follow-up. Some prospectively designed studies are now reporting decades of follow-up data (Annegers, and others 1979; Kurtz, and others 1998; Sillanpaa, and others 1998).

1.1.10 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-responder does not resemble the responders, many groups have ignored this problem (Casetta, and others 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.

1.1.11 Statistical analysis

Early in the course of their epilepsy, most patients will go into remission; fewer do so 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 and Shorvon 1983a).

In the statistical analysis of prognostic factors, the use of uni-variate analysis has confounded many studies. Uni-factorial models are not appropriate for a 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 H, and others 1998)and has been used in the NGPSE (MacDonald BK, and others 2000)

1.1.12 Treatment and remission

Most studies of prognosis and remission in epilepsy do not address the effect of treatment on seizure outcome very well. There are few studies that have randomised treatment at the population level, which would be a requirement for assessing this issue to any meaningful extent. (Placencia, and others 1994; Feksi, and others 1991; Pal, and others 1998)

Interventional studies have demonstrated that most patients presenting with epilepsy entered long-term remission when treated. (Turnbull DM, and others 1982; Shorvon, and others 1978; Shorvon and Reynolds 1982; Elwes, and others 1984; Beghi and Tognoni G 1988; Okuno *et al.*, 1989; Collaborative Group for the Study of Epilepsy 1992; Mattson, and others 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 although there is little evidence to uphold this view, and gathering evidence from interventional and epidemiological studies to refute it.

A study examining the effect of treating patients after their first generalised tonic-clonic seizures showed no difference in long-term (1 or 2 years) remission rates (Musicco, and others 1997). Drug withdrawal, however, is an important cause of seizure relapse (Medical Research Council Antiepileptic Drug Withdrawal Study Group 1991).

1.1.13 Mortality

The calculation of mortality statistics has been a source of error in past studies of the mortality of epilepsy. The use of the average age of death,

and the life expectancy of a patient, are not useful measures and serve little purpose in the investigation of the mortality of any condition, including epilepsy (Bradford-Hill A 1984). One commonly used measure of death rates that can be used to compare rates in different populations is the standardised mortality ratio (SMR). The SMR is a proportional rate and adjusts for age and sex. However, with low numbers of expected deaths in different strata of analysis, this can be misleading as assumptions about the normal distribution of SMRs and their confidence limits are not valid (Kahn HA and Sempos CT 1989).

Discovering the cause of death in patients with epilepsy is difficult. Determining a single cause of death for each patient based on data from death certificates is the commonest method, because of the accessibility of this information in most countries. Death certificates used alone, however, are inaccurate sources of information, and between 11% and 29% of patients with epilepsy do not have epilepsy included on the death certificate (Silfvenius H and Olivecrona M 1988; Massey EW and Schoenberg 1985). Death certificate information is often supplemented with data from post-mortems, hospital records and other sources, where available, leading to a selection bias towards younger patients with more unusual causes of death.

Selection of patients is critical. The majority of studies have not mentioned the criteria which define epilepsy. Inclusion or exclusion of potentially benign or malignant categories, such as isolated single seizures or acute symptomatic seizures, will result in major bias. Hauser, for instance, defined epilepsy as the state of having two or more seizures (Hauser, and others 1980), but this is not uniform practice. Studies employing proportional mortality rates calculated from death certificates (Krohn W 1963; Schwade E and Otto O 1954) are biased for the reason mentioned above, i.e., that epilepsy is often not put on the death certificate of patients with fewer seizures or seizures in the more distant past. There have been a number of studies on the death rates in populations of epileptics looked after in special epilepsy institutions or clinics (Klenerman, and others

1993; Henriksen PB, and others 1967; White SJ, and others 1979; Birnbach CD, and others 1991; Hashimoto K, and others 1989; Iivanainen M and Lehtinen J 1979) or in populations of insured patients with epilepsy (Lewis JA 1978). The highly selected nature of these cohorts means that results are not directly applicable to the wider epilepsy population .

The general population is the most desirable source of information on death rates of patients with epilepsy as all patients regardless of cause will be included (Zielinski JJ 1974a; Hauser, and others 1980; Satishchandra, and others 1988). However, the studies to date have been retrospective and so have a tendency to exclude patients with less severe seizures in whom the diagnosis may never have been finalised, or who may have gone into remission and become lost to medical surveillance.

1.2 Mortality in Epilepsy

It is often not appreciated that epilepsy may be a life threatening condition. Although some of the early studies found that patients with epilepsy had a normal life expectancy (Livingston S 1963; Schwade E and Otto O 1954), it is now generally accepted that patients with epilepsy have a higher standardised death rate than the general population (Annegers, and others 1984; Hauser, and others 1980; Klenerman, and others 1993; Massey EW and Schoenberg 1985; Zielinski JJ 1974a).

1.2.1 Historical perspective

Gowers in his observations of patients at the National Hospital for the Paralysed and Epileptic opined that "the danger to life of patients with epilepsy was not great" and that the main risk was one of drowning (Gowers WR 1885). Rodin, in his influential monograph on the prognosis of epilepsy in 1968, (Rodin EA 1968) was somewhat more ambiguous in his comments on mortality. Whilst stating that "general statements covering all epileptics are likely to be an oversimplification", he also said that it was "quite obvious that the life expectancy of the epileptic individual does not reach that of the average person". He based the latter assumption on a review of literature that dealt almost solely with institutionalised patients who had chronic and refractory epilepsy in whom mortality has always been reported to be high. Munson in 1910 reported on patients from the Craig Colony where, of 2,732 patients, 582 had died in the institution (Munson JF 1910). The mean age at death was 30.08 years and 30% deaths were related to epilepsy. Studies done at the Chalfont Centre for epilepsy have shown that this trend has not changed over time (O'Donoghue and Sander 1997; Klenerman, and others 1993).

1.2.1 Mortality rates in patients with epilepsy

In the past there has been a conspicuous dearth of comprehensive, population based studies of the issues involved although more selected groups of patients have been studied. The fact that as many as 20% of patients with epilepsy may not seek medical advice (Miller FJW, and others 1960) emphasizes the importance of proper, representative studies. In their review of death certificates in Wisconsin for the year 1953, Schwade and Otto appeared to confirm that risks of mortality were insignificant (Schwade E and Otto O 1954) although we now know that this method is notoriously unreliable for any meaningful analysis (Hauser, and others 1980; Hopkins and Scrambler G 1977; Zielinski JJ 1974a). Alstroem's study of outpatients in 1950 also stressed the absence of risk in patients who had no known cause for their epilepsy and were mentally normal. (Zielinski JJ 1974a; Alstroem CH 1950) Livingston, in 1963 was quite categorical about the essentially benign nature of the disease and said that there was "no reason why an epileptic should not live as long as he would if he did not have epilepsy". (Zielinski JJ 1974a)This conclusion was gleaned from his experience with 15000 patients with epilepsy on an insurance register. Henriksen in 1967 then reported an excess mortality from epilepsy in a large clinic population despite excluding people with cerebral tumors and cerebrovascular disease from his study in which he found SMRs to be elevated up to 3.5 times that of the general population (Zielinski JJ 1974a; Henriksen PB, and others 1967). His figures, however, were compared with Danish life insurance statistics based on an insured population that would necessarily have been vetted and healthier, and this may have exaggerated the comparison.

Since then, three major population based studies have made it clear that there is indeed a significant elevation of SMRs in epilepsy. In 1974 Zielinski found that the overall SMR was 1.8 in a cohort of all epileptic patients in Warsaw, and 3.5 when only patients under the age of 50 were considered (Zielinski JJ 1974a; Henriksen PB, and others 1967). Epilepsy was the commonest cause of death, being responsible for 14% of all

deaths in patients with epilepsy. This figure rose to 24% when people with cerebrovascular disease and brain tumors were excluded from the analysis. Hauser in 1980 described mortality in a retrospectively identified cohort of 618 patients from Rochester, Minnesota that had been followed up for more than 8000 patient years (Hauser, and others 1980). Febrile convulsions, single seizure and acute symptomatic seizures were excluded from the study. The overall SMR was highly significantly raised at 2.3 (CI 1.9-2.6) indicating substantial mortality in epilepsy. The SMR in the first two years was 3.8 and remained elevated for the first decade. It subsequently dropped below significance and became elevated again in the third decade, indicating prominent early and late mortality. The early increased mortality was mainly due to underlying pathologies rather than the epilepsy itself, but the late increase in mortality was thought to be due to epilepsy itself. The NGPSE reported on mortality in 1994 in the first prospectively followed up, population-based cohort of 1091 patients (564 with definite epilepsy, 228 patients with possible epilepsy and 220 patients with febrile convulsions (Cockerell, and others 1994a). There were 161 deaths in 7500 person years of follow up and none died in the group with febrile convulsions. Some deaths were directly due to seizures. The SMR was 6.6 in the first year for patients with definite epilepsy and 5.1 when those with both definite and possible epilepsy were combined. SMRs dropped below significant levels during the fifth year and remained so for the remainder of the 9-year follow up period. This early trend in mortality was reminiscent of the Rochester study and was attributed to the high death rates due to the underlying cause of epilepsy such as brain tumors and cerebrovascular disease. With continued follow-up, a later increase in mortality related to refractory epilepsy had been anticipated in the 20-30% of patients who were likely to be in this group.

In 1997, Nilsson described a Swedish cohort study of 9000 patients who had once been hospitalized for epilepsy (Nilsson L, and others 1997). Cases were retrospectively gathered from a discharge register and causes of death were obtained from death certificates. 4000 deaths were reported and an SMR of 3.6 (CI 3.5-3.7) was noted for the whole cohort,

confirming the high standardized mortality of epilepsy. However, the study was not truly representative with its bias towards hospital admitted patients and no conclusions were drawn on epilepsy related deaths due to the usual unreliability of death certificates.

1.2.3 Cause specific mortality in epilepsy

1.2.3.1 Cancer

There has been concern that there is an increased risk of cancer in patients with epilepsy. Many AEDs have a liver enzyme inducing effect, and phenobarbital in particular has been shown to cause liver tumours in rodents when fed in high enough dosage (International Agency for Research on Cancer, 1974). Against this is the fact that induction of liver enzymes may actually protect against carcinogenesis by diverting any harmful metabolites down safer metabolic pathways (White SJ, and others 1979). There are anecdotal reports of an association between neuroblastoma and phenytoin therapy (Pendergrass JW and Nanson JW 1976), and an increased risk of brain tumours in children of mothers on long term AEDs (Gold E, and others 1978). Also, the lymphadenopathy syndrome produced by phenytoin may be a precursor of lymphoma, and one retrospective study of all patients dying of lymphoma in a hospital population reported a ten-fold increase in the lymphoma rate; 4 out of the 85 patients were on long-term phenytoin (Anthony V 1970). Hauser reported an SMR for all neoplasms, excluding cerebral neoplasms of 1.8, but interestingly most of this excess was accounted for by a diagnosis of malignancy before the diagnosis of epilepsy was made (Hauser, and others 1980). In patients resident in institutions, such as the Chalfont Centre, two studies have reported an increased SMR from cancer, 1.4 and 2.0 for all types of cancer, excluding brain (White SJ, and others 1979; Klenerman, and others 1993). One study from Denmark in an analysis of 9136 patients with epilepsy admitted to a specialist centre did not confirm this increased rate (Munson JF 1910; Clemmensen J 1974) and neither did a much smaller sample of 300 people with epilepsy in a hospital for mental

handicap (Munson JF 1910; Jancar J 1980; Jancar J 1990). Analysis of the different types of malignancy in epilepsy patients does not confirm the possible higher risks of liver cancer that was a particular concern (White SJ, and others 1979; Klenerman, and others 1993; Hauser 1992). However, lung tumours (Friedman GD 1981) and gut malignancies (Klenerman, and others 1993) are over represented, although no reason for this has been forthcoming. It should be noted that no study has allowed for other risk factors such as diet or smoking habits, which may have profound effects on the risk of developing cancer.

An increased mortality rate from cerebral malignancy is not surprising considering the association with the aetiology of many patients with epilepsy. More sophisticated investigation of patients performed before, and after, death will tend to raise the known incidence of intracranial malignancy (Iivanainen M and Lehtinen J 1979). A better prognosis for those patients with gliomas who develop epilepsy has been reported, and must reflect earlier diagnosis, rather than any beneficial effect (Scott & Gibberd, 1980). There does not seem to be any evidence of an increased rate of cerebral tumours in patients on long term AEDs (Hauser, and others 1980).

1.2.3.2 Ischaemic heart disease (IHD)

There are a number of reasons why the mortality rate due to IHD in patients with epilepsy may be different from that of the general population. Phenytoin has an anti-arrhythmic effect and a reduced mortality rate might be expected in patients on long term AEDs, and this is supported by anecdotal evidence (Munson JF 1910; Linden V 1975). Also, all the AEDs reduce serum high density lipoproteins, and may thus reduce the accumulation of atherosclerosis (Munson JF 1910; Berlit P, and others 1982). Most studies have not been able to support this hypothesis, with SMR rates of 0.8 to 1.4 reported (Munson JF 1910; Annegers, and others 1984; Klenerman, and others 1993). The higher rates are found in patients with symptomatic seizures and probably represent increased deaths associated with strokes, which are a common cause of epilepsy in the

elderly. One study from Finland considered all the deaths occurring during 1978-80 in patients with epilepsy registered with an insurance company against age and sex matched controls (Munson JF 1910; Muuronen A, and others 1985). Of the 1399 deaths in patients with epilepsy, 258 were due to IHD compared with 382 in the control group, indicating a 29% lower risk for patients with epilepsy.

1.2.3.3 Cerebrovascular disease

Cerebrovascular disease accounts for 5% of all epilepsy in the community (Hauser, and others 1980) and so a higher mortality from strokes would not be unexpected. The rate of stroke deaths is about twice the expected rate (Hauser, and others 1980; Klenerman, and others 1993) (Zielinski JJ 1974a). In one study, once the symptomatic cases of epilepsy were removed the rate of strokes in the idiopathic group was about normal (Klenerman, and others 1993).

1.2.3.4 Bronchopneumonia

An increased bronchopneumonia death rate has been a feature of most mortality studies in epilepsy since Munson's original description that "pulmonary conditions are peculiarly dangerous to him" (Munson JF 1910). Pneumonia is a frequent end point of many illnesses and is a frequent death certificate recourse, when there is a lack of other data to support another cause. It is also difficult to delineate those cases of pneumonia that occur de novo and those cases that follow aspiration during a seizure (Munson JF 1910; Karalus MC, and others 1991), or prolonged inactivity secondary to the cause of epilepsy, such as strokes, brain tumours, or congenital deficits, or to AED intoxication. In support of this is the high rate of pneumonia rates in institutionalised patients who are more likely to have frequent seizures, and associated mental handicap (Iivanainen M and Lehtinen J 1979; Krohn W 1963) Penning, Muller & Ciompi 1969; (Munson JF 1910; White SJ, and others 1979; Zielinski JJ 1974a) compared to the lower rates in population studies (Hauser, and others 1980). Death rates from pneumonia are also more likely to be

higher in institutions because of facilitation of spread of viral and bacterial infections. In spite of lower rates in community studies, these are still in excess of those expected, and are still significant in the group of patients with idiopathic epilepsy (Hauser, and others 1980). It has been suggested that there is an increase in the rate of pulmonary fibrosis due to long term phenytoin therapy (Moore, 1959), but a link with a susceptibility to infection has not been established.

1.2.3.5 Psychiatric causes

Gowers was the first to note a high rate of suicide in patients with epilepsy (Gowers, 1885). Psychiatric morbidity is common in the epilepsy population, and many studies have found high rates of attempted self harm (Hawton, Fagg & Marsack, 1980), and suicide (Barraclough, 1987, Hashimoto et al., 1989; Krohn W 1963; Wolfersdorf & Froscher 1987; Zielinski JJ 1974a). There are a number of theoretical reasons why patients with epilepsy should have a higher suicide rate. Neurological handicap may result in social isolation and depression, and various causes of epilepsy such as temporal lobe abnormalities and alcohol abuse, as well as sedative AEDs will all increase the suicide risk (Barraclough, 1987). There is a greater risk in patients with temporal lobe epilepsy, related to the degree of severity of the seizures (Lindsay, Ounsted & Richards, 1979), and in those patients who have undergone surgery.

1.2.3.6 Epilepsy related deaths

The concept of epilepsy-related death (ERD) is finding increasing usage. ERD refers to death that arises as a direct consequence of the epilepsy rather than the underlying cause of the epilepsy. The causes of ERD include accidents, seizures themselves, status epilepticus, and sudden unexpected death (SUDEP).

1.2.3.7 Accidents

The chance of a patient dying of an accident is higher than in the general population (Iivanainen M and Lehtinen J 1979; Klenerman and others 1993; Krohn W 1963; Schwade E and Otto O 1954; Zielinski JJ 1974a). The usual cause is the occurrence of a seizure whilst swimming, or bathing, and death rates from these causes are higher in epilepsy hospitals near lakes or the sea, or sites remote from attendants (Iivanainen M and Lehtinen J 1979; Quan, Gore, Wentz, Allen & Novack, 1989). The safety of the environment and the level of supervision are significant factors in reducing the mortality in certain institutionalised patients (Klenerman, and others 1993).

1.2.3.8 Status epilepticus

This condition is a significant cause of death in patients with epilepsy with a mortality of 8.3% with the first episode (Aicardi, 1986; Maytal, and others 1989; Oxbury & Whitty, 1971) and up to 43% in the long-term. (Chin RF, and others 2004). This is largely accounted for by patients with underlying lethal conditions such as frontal lobe gliomas, and degenerative conditions. Older studies have found higher mortality rates of status compared to more recent studies, which is probably due to advances in status treatment (Klenerman, and others 1993; Krohn W 1963; Zielinski JJ 1974a).

1.2.3.9 Antiepileptic drug toxicity

As well as the risk of malignancy discussed above, there are other hazards of AEDs. For instance valproate is associated with acute and chronic hepato-toxicity (Dreifuss FE, and others 1989; Suchy FJ, and others 1979). These and other idiosyncratic drug reactions, however, are rare and are unlikely to be major causes of death.

1.2.3.10 Death due to an isolated seizure

Apart from death due to status, accidents, or asphyxiation, an isolated seizure itself may immediately precede death. The reason for this is discussed with the aetiology of SUDEP below. Whether this is aetiological or coincidental is unknown. In any event it is a rare phenomenon, 6 out of 113 deaths being recorded from Chalfont over 10 years (Klenerman, and others 1993).

1.2.3.11 Sudden Unexpected Death (SUDEP)

In 1910, Munson reported on mortality from the Craig Colony for Epileptics in New York where patients with chronic and intractable epilepsy resided and found that 99 out of 582 deaths were "sudden" (Munson JF 1910). Though several were what we would now refer to as seizure related accidental deaths, the remainder occurred in patients found mysteriously dead in bed by their carers. He concluded, not entirely incorrectly, that these deaths had occurred in the midst of a seizure, noting that "these deaths occur very rapidly at times - seizures not infrequently take place silently". Since then, there has always been somewhat of an acceptance, grudgingly at times, of a small but probably significant risk of death directly attributable to seizures, and sudden death has appeared sporadically through the decades in several mortality series as a cause of death (Gowers WR 1885). With present day knowledge of increased all cause mortality in epilepsy, (Cockerell, and others 1994a; Hauser, and others 1980) there has been increasing interest in the enigma of sudden unexpected death in epilepsy or "SUDEP" and several studies have been conducted in the last few decades in an attempt to quantify risk, to identify risk factors and to determine it's phenomenology. It has become increasingly clear that SUDEP is a very real problem and perhaps the commonest cause of seizure related death in patients with chronic epilepsy (Nashef L and Sander JWAS 1996).

The National Sentinel Clinical Audit of Epilepsy-Related Death (Hanna NJ et al 2002) investigated 2412 deaths reported with epilepsy on the death certificate. A large proportion of deaths (39% of adults and 59% of children) were found to have been potentially preventable and recommendations were made at both primary as well as secondary level care to improve the existing quality of service provision.

1.2.3.11.1 Incidence studies of SUDEP

The true incidence of SUDEP is unknown and there are no truly community based, prospective incidence studies though observations have been made about the phenomenon in some cohort studies. The National GP Study of Epilepsy in the United Kingdom (Sander, and others 1990) has had one confirmed SUDEP death in a community based, prospective cohort of 564 patients with definite epilepsy followed up for approximately 8000 person years. The MRC Antiepileptic drug withdrawal study had two deaths attributable to SUDEP after 5000 person years of follow up (Medical Research Council Antiepileptic Drug Withdrawal Study Group 1991). These figures may be misleadingly low as in the NGPSE, almost 70% of the cohort had achieved 5-year remission, a significant number of patients suffered early mortality due to symptomatic seizures and only a minority (55 out of an original 564 when last followed up) continue to have epilepsy. (Cockerell, and others 1997b) Similarly, the majority of the MRC study population was in remission and there is strong evidence that SUDEP is mainly a problem in the patient with chronic and intractable epilepsy.

Case ascertainment methods have varied in different studies, but can be broadly categorised into studies that have used death certificates and coroner's registers, (Leestma JE, and others 1984; Leestma, and others 1989; Terrence CF, and others 1975)studies that have used treatment data - medical, (Derby LE, and others 1996; Jick SS, and others 1992; Leestma, and others 1997; Tennis, and others 1995) surgical (Dasheiff

1991; Sperling MR, and others 1996; Vickery BG 1997)or palliative (Annegers, and others 1998), and those that have been based on data from epilepsy clinics or institutions. (Klenerman, and others 1993; Lip GY and Brodie 1992; Nashef, and others 1995a; Timmings PL 1993) Coroner based studies have been both retrospective (Klenerman, and others 1993; Leestma JE, and others 1984; Terrence CF, and others 1975) as well as prospective (Leestma, and others 1989) and have shown incidences varying between 1:525 to 1:2100 and 1:370 to 1:1100 respectively. The higher incidence in prospective studies may be attributable to better case ascertainment methods. However, these studies are fundamentally flawed due to the fact that death certificates are notoriously unreliable and because the presumed prevalent epilepsy population is used as denominator - a figure prone to variation and inaccuracy. (Zielinski JJ 1974a)

SUDEP incidence rates of up to 1:200 have been reported by several studies based on epilepsy clinic data; (Lip GY and Brodie 1992; Nashef L, and others 1995a; Timmings PL 1993) these figures are much higher than those from studies based on coroners' registers. Slightly higher figures have been reported from institutionalised patients who share features of seizure intractability and chronicity with clinic subjects (Klenerman, and others 1993; Nashef, and others 1995b). Walczak et al pooled prospective data from three epilepsy centres and followed patients for 16,463 years. They found an incidence of 1.21/1000 patient years for SUDEP, 1.45/1000 among women and 0.98/1000 among men (Walczak and others 2001).

Several studies have used antiepileptic drug therapy lists for case ascertainment and individual methodologies have varied within this group. Some have excluded symptomatic cases, (Jick SS, and others 1992) others have used patients on more than 2 antiepileptic drugs (Derby LE, and others 1996) and others have considered patients on drug therapy for more than 2 years (Tennis, and others 1995). More recent studies have been based on newer antiepileptic drug registers such as those on

lamotrigine (Leestma, and others 1997). There have also been some studies based on surgical data which have shown particularly high incidences of sudden death, especially in post surgical patients in whom the operative procedure has not been successful in containing seizures (Dasheiff 1991; Sperling MR, and others 1996). A more recent study of 791 patients who had received vagal nerve stimulation system implants and were followed up for 1335 person years showed an incidence of definite or probable SUDEP of 4.5 /1000 person years of follow up (Annegers, and others 1998). The high mortality and incidence figures in most of these studies reflect the severity and intractability of epilepsy suffered by patients in these study populations and therefore is not truly representative of the population at large with epilepsy.

1.2.3.11.2 Important factors implicated in SUDEP

Seizure status

It is obvious from most studies that seizure status is vitally important in the mortality statistics of SUDEP and incidence figures are considerably higher in studies of cohorts of patients with refractory and chronic seizures than in studies that are more community based. One surgical study found a particularly high incidence of SUDEP in patients unsuccessfully treated surgically for their epilepsy, with mortality approaching 1:50 when such patients were considered in contrast to 1:150 when both pre and post surgical candidates were analysed together (Dasheiff 1991; Sperling MR, and others 1996). In contrast, the NGPSE and MRC Drug Withdrawal studies have both shown very low incidence figures for sudden death. A recent study has shown that a cohort of post-surgery patients in long-term remission has a risk of sudden death that approaches that of the general population. Thus active epilepsy appears to pose a significant risk (Sperling MR, and others 1999; Nilsson L and others 1999; Walczak and others 2001).

Medication

Non-compliance with prescribed antiepileptic medication has been implicated in the occurrence of sudden death and several patients have been found to have sub-therapeutic serum levels of antiepileptic drugs at post mortem (Leestma, and others 1989; Vickery BG 1997). The significance of drug levels, however, is arguable as patients may have well-controlled epilepsy despite low drug levels and vice versa. Conversely, there are reported instances of patients experiencing sudden arrhythmic deaths possibly due to the cardiac side effects of carbamazepine (Boesen F, and others 1983) though this is obviously not the case in the majority of SUDEP cases.

Neurological status

A higher incidence of SUDEP has been found in patients with neurological deficits and learning difficulties (Klenerman, and others 1993). This may be attributed to the severity of epilepsy that is usually present in these patient groups and the higher all cause mortality generally found in such patients.

Alcohol abuse

Alcohol abuse has also been implicated in some patients, (Leestma, and others 1989) as have psychotropic drugs (Tennis, and others 1995).

1.2.4 Other factors affecting the mortality rate in patients with epilepsy

1.2.4.1 Age at diagnosis

Age has a critical affect on death rate, and it is important to adjust for this, such as by using the SMR. Most studies have found that the SMR is highest in younger patients (Munson JF 1910; Kurokawa T, and others

1982; Munson JF 1910; Miyake S, and others 1991) showing a progressive decline, in spite of the increased percentage of patients dying at an older age, with the lowest SMR in the over 65 age groups (Hauser, and others 1980) (Zielinski JJ 1974a). Epilepsy in the first year of life has a high mortality because of associated neurological dysfunction in many of these patients (Brorson LO and Wranne L 1987; Munson JF 1910; Munson JF 1910; Chevrie JJ and Aicardi J 2003), so that in older patients the high-risk patients have already been selected out. As discussed above, patients in the middle years between 15 and 50, are most likely to suffer SUDEP, and other ERD. Later the mortality due to strokes and tumours increases (Hauser, and others 1980) (Luhdorf K, and others 1987).

1.2.4.2 Sex

There are small differences between the mortality rates for men and women. Zielinski found the SMR to be the same until the fourth decade, when men started to have a higher SMR (Zielinski JJ 1974a). Hauser found that the SMR of idiopathic epilepsy for men was 2.1 and women 1.6 (Hauser, and others 1980).

1.2.4.3 Time from diagnosis

This has only been examined in two studies (Hauser, and others 1980; Luhdorf K, and others 1987). The death rates for the first years after diagnosis are far higher than in subsequent years. In Rochester the SMR was 2.5 in year 0-1 declining to 1.7 in the year after (Hauser, and others 1980). The high SMR in years 25-29 is a function of the small numbers followed up for this length of time, as discussed above in the misuse of the SMR. The high earlier rates can be accounted for by the poor prognosis from lethal causes such as tumours. All patients in the Danish study with cerebral tumours died in the first year (Luhdorf K, and others 1987).

1.2.4.4 Type of epilepsy and type of seizures

Because of variation in classification of epilepsy and seizures in mortality studies, there is sparse evidence for an effect of these variables on the mortality rate of epilepsy. There is some evidence that patients with idiopathic epilepsy have a lower mortality and that patients with absence seizures, or partial seizures only, in the younger ages, do not have an increased risk of dying (Hauser, and others 1980). Patients with generalised tonic clonic seizures were found to be an independent risk factor for SUDEP in one study (Walczak and others 2001).

1.2.4.5 Seizure frequency

Patients with more frequent seizures might be expected to have a higher mortality because of the deleterious effect of the seizures, increased risks of accidents, and increased incidence of status epilepticus as well as an association with more lethal causes of epilepsy. However, this has not been examined in detail apart from the risk of SUD with respect to seizure frequency already mentioned. In relation to this, Hauser still found a higher SMR in patients in prolonged seizure remission, and in patients who had only suffered one seizure (Hauser, and others 1980), suggesting an independent risk of having epilepsy apart from frequent seizures.

1.3 THE DYNAMICS OF THE TREATMENT OF EPILEPSY

The most widely followed model of epilepsy management in the United Kingdom is one of referral from primary care to hospital clinics followed by investigation, treatment and follow-up at primary, secondary or shared care levels. A description of the evolution of therapy in this model over time at a population level should provide important data for knowing where to target treatment improvements and for the planning of health care. In a hospital setting, the various facets of this model are easily studied, but the bias towards more complicated cases is likely to present a distorted picture (Sander JWAS and Shorvon SD 1996). Unselected, population based studies provide a more accurate picture of the generality of therapy, in a representative patient sample, although the potential logistical difficulties involved have resulted in a considerable dearth of such studies (Sander JWAS and Shorvon SD 1996). In particular there have been no previous prospective, long-term studies of treatment dynamics in a population-based cohort with epilepsy, although treatment characteristics in a community based prevalent population have been reported on before (Hart YM and Shorvon SD 1995).

Several questions remain unanswered. How many patients with newly diagnosed epileptic seizures receive treatment and who initiates therapy? How many patients change treatment, and when, in the course of the epilepsy? What are the reasons for drug change and which drugs and drug combinations are used initially and how often is treatment switched or added? Is there uniformity in the choice of antiepileptic drugs for different seizure types? How often were the newer antiepileptic drugs used by an unselected population with epilepsy? To what extent were seizures controlled by drug changes in patients with uncontrolled epilepsy?

1.3.1 Medical services for people with epilepsy

1.3.1.1 *Government reports about services for people with epilepsy*

Between 1953 and 1999 there were six government-sponsored reports assessing service provision for people with epilepsy and making recommendations about their care.

The 1953 report "National Assistance Act 1948: Welfare of handicapped persons: the special welfare needs of epileptics and spastics" (Ministry of Health 1953) evaluated service provision at the local authority level. The Cohen Report (Central Health Services Council 1956) emphasised the role of GPs, and the need for them to be regularly updated in epilepsy care, but also examined hospital services. It recommended regional diagnostic and treatment clinics although this was not implemented.

In 1969, the Central Health Services Council published its report "People with Epilepsy: Report of a joint sub-committee of the standing medical advisory committee and the advisory committee on the health and welfare of handicapped persons" (The Reid Report; Central Health Services Council 1969). This reviewed the existing services and recommended the establishment of specialist epilepsy clinics. All patients with epilepsy were to be referred for evaluation by a multidisciplinary team at a district level, and a minority requiring more detailed investigation would go on to tertiary units with specialist neurological and neurosurgical investigational facilities. The Reid Report envisaged clinics on the lines of diabetic clinics, where patients with chronic conditions avoided being followed up by inexperienced junior doctors on short-term contracts.

In 1987 the Bennet Report (Kurtz Z and Morgan JD 1987) was completed and evaluated the response to the recommendations of the Reid Report. Unsurprisingly, it found that regional conferences had not responded positively: for example, nine conferences had disapproved of epilepsy clinics, and three had not indicated their views, whilst only four had

approved. Health authorities were similarly reticent; 23 approved of epilepsy clinics, 31 did not and 42 abstained from comment. The report recognised the inadequacies of existing facilities and the lack of continuity of care. Again, it recommended the establishment of specialist clinics for people with chronic epilepsy.

The Winterton Report (Department of Health and Social Security 1986), in contrast to the Reid Report, concluded that patients could be managed by neurologists or specialists, rather than by a multidisciplinary team. It felt that epilepsy clinics should be established for people with intractable epilepsy and suggested specialist pilot clinics. They again noted the existing problems of appointments, follow-ups and the shortcomings of existing investigational facilities.

The Reid Report suggested the establishment of five or six supra-regional centres for patients with disabling epilepsy. Such centres were evaluated in the Bennett Report as being beneficial and were recommended by the DHSS Working Group (Department of Health and Social Security 1986).

The DHSS Working Group 1986 also recommended that medical care for children should be of the same standard as for adults, with specialist referral for evaluation and recommendation of the appropriate management. The general practitioner was to provide ongoing care. The consensus of the Welfare Report (Ministry of Health 1953) and the Cohen and Reid Reports was that there was a need for accurate diagnosis and careful review of children with epilepsy, and for communication between school medical services, teachers and general practitioners. This was further reiterated in the 1981 Education Act (Education Act 1981).

The Clinical Standards Advisory Group (CSAG) 1999 (Clinical Standards Advisory Group 1999), set out to determine the organisation, configuration and standards of clinical care for epilepsy in the UK. This used evidence from a variety of published sources, professional and lay experts, as well as data from primary research with service providers and users. It looked

at patient as well as clinician, perspectives and identified the special needs of children and adolescents, women of reproductive age, the elderly, and people with learning disability. Various recommendations were made, as in previous reports. In addition, the setting up of a network of Epilepsy Centres was recommended that would support primary care for epilepsy in the local population and provide comprehensive secondary care of epilepsy. The special care of specific groups such as children, women of reproductive age, the elderly and people with learning disability was made. The setting up of Regional Epilepsy Implementation Groups was recommended to develop care standards at regional levels.

A further report in 2002, The National Sentinel Clinical Audit of Epilepsy-Related Death (Hanna NJ et al 2002) investigated the pathology behind sudden deaths in epilepsy along with primary and secondary care prior to death. During the study period, there were 2412 deaths reported with epilepsy somewhere on the death certificate. 1023 were subjected to autopsy and the audit examined 43% of these autopsies. A further 156 deaths not subjected to post mortem were also studied. In 812, epilepsy was identified as the primary cause of death. Access to appropriate specialist care, record keeping, provision of support and the sharing of information regarding the hazards of epilepsy, drug treatments and the importance of adherence to drug regimens were all identified as inadequate. A large proportion of deaths (39% of adults and 59% of children) were found to have been potentially preventable and recommendations were made at both primary as well as secondary level care to improve the existing quality of service provision.

1.3.1.2 Problems associated with studies

1.3.1.2.1 Selection bias and case ascertainment in studies of medical care for people with epilepsy.

As with many population studies, selection bias is a potential hazard. Patients at opposite ends of the spectrum of severity often encountered

with the epilepsies will have different degrees of social problems and will require varying levels of input from healthcare facilities.

There is tremendous variability in surveys; some have included people who have had single seizures whilst others have concentrated on those with "active" epilepsy. This is usually defined as those having had at least one seizure in the past two years, with more than one afebrile seizure ever, and those taking antiepileptic drugs.

Disease registers are a relatively new phenomenon in many practices and those that exist may be inaccurate. Mant and Tulloch (Mant D and Tulloch A 1987) showed that only 56% of patients with chronic diseases were recorded. Thus, many studies have surveyed patients presenting for repeat prescriptions of antiepileptic medication. Nevertheless, this method has drawbacks because many patients with epilepsy will not be on medication for various reasons. Goodridge and Shorvon (Goodridge and Shorvon 1983b) in their general practice study found that 44% of patients with active epilepsy were not taking antiepileptic drugs, and Zielinski (Zielinski JJ 1974b) found that almost one quarter of patients with epilepsy known to specialist facilities and two thirds of those identified during a field survey were on no medication. Although not all had active epilepsy, more than one third of those identified form the field survey had never received medication. This group may be less severely afflicted by their epilepsy. On the other hand, it might include patients who have failed to derive benefit from medical care, and those who have recently ceased medication but are still at significant risk of seizures. Nevertheless, unless a well maintained disease register is available, identifying patients with epilepsy through AED prescriptions may be the only means possible, short of extensive case records scrutiny. The latter method is labour-intensive and not practicable for large-scale surveys; it would itself be liable to bias, such as participating GPs having a particular interest in epilepsy.

Information about medical services for people with epilepsy needs to be obtained from a community base, since only a small proportion of people

with epilepsy attend hospital for long-term follow-up (Lloyd Jones A 1980; Goodridge and Shorvon 1983b; Taylor MP 1987). Some small scale audits of care within the community have been performed (Lloyd Jones A 1980; Goodman I 1983; Taylor MP 1987), but information is required from throughout the country to take into account such variables as the availability of resources, difference in numbers of neurologists and the lengths of outpatient waiting lists. Various studies have done this with varying success. The Research Committee of the Royal College of General Practitioners (Crombie DL, and others 1960) collected details from 67 practices in England and Wales, and Cooper and Huitson's (Cooper GL and Huitson A 1986) study involved 30 practices throughout the UK. There have been no recent large scale studies addressing these issues.

Most surveys during the past 30 years have dealt only with people with active epilepsy; some have included only those taking anticonvulsant drugs. The prevalence varies from 2.3/1000 for people with epilepsy undergoing treatment in one practice (Munson JF 1910; White PT and Buckley EG 1981), to 10.5/1000 with active epilepsy and/or taking medication in another (Goodridge and Shorvon 1983b), where cases were identified by scrutiny of case records. The prevalence in most studies ranges from 3.4-6.1/1000, regardless of method.

1.3.1.2.2 Accuracy of information

Assessing epilepsy severity on a community basis is similarly fraught with difficulty. As has been discussed, the frequency and intensity of a patient's seizures have considerable bearing on the requirement of medical services. Knowledge of seizure frequency and classification is thus important in assessing optimum management, but this is often difficult to obtain even in a hospital setting. Patients' seizure disorders can render seizure counts and accounts inaccurate since alteration of consciousness is often integral to these. Patient literacy and communication problems are further obstacles. Finally, on a practical note, where surveys are undertaken by patient questionnaire, respondents may be unwilling to report aspects of care

about which they are unhappy if they suspect the questionnaire may be seen by those involved in their care. A number of studies have been undertaken. With the exception of Zander et al (Zander LI, and others 1979), there is considerable agreement about the deficits in the care of people with epilepsy.

1.3.1.2.3 Severity of epilepsy and the control of seizures

As above, the situation is often complex: Taylor (Taylor MP 1987) found that many patients only reported tonic clonic convulsions when asked about attacks. The proportion of patients with partial seizures varies between studies, the issue being complicated by the use of different classifications, with stated values between 18% and 61%. Different criteria for assessing seizure frequency also make comparison between studies difficult.

Lloyd Jones (1980) found that 71% of patients taking antiepileptic drugs had less than 3 seizures per year, and Cooper and Huitson (Cooper GL and Huitson A 1986) reported that 68% had less than one seizure in three months. Taylor (Taylor MP 1987) found that 33% of patients had more than 3 fits per year (all of these having complex partial seizures) and in the study of Hopkins and Scambler (Hopkins and Scambler G 1977), 66% of patients with partial seizures and 27% of those classified as having grand mal attacks had had seizures in the past 2 months.

A less optimistic view of the likelihood of seizure control in epilepsy is seen in studies in which only cases of active or treated epilepsy have been included. The proportion of patients seizure-free for 1 year ranges from 30% in a study in which patients were identified as they presented for repeat prescription (McCluggage JR, and others 1984), to 76% of those in a group with "active" epilepsy (Zander LI, and others 1979). Most studies suggest values of around 40%; e.g. 42% of patients with treated or active epilepsy in the study of the research committee of the Royal College of General Practitioners (Crombie DL, and others 1960), 41% of Taylor's

1987 study (Taylor MP 1987), and 42% in White and Buckley's study (White PT and Buckley EG 1981). In the three studies quoting figures for patients having more than one seizure per month (Lloyd Jones A 1980; Cooper GL and Huitson A 1986; Taylor MP 1987) 18-20% of patients fell into this category.

1.3.1.2.4 Hospital referrals and consultation rates

The DHSS report (Department of Health and Social Security 1986) recommended that people with new onset seizures should be seen by a hospital doctor for initial evaluation and treatment. Follow-up for the majority in whom seizures are easily controlled should then devolve to the GP. Patients with intractable epilepsy should continue to be followed up by a specialist, preferably in an epilepsy clinic.

Most studies suggest that the figure for patients ever attending a hospital for their seizures is around 90% (Hopkins and Scambler G 1977; Zander LI, and others 1979; Lloyd Jones A 1980; Munson JF 1910; White PT and Buckley EG 1981) (Taylor MP 1987), although some are seen by consultants other than neurologists or paediatricians (Munson JF 1910; White PT and Buckley EG 1981) (Goodridge and Shorvon 1983b). The percentage under continued follow-up is much smaller, ranging from 10% of patients who have ever had a seizure in Goodridge and Shorvon's study (1983) to 58% in practice A of White and Buckley's study (1981), but was around 10-30% in most surveys (Hopkins and Scambler G 1977; Zander LI, and others 1979; Lloyd Jones A 1980) (Taylor MP 1987).

The CSAG study found that 81% of respondents with controlled epilepsy had not seen their GP in the past year; 30% with new onset epilepsy and 35% with established epilepsy had not done so either (Clinical Standards Advisory Group 1999). Patients tended to make contact only when they deemed it necessary because of problems that may have arisen. Only 30% had attended hospital in the last 12 months. Attendance appeared linked to

severity; 57% with severe epilepsy had attended as opposed to 16% with mild epilepsy.

Several studies have found that most patients had seen a doctor within the last year (85% in the study of Hopkins ands Scambler (Hopkins and Scambler G 1977), and 92% in Taylor's study (Taylor MP 1987). However, there was considerable variation. In Lloyd Jones' study in 1980 (Lloyd Jones A 1980), 60% of patients had not seen a doctor in the preceding year, and 9% had apparently not seen a doctor to discuss their seizures during the past 10 years. Nine out of 17 patients having problems with fit control or antiepileptic medication were not being followed up regularly by any doctor. 25% of patients in the study by McCluggage et al had not seen a doctor for more than 1 year and 50% of these were continuing to have seizures (McCluggage JR, and others 1984). Hopkins and Scambler also reported little correlation between the severity of epilepsy and the frequency of follow-up (Hopkins and Scambler G 1977).

1.3.1.2.5 Patterns of follow-up in patients with epilepsy

Several investigators have commented on the quality of follow-up amongst patients with epilepsy. Hopkins and Scambler (Hopkins and Scambler G 1977) noted that in small units the patient would usually see the consultant, whereas in large units this would be unlikely, and Goodman (Goodman I 1983) commented that "... most of the follow-up was performed by junior hospital doctors."

1.3.1.2.6 Medication

In the last 15 years, there has been a huge change in the manner and range of prescribing in the United Kingdom. Thus data from older studies has less relevance today. In McCluggage's study (McCluggage JR, and others 1984), 59% of patients had been treated for epilepsy for 10 years or more

and 30% for 20 years or more, and in White and Buckley's study 73% had been treated for epilepsy for at least 5 years (White PT and Buckley EG 1981). Most studies quote phenobarbital and phenytoin as being the two most widely prescribed drugs, either alone or in combination (Crombie DL, and others 1960; Taylor MP 1987), with 80-90% of those on medication taking these drugs in several studies (Hopkins and Scambler G 1977; Goodridge and Shorvon 1983b; Cooper GL and Huitson A 1986; Taylor MP 1987).

The proportion of patients taking medication who were on monotherapy ranged from 33% in Goodman's study (1983) to 68% in that of Goodridge and Shorvon (1983), with the proportion on three or more drugs ranging from 2-14%. With the exception of Taylor's studies (Taylor MP 1983; Taylor MP 1980; Taylor MP 1987) in which an active effort was made to decrease polytherapy, there was little evidence of monotherapy being commoner in the most recent surveys. This is despite the finding by Shorvon et al (1979) that 76-88% of newly diagnosed, untreated patients can be completely controlled with a single drug (phenytoin or carbamazepine) (Shorvon and Reynolds 1977).

1.3.2 Treatment of the first seizure

1.3.2.1 *Drug treatment of the first seizure*

Treatment of the first seizure and its influence on recurrence is a controversial issue. In the UK, current guidelines suggest initiation of treatment in first seizures in specific situations. These include patients with congenital neurological deficits, patients with brain imaging abnormalities, patients with unequivocal epileptiform discharges and patients with previously unrecognised absences, myoclonic jerks or partial seizures as the risk of seizure recurrence is high in these groups (NICE guidelines 2004; SIGN guidelines 2003). These guidelines also include recommendations for commencing treatment in first seizure patients who deem the risk of subsequent seizures to be unacceptable. Approximately 70% of first seizure patients in the USA are given drug treatment (Hauser,

and others 1982); the corresponding figure in the UK is largely unknown. An inherent bias in most studies examining this has been the tendency for the physician to prescribe antiepileptic medication to patients they deem to be at risk of recurrence. (Annegers, and others 1986; Hauser, and others 1982; Hopkins, and others 1988) Two randomised, controlled trials have suggested that there is a significant reduction in the risk of recurrence in patients treated after the first seizure (Musicco, and others 1997; Camfield P, and others 1989) although one study included only 31 patients (Camfield P, and others 1989) and the other included only tonic clonic seizures (Musicco, and others 1997). Undoubtedly, further trials are needed to clarify the influence of treatment in preventing recurrences. An MRC study group (MESS – The Multi-centre Study of Early Epilepsy and Single Seizures) is currently carrying out a controlled trial, randomising patients with seizures at the time of a first epileptic attack to either treatment or delayed treatment. It is hoped that the results of this study will shed light on the role of treatment in the long-term prognosis of epilepsy. This study randomised 1443 patients to immediate therapy or deferred therapy and the outcomes to be examined will be both the short-term prevention of seizures and the proportion of patients in the two groups achieving long-term remission.

1.3.3 Treatment of epilepsy with conventional antiepileptic drugs

Drugs such as carbamazepine, phenytoin, valproate and phenobarbital are loosely grouped under the rubric of "conventional" AEDs, largely by virtue of their long-established presence and efficacy in the antiepileptic armamentarium. They are licensed for use as monotherapy and where indicated also serve as effective adjunctive therapy for about half of all patients with seizures not controlled by a single drug. Over the last few decades, carbamazepine and valproate have established themselves as first line therapy for partial and generalised seizures respectively whereas an unfavourable pharmaco-kinetic and adverse event profile has resulted in the relegation of phenytoin to a more secondary role (Table I).

In earlier studies, not surprisingly, the drugs used most often have been phenytoin or phenobarbital, either singly or in combination (Crombie DL, and others 1960; Taylor MP 1987). In several studies, 80-90% of patients taking medication were on these drugs (Hopkins and Scambler G 1977; Goodridge and Shorvon 1983b). Phenobarbital, due to its sedative effects and its propensity to cause behavioural disturbances in children, is now rarely prescribed as a first line drug for any type of seizure. Both drugs, however, have a prominent role as parenteral therapy for status epilepticus.

TABLE I. Choice of Antiepileptic Drugs

	First-line	Second-line
Generalized epilepsy		
Idiopathic		
Simple absence	VPA	ESM, LTG, BZPs
Juvenile myoclonic	VPA	LTG, TPM
Tonic clonic	VPA	LTG, TPM, LVT, CBZ, PHB, PHT
Symptomatic		
Partial epilepsy	CBZ, VPA	LTG, GBP, TPM, LVT, OXC, TGB, VGB
Generalised epilepsy	VPA, CBZ	LTG, TPM, LVT, OXC, VGB
Unclassified epilepsy	VPA, CBZ	LTG, GBP, TPM, LVT, TGB, OXC, VGB

Note: VPA, sodium valproate; CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; PHB, phenobarbital; ESM, ethosuximide; BZPs, benzodiazepines; LTG, lamotrigine; GBP, gabapentin; TPM, topiramate; LVT, levetiracetam; VGB, vigabatrin (used only as a last resort); TGB, tiagabine

1.3.3.1 *Treatment with carbamazepine*

Carbamazepine is the first choice drug for partial seizures with or without secondary generalisation. It may also be used in the tonic-clonic variety of

idiopathic generalised epilepsy in which valproate is ineffective or contraindicated. However, it is contraindicated in absence and myoclonic seizures, both of which may be aggravated by its use and it is therefore important to exclude the presence of these seizure types in patients who have primary generalised epilepsy. It can also be used in various childhood epilepsy syndromes.

Most of the common adverse events with carbamazepine therapy are CNS related. These consist of drowsiness, unsteadiness, dizziness and visual disturbances. Cognitive dysfunction is not uncommon although this may be less frequent than with phenytoin or phenobarbital. Skin reactions are also frequently seen and may be life threatening in a minority. Fulminant liver failure has been reported although minor elevations in liver enzymes are much more common due to enzyme induction.

1.3.3.2 *Treatment with sodium valproate*

Valproate is the drug of choice for primary generalised epilepsy, including absence and myoclonic seizures. It is also effective therapy in partial seizures and has a wide spectrum of activity.

CNS-related adverse events such as sedation and cognitive dysfunction are uncommon but may occur. Small elevations in ammonia levels maybe seen quite frequently in normal individuals however but symptomatic hyperammonemia is rare. Hepatotoxicity, although a well publicised adverse event, is uncommon and occurs in less than 1 in 37000 patients on monotherapy. However, in children with neurological handicaps on polytherapy under the age of 2 years, the incidence may be nearer 1 in 500.

More common and less serious adverse events are weight gain, postural tremor, hair loss and gastrointestinal upsets. There have been recent reports of polycystic ovarian disease due to valproate therapy and this should be mentioned to young female patients before initiating therapy.

Teratogenicity may be more commonly seen with valproate than with many other antiepileptic drugs. This includes neural tube defects and more uncommonly, the foetal valproate syndrome. There is some suggestion that valproate exposure in utero may affect neuropsychological outcomes in offspring although this has not been ascertained in a prospective, controlled fashion.

1.3.3.3 *Treatment with phenytoin*

Phenytoin is effective in a wide variety of seizure types and syndromes although its adverse event profile has resulted in it mainly being used as second line or adjunctive therapy where carbamazepine or valproate are ineffective or have caused treatment limiting side effects. In convulsive status epilepticus, however, it is still considered a drug of first choice. Like carbamazepine, it has no role in the treatment of absence and myoclonic seizures.

PHT has both acute as well as chronic side effects. The former are often dose related and usually occur above the therapeutic range of 10-30mcg/ml. Nystagmus and ataxia occur at levels above 30mcg/ml, drowsiness and dysarthria between 30-40mcg/ml and stupor at levels above 40-60mcg/ml. Also common as early side effects are hypersensitivity reactions such as rash, fever, lymphadenopathy, blood dyscrasias and renal failure. Several chronic side effects have also been described, gum hyperplasia probably being the best known of these. Folate deficiency megaloblastic anemia is also occasionally seen, as is osteomalacia. Other side effects include hirsutism, facial coarsening and pigmentation, and acne. Teratogenicity can occur with phenytoin therapy.

1.3.3.4 *Treatment with phenobarbital*

Phenobarbital was commonly used as first line therapy for a variety of partial and generalised seizures as well as many neonatal and childhood

seizure disorders. Its role in the long-term treatment of the epilepsies has now become somewhat limited in developed countries due to the advent of equally or more efficacious drugs with better adverse event profiles, although it remains a cheap and effective therapy in many developing countries. In the treatment of status epilepticus, however, it still occupies a prominent position in parenteral form and is used as a drug of first choice by many specialists in this situation.

The side effects that have primarily been responsible for the decline in its use are impaired cognition and behavioural problems, particularly in children. Drowsiness and sedation are most often dose-related, although habituation with continued therapy can occur in some patients. Higher doses can have prominent depressive effects on the CNS and phenobarbital overdoses can be fatal without prompt remedial action. Hyperactivity and irritability can be especially irksome in children. Other acute side effects such as ocular and gait disturbances may also occur although non-dose related hypersensitivity reactions such as skin rashes and hepatitis are uncommon. Like phenytoin, it can also cause folate deficiency anemia and osteomalacia.

1.3.3.5 *Treatment with ethosuximide*

Ethosuximide is primarily used as therapy in absence epilepsy although it can also be used as sole or adjunctive therapy in juvenile myoclonic epilepsy where valproate has been ineffective or is contraindicated. A related compound, methsuximide has similar indications for use although it can also be used as adjunctive therapy in partial seizures.

Gastrointestinal adverse events are common with ethosuximide and consist mainly of nausea, abdominal discomfort and hiccups. These uncommonly culminate in termination of therapy. Sedation may be observed at higher doses although it has a minimum of cognitive side effects. Neuropsychiatric disturbances such as anxiety, depression and acute psychosis have also been described. Skin reactions such as rashes and

erythema multiforme have been noted to be common occurrences. Potentially fatal adverse events such as Steven Johnson's syndrome and blood dyscrasias have also been reported.

1.3.4 **Treatment with new antiepileptic drugs**

Several new AEDs are now available for the treatment of refractory epilepsy. Apart from lamotrigine and topiramate, which are licensed for use as monotherapy, all the others are used as adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. New drugs however, produce long-term seizure remission in less than 15% of patients with chronic epilepsy and less than a third of such patients continue with new drugs such as lamotrigine, topiramate, gabapentin and levetiracetam beyond 5 years despite lack of seizure remission (Krakow, and others 2001; Lhatoo, and others 2000)

An overriding worry about the new AEDs has been the possibility of the occurrence of long-term side effects. A considerably longer study period is required than those currently utilised in clinical trials, to allow the discovery of uncommon though serious side effects. Fulminant hepatic failure and aplastic anemia were found to be potentially fatal adverse events due to felbamate therapy long after it was approved for use in patients with epilepsy. Similarly, the discovery of serious impairment of vision due to visual field defects with vigabatrin therapy has considerably restricted its use and is now only prescribed when absolutely necessary. In addition, clinical trials do not recruit elderly and very young patients or female patients on inadequate contraception; thus inadequate information exists for whole sections of the patient population.

At the current time, topiramate, levetiracetam, gabapentin, vigabatrin, tiagabine, and lamotrigine are available for use as adjunctive therapy in the treatment of partial epilepsy with or without secondary generalisation, the latter also for use in primary generalised epilepsy and as monotherapy.

1.3.4.1 Gabapentin

Gabapentin is a mild to moderate efficacy antiepileptic drug useful as add-on treatment of refractory partial seizures. Clinical trials showed that 22% of patients with partial seizures will experience at least a 50% reduction in seizure frequency. Gabapentin is not effective for treatment of idiopathic generalized epilepsy. As with standard antiepileptic drugs, secondarily generalized tonic-clonic seizures may respond better than simple or complex partial seizures. The side effects of gabapentin are usually mild and include diplopia, ataxia, fatigue, and headache. Male rats developed acinar pancreatic tumors in a dose-related fashion, and gabapentin has therefore been termed a potential human carcinogen with an acceptable low risk. An advantage of Gabapentin is its lack of interaction with other drugs, which makes plasma drug monitoring unnecessary. It is however, known to cause seizure exacerbation in some cases and is not particularly effective in patients with severe epilepsy.

1.3.4.2 Lamotrigine

Lamotrigine can be effective as monotherapy in newly diagnosed partial seizures and generalized tonic-clonic seizures, and as add-on treatment of refractory partial seizures. Clinical trials showed a reduction of at least 50% in about 24% of patients, with up to 5% of patients becoming seizure-free at doses of 100-300 mg/day. Lamotrigine is of mild to moderate efficacy as add-on treatment of refractory generalized epilepsy with atypical absences, atonic seizures, and myoclonic seizures. Lamotrigine is a triazine derivative and, like phenytoin or carbamazepine, causes an extended inactivation of neuronal membrane sodium channels, thus inhibiting repetitive discharges in experimental models. The pathological release of glutamate, a major excitatory neurotransmitter in human brain, is also blocked. The elimination of lamotrigine is accelerated by enzyme-inducing antiepileptic drugs, such as carbamazepine, phenytoin, and phenobarbital, and inhibited by valproate. Even in monotherapy, the initiation of lamotrigine therapy should be at a very low dose (25 mg/day)

to avoid the development of a rash in up to 5% of patients, particularly younger age groups and those on concurrent valproate. The rash may be severe, amounting in some cases to a Stevens-Johnson syndrome. Other side effects include sedation, dizziness, diplopia, and ataxia but generally the drug is well tolerated.

1.3.4.3 Levetiracetam

Levetiracetam is the most recently marketed antiepileptic drug, a pyrrolidone derivative whose mode of action remains unknown (Shorvon SD 2000). It is well tolerated and the most frequent central nervous system adverse events in trials were dizziness, asthenia and somnolence. An increased frequency of upper respiratory tract "infections" were noted but these were not treatment limiting. Placebo controlled trials in refractory partial epilepsy have shown 50% seizure reduction in up to 33% on 1000mg and 40% on 3000mg compared to 11% in the placebo groups. There are no formal trials examining its usefulness in the primary generalised epilepsies although it has been shown to be effective in eliminating photoparoxysmal responses on EEG, and has been successfully used in juvenile myoclonic epilepsy and myoclonic jerks. It is useful in the treatment of refractory epilepsy.

1.3.4.4 Oxcarbazepine

Oxcarbazepine was developed as a structural variant of carbamazepine. It is a pro-drug, as its 10-hydroxymetabolite is responsible for the antiepileptic effect. When compared to carbamazepine, oxcarbazepine has shown similar efficacy as an add-on drug for refractory partial seizures and as a first-line agent in previously untreated patients with tonic-clonic and partial seizures. Common side effects include drowsiness, dizziness, ataxia, headache, and hyponatremia. The hyponatremia is more marked than with carbamazepine and occasionally leads to confusion and increase of seizures. Other side effects include rashes, diarrhea, nausea, vomiting, and anorexia. The enzyme-inducing activity of oxcarbazepine is probably

limited to the P450 IIIa isoenzyme of the cytochrome P450 complex; nevertheless, interactions occur, for instance with oral contraceptives.

1.3.4.5 Tiagabine

Tiagabine is another new drug with mild to moderate efficacy in seizure control. Its proposed mechanism of action is by inhibiting glial cell GABA reuptake. It is used as adjunctive therapy in partial seizures with or without secondary generalisation. Results from controlled trials have shown that up to one third of patients on tiagabine achieve a 50% reduction in seizure frequency, although complete remission from seizures is an infrequent occurrence. The commonest adverse events related to therapy are central nervous system related and consist of sedation, tremor, headache, mental slowing, tiredness and dizziness. Confusion, irritability and depression may occur. Increases in seizure frequency and episodes of non-convulsive status have also been reported. So far, no life-threatening idiosyncratic reactions have been encountered. Use in pregnancy is not recommended although no teratogenicity has been reported in humans.

1.3.4.6 Topiramate

Topiramate is a sulfamate-substituted D-fructose, a naturally occurring monosaccharide. Its antiepileptic action was discovered during a search for antidiabetic drugs. It has a variety of mechanisms of action, the major being its effect on the voltage-dependent Na channels in the neuronal membrane. It affects glutaminergic (via the AMPA receptor) and GABA-ergic (at the GABA receptor) transmission. The drug also has carbonic anhydrase action. Animal experimentation showed topiramate to be effective against a wide variety of experimental epilepsy models, and the experimental profile suggests a wide spectrum of activity in human epilepsy. Animal toxicology showed only mild effects, but the drug was shown to have teratogenicity at high doses. The drug has excellent pharmacokinetic properties and there are no active metabolites. In

randomized clinical trials, topiramate has been shown to be effective against partial and secondarily generalized seizures. Topiramate can cause predominately neurological side effects, particularly at high dosage and if titrated too fast. These adverse effects include headache, sedation, asthenia, and confusion. Loss of weight is common, and the drug also causes renal stones in less than 2% of patients. There are no serious recorded idiosyncratic reactions, and there is no hematological toxicity. To lessen the incidence of treatment limiting side effects, drug intitiation at low doses and slow upward titration is necessary.

1.3.4.7 Vigabatrin

Vigabatrin is effective as add-on treatment of refractory partial seizures. In clinical trials, the addition of 1-3 g/day led in about 46% of cases to a reduction of at least 50%, with 5% of patients becoming seizure-free. Vigabatrin is not effective in patients with idiopathic generalized epilepsy. The antiepileptic effect of vigabatrin is due to the irreversible inhibition of GABA-transaminase that leads to a permanent severalfold rise in GABA, the major inhibitory neurotransmitter in human brain. The most common side effects are transient drowsiness and weight gain, which may be unacceptable in some patients, and less often, depression and manic-depressive disorder, confusion, and psychotic episodes. Recent, well documented descriptions of visual field defects in patients on long-term therapy with the drug have drastically limited its use. The visual field defects, which may be asymptomatic, may occur in upto half of all patients, and are thought to be as a result of GABA mediated retinal toxicity. It can lead to blindness and when vigabatrin is used, therefore, visual fields need to be carefully monitored. Rare cases of encephalopathy with stupor and an increase in seizures have been reported.

1.3.5 **Duotherapy in newly diagnosed epilepsy**

Therapy with more than one drug for newly diagnosed epilepsy has been recommended in the past (Yahr MD, and others 1952), and until two

decades ago, this was common practice. The lack of evidence supporting this has been pointed out (Shorvon, and others 1978) and it is no longer considered acceptable or safe practice to consider this. Whilst there is no convincing basis to support the hypothesis that drugs with differing modes of action are likely to have synergistic actions in epilepsy treatment, it is difficult to endorse duotherapy. It is no longer common practice and it is unusual in newly diagnosed epilepsy.

1.3.6 **Treatment changes in epilepsy**

There are no studies which have longitudinally assessed treatment changes in the community treatment of epilepsy. We know that 70-80% of patients with epilepsy achieve long term remission from seizures, usually with one antiepileptic drug and a further 10-15% may be able to achieve long term remission with two or more drugs (Sander JWAS 1993). In the remaining, seizure control is difficult and requires the addition or replacement of drugs with each new antiepileptic drug in turn in the hope of attaining seizure remission. A proportion of patients (0.33-1.33%) with newly diagnosed epilepsy are said to eventually require epilepsy surgery for the treatment of refractory epilepsy (Engel 1996).

In the work of Kwan et al, where the study population consisted of 525 patients with newly diagnosed epilepsy, 92% of whom were referred to the epilepsy clinic by general practitioners, 470 patients had never previously received treatment for seizures. In 222 of 470 patients (47%), seizure control was achieved with the first drug, whereas with drug changes, only 13% and 4% became seizure free with the second and third (or more) drugs respectively. This suggested that failure to respond to the first drug was a good predictor of subsequently refractory epilepsy. If the initial drug change was because of lack of efficacy rather than side effects, a much smaller percentage of patients became seizure free (11% compared to 41%). (Kwan and Brodie 2000) This is a hospital-based study in most respects and patient enrolment took place between 1984 and 1997.

2. METHODS

2.1 The United Kingdom General Practice Study of Epilepsy

The NGPSE began by identifying 1200 patients newly diagnosed by their general practitioners as having epilepsy. Diagnosis was confirmed by means of an expert panel after a period of time (6 months) that sufficiently allowed for any change or evolution of the initial diagnosis, and the cohort was then monitored in a prospective manner by means of yearly follow-up questionnaires.

The initial aims of the study were to assess the demographics of the cohort with confirmed epilepsy and make observations of the clinical phenomenology of their seizures, to follow up this cohort prospectively to assess the risk of recurrence following the first seizure, and finally to assess the prognosis of epilepsy, including remission from seizures and the mortality of epilepsy.

2.1.1 Ethical considerations

The Joint Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery at Queen Square, London approved the study. The Research Committee of the Royal College of General Practitioners recommended participation to its members. Strict confidentiality was maintained at all times, in keeping with the Data Protection Act and all patients were assigned code numbers. The study is registered with the Office of National Statistics and the Office of the Data Protection Registrar.

2.1.2 Identification of the incident cohort

2.1.2.1 *Community base*

Participation in the study was encouraged through widely publicised notices in medical journals and periodicals as well as through personal contact with general practitioners. A total of 275 individual general practitioners throughout the United Kingdom volunteered for the study and reported all newly diagnosed cases of epilepsy to the study panel.

2.1.2.2 *Study design and registration*

2.1.2.2.1 *Inclusion criteria*

All patients newly diagnosed with, or suspected as having, epilepsy were recruited into the study and this included childhood febrile convulsions, single seizures and seizures associated with acute illnesses.

2.1.2.2.2 *Exclusion criteria*

All patients with a suspected previous diagnosis of epilepsy and patients with neonatal seizures were excluded because these types of seizures have a distinct clinical picture and prognoses that are well defined and documented.

2.1.3 **Initial registration**

GPs were provided with patient registration forms and throughout the patient recruitment period, which began in June 1984 and lasted until October 1987, contact with each GP was scrupulously maintained to ensure that every single patient appropriate for the study was recruited. This active surveillance ensured a complete and unselected cohort. Each patient was flagged at the NHS Central Register. This allowed tracing of any patient who changed GP and the study was automatically informed of any deaths in the cohort, and provided with a copy of the death certificate.

2.1.4 Prevention of bias

2.1.4.1 Random selection

Patients were recruited from both rural and urban practices to reflect a balanced mix of cases. As patients do not choose their GPs in anticipation of a seizure, choice of GP did not bias the study. Equally, since reported cases were those with suspected newly diagnosed epilepsy rather than those with established epilepsy, a diminution of ascertainment bias, if any, was expected.

2.1.4.2 Completeness of case ascertainment

To avoid the main shortcoming of many epidemiological studies of epilepsy, GPs were asked to consider all patients with symptoms attributable to seizures for recruitment. This was to ensure that patients with milder symptoms would also be ascertained. This ensured sensitivity but resulted in a potential compromise of specificity during the recruitment period.

2.1.5 Initial data collection

Demographic and clinical details were collected, together with characteristics of the index seizure. The study offices located at the Institute of Neurology and the Chalfont Centre for Epilepsy received all the registration forms and, with the available information, case folders were created. A coded, computerized database was designed, with GP and patient records linked together for convenience. Patient details with registration numbers and codes were sent back to the GPs with a 'green card' to be inserted in the practice notes that detailed the patient's involvement in the study. This was designed to inform the new GP in case the patient changed practices. The seizure that resulted in the patient being registered in the study was designated the index seizure which was not necessarily the same as the first seizure. This was because, in retrospect,

there were several patients newly recruited who had suffered seizures in the past without a diagnosis of epilepsy having been made.

2.1.6 **Follow-up**

At 6 months, further information was collected from the GP through a detailed questionnaire; details of seizures and treatment were requested, as well as 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 co-ordinator and the questionnaire filled out. Frequent changes of GP practice in a minority of patients, and retirement or changes of GPs themselves were anticipated problems.

2.1.7 **Hospital enquiry**

Six months after registration, letters and forms were sent to hospital consultants for details regarding all patients who had been seen in hospital clinics or had been admitted to hospital with suspected or definite seizures. Confirmation of the diagnosis was sought and specific questions on seizure classification, results of neuro-imaging and EEG, nature of treatment given and details of follow-up were asked. Where no responses were obtained, personal inquiry, examination of copies of hospital notes and examination of GP's copies of hospital correspondence followed up requests.

2.1.8 **Change of GP**

When patients changed GP, the new GP would be alerted to their involvement in the study by the card that had been put in 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.

2.1.9 **Classification of patients**

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

2.1.10 **Study panel**

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

2.1.11 **Seizure classification**

On the basis of all the information available at 6 months, the panel classified seizures and epilepsy after the index seizure into the four groups of definite epilepsy, probable epilepsy, febrile convulsions and non-epileptic episodes. The probable group comprised those cases in which, even at 6 months, a definite diagnosis of epilepsy was not possible, but remained in question.

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 an EEG.

2.1.12 **Aetiological classification**

The cases were further classified in to the following groups:

1. Idiopathic/Cryptogenic – no identified underlying cause
2. Remote symptomatic – postnatal CNS lesions
3. Acute symptomatic – seizures starting within 3 months of a CNS insult
4. 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, and others 1982). The study classification predated the ILAE's aetiological classification of the epilepsies. Those cases classified as symptomatic were further divided into aetiological groups.

1. Vascular – where there was clear evidence of vascular or embolic disease
2. Tumour – either radiological or an otherwise clear clinical picture of an expanding lesion
3. Trauma – definite history of head injury with loss of consciousness of more than 1 hour
4. Alcohol – where seizures occurred during withdrawal or due to excessive intake
5. Post-infective – during or in the aftermath of a confirmed episode of encephalitis, bacterial meningitis or cerebral abscess

2.1.13 **Sample size**

A sample size of 1,200 patients was chosen in order to achieve 700 cases of probable and definite epileptic seizures.

2.1.14 **Long-term follow-up**

Regular active surveillance was chosen as the method to follow-up these patients. This ensures that data collection is carried out at reasonable intervals, so that no information is lost. It puts the responsibility of data collection on the central study office, removing as much responsibility from GPs as possible. Active surveillance is also 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 of the patient's epilepsy, medication and medical developments. In 1993, a second hospital follow-up was carried out.

In 1997, the Office for National Statistics took on responsibility for mortality reporting and patient migration from the NHSCR.

2.3 Mortality in the long-term in epilepsy

2.3.1 *Case ascertainment*

All deaths were notified to the investigators, initially by the NHSCR and after 1997 by the Office for National Statistics. All notifications were accompanied by the patient's death certificate and where done, by the coroner's autopsy report. In some cases, deaths were also notified with relevant details, by patients' GPs.

2.3.2 *Identification of exact cause of death*

Cause of death was noted from the death certificate and in every case, confirmatory details were sought from hospital specialists, coroners or from the certifying doctor before being assigned an International Classification of Diseases (ICD-10) classification number. Autopsy

reports were obtained for all cases that underwent post-mortem examination.

2.3.3 *Statistical analysis*

Three different methods of analysis were used. As in the previous short-term analysis of mortality in the NGPSE, SMRs were calculated using the person-years method. A Cox model analysis and a time dependent co-variate analysis were also carried out, both for the first time in the analysis of mortality in epilepsy.

2.3.3.1 *The person years method*

The first analysis was by the person years method (Coleman MP, and others 1989) and summarised by standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) based on the Poisson distribution and two-tailed significance tests; it utilised all deaths in the NGPSE up to 31st December 1997. Expected numbers of deaths were calculated for all causes, and for specific causes of death, by sex, age (0, 1, 2, 3, 4, 5-9, 10-14,.....85-89, 90-100 years) and year (1984-1997) for the population of England and Wales (Registrar General's Mortality Statistics). SMRs were calculated (Coleman MP, and others 1989) for the whole cohort as well as individually for definite epilepsy, probable epilepsy and febrile seizures. SMRs for individual causes of death and for aetiology of epilepsy were also calculated.

2.3.3.2 *The Cox proportional hazards analysis*

Cox proportional hazards models were used in this analysis as well as in analysis 3, implemented with the program 2L from the BMDP suite (Dixon WJ 1992). Baseline characteristics that influenced mortality up to 31st December 1997, including age at index seizure, sex, number of pre-index seizures, aetiology, seizure type and seizure classification

(idiopathic/cryptogenic, acute symptomatic, remote symptomatic and congenital neurological deficits) were assessed.

2.3.3.3 *Time dependent co-variate analysis*

The third analysis used time-dependent co-variates in the Cox model (in addition to the baseline characteristics), to assess the influence of events that occurred during follow-up. The follow-up period from index seizure to death or censoring for each patient was divided into contiguous 3-month intervals. During each of these intervals, the recurrence of seizures and use of AEDs were noted. Seven time-dependent co-variates were derived:

(i) any recurrence of seizures in each 3 month interval of follow-up was coded as a step function, as shown for a typical patient in Fig.1; in the figure, the step function is equal to zero throughout any 3 month period during which there are no seizures (the 1st, 3rd, 6th, 7th and 8th), and equal to one throughout any 3 month period during which a seizure occurs (the 2nd, 4th and 5th).

(ii) use of AEDs was similarly coded as a step function where the step function equalled zero throughout any 3month period when no treatment was received and equal to one where treatment was received;

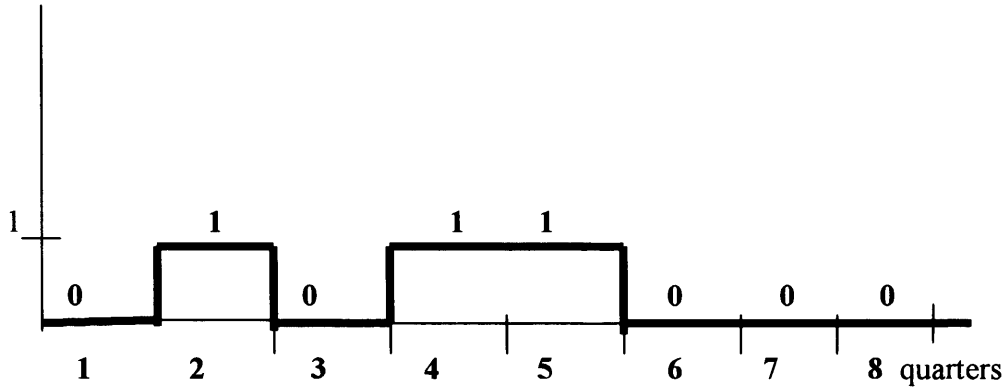
(iii) for each 3-month interval, the cumulative number of 3-month intervals during which a seizure occurred (for the patient whose seizure recurrence is illustrated in Fig. 1, the values of this time-dependent co-variate are 0,1,1,2,3,3,3 and 3 for the first eight 3-month intervals respectively [Fig.2]);

(iv) a similar time-dependent co-variate for cumulative use of AEDs;

(v) a step function as in (i) equal to one when the two preceding 3-month intervals were seizure-free (i.e. patient in 6 month remission from seizures) and zero otherwise (for the patient in Fig.1, the values of this co-variate are zero for the first seven 3-month intervals and one for the eighth); and are similar to (v) but indicate 1-year and 2-year remission respectively.

Deaths in the 3-month interval following the index seizure were excluded since complete information about the time-dependent co-variates was unobtainable. This removes the potential bias of early mortality in co-variate analysis in patients who had few seizures but nevertheless died due to serious underlying pathologies. Further, for some patients information about seizures and use of AEDs was not available up to the date of death; for these patients, follow-up was censored at the end of the last complete 3-month interval.

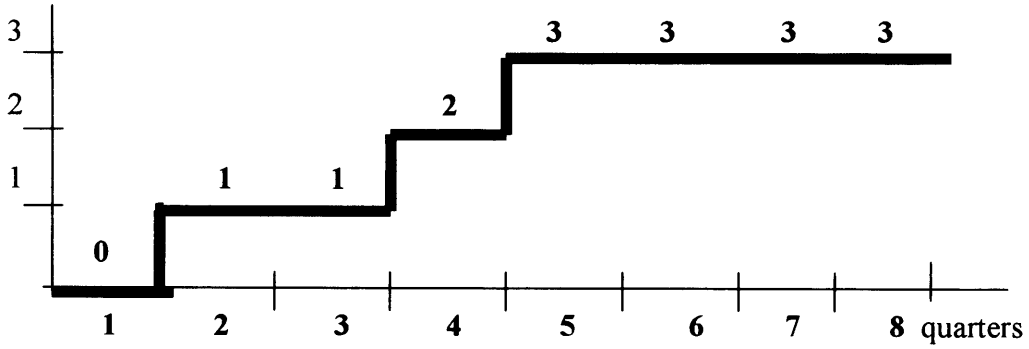
Fig.1 Example of seizure recurrence as a time-dependent co-variate during each 3-month follow-up period.



3- monthly time periods (quarters) from index seizure

- 1= one or more seizures in a 3 month interval.
- 0= no seizures during a 3-month interval.

Fig.2 Example of cumulative seizure recurrence as a time-dependent co-variate during each 3-month follow-up period.



3- monthly time periods (quarters) from index seizure

- 1= one or more seizures in a 3 month interval.
- 0= no seizures during a 3-month interval

2.3 THE DYNAMICS OF TREATMENT IN EPILEPSY

2.3.1 Case ascertainment

Treatment patterns were analysed in the 564 patients with definite epilepsy. Data recorded included age, sex, date of index seizure, date of onset of seizures if different from index seizure, seizure type (The Commission on classification and terminology of the International League Against Epilepsy, 1981), person prescribing initial treatment, duration of treatment, number of treatment changes, reasons and types of changes, use of newer antiepileptic drugs and seizure status.

2.4.2 Statistical Methods

Kaplan Meier survival analyses were carried out using SPSS version 7.5.1, to estimate the time taken to change treatment for the first time, by either adding a drug or substituting a drug. The time taken to first change for individual drugs and the percentage of patients continuing on a particular drug was also calculated using the same method. Life table survival analyses were carried out to estimate the total number of patients continuing on medication at the end of the follow-up period.

3. RESULTS

3.1 THE MORTALITY OF EPILEPSY

3.1.1 Follow-up period

Median (25^{th}, 75^{th} centiles) follow-up of patients was 11.8 (10.6,12.7) years, equivalent to 11,400 person years. 17 (2%) patients were untraceable at last follow-up. A total of 214 deaths (106 males, 108 females) occurred in the entire cohort (SMR 1.9[95% CI=1.6,2.2;p<0.001]) suggesting increased long term mortality twice that of the general population (Table 2).

Table 2. All cause mortality for whole cohort and specific subgroups

Number at Risk		Number of Deaths								
		Males		Females		Totals				
		Obs	**Exp**	**Obs**	**Exp**	**Obs**	**Exp**	**SMR**	**(CI 95%)**	**P***
Definite epilepsy	564	79	33.0	70	25.3	149	58.3	2.6	(2.1, 3.0)	<0.001
Probable epilepsy	228	21	13.7	29	22.8	50	36.5	1.4	(1.0, 1.8)	<0.04
Sub-total	792	100	46.7	99	48.1	199	94.8	2.1	(1.8, 2.4)	<0.001
Not epilepsy	79	6	6.5	9	7.9	15	14.4	1.0	(0.5, 1.7)	0.94
Febrile seizures	220	0	1.3	0	0.6	0	1.9	0	(0, 1.9)	0.72
Total	1091	106	54.5	108	56.6	214	111.1	1.9	(1.6, 2.2)	<0.001

*Significance test based on Poisson distribution for SMR different from 1 (2-sided)

3.1.2 *Analysis 1 – the person years method*

3.1.2.1 **Overall mortality**

Patients with definite epilepsy had an SMR of 2.6 [95% CI=2.1,3.0;p<0.001] whilst those with probable epilepsy had an SMR of borderline significance (1.4[95% CI=1.0,1.8;p<0.04]). Combined analysis of the definite and probable groups, to allow for possible under-diagnosis of epilepsy in the cohort confirmed significantly elevated mortality (SMR 2.1 [95% CI=1.8,2.4;p<0.001]).

3.1.2.2 **Age-specific mortality**

Analysis of age-specific mortality (Table 3) showed significant increases in all age bands. In the group with definite epilepsy this was highest in the 50-59 years (SMR 8.4 [95% CI=5.3,12.7]) and 0-49 years (SMR 5.4 [95% CI=3.2,8.4]) age bands, and lowest in the 70-79 years age band (SMR 1.7 [95% CI=1.1,2.4]). An identical pattern was seen when those with definite and probable epilepsy were combined.

Idiopathic/cryptogenic epilepsy was analysed separately because of the inclusion of patients in this group with primary generalised epilepsies in which the seizure disorder typically starts in the first two decades of life. No significant elevations of SMRs were noted (Table 3).

Table 3 – All cause mortality by age group in the combined group with definite and probable epilepsy, patients with definite epilepsy and the subgroup with idiopathic/cryptogenic epilepsy.

	Number of Deaths			
Age (years)	Obs	Exp	SMR	(95%CI)
Definite and probable epilepsy (n=792)				
0-49	20	4.8	4.2	(2.5, 6.4)
50-59	25	3.8	6.6	(4.2, 9.7)
60-69	32	11.9	2.7	(1.8, 3.8)
70-79	48	27.5	1.7	(1.2, 2.3)
>80	74	46.8	1.6	(1.2, 2.0)
Definite epilepsy (n=564)				
0-49	19	3.5	5.4	(3.2, 8.4)
50-59	22	2.6	8.4	(5.3, 12.7)
60-69	26	8.5	3.1	(2.0, 4.5)
70–79	35	20.6	1.7	(1.1, 2.4)
>80	47	23.0	2.0	(1.5, 2.7)
Idiopathic/cryptogenic epilepsy (n=346)				
0-49	5	2.3	2.2	(0.7, 5.1)
50-59	3	1.5	2.0	(0.4, 6.0)
60-69	5	5.3	1.0	(0.3, 2.2)
70-79	9	9.6	0.9	(0.4, 1.8)
>80	12	7.1	1.7	(0.4, 2.9)

3.1.2.3 **Mortality according to aetiology**

Analysis of mortality according to aetiology is shown in Table 4. There was some suggestion of excess mortality in the idiopathic/cryptogenic epilepsy group, though this was not statistically significant (SMR 1.3[95%CI=0.9,1.9)]. Mortality was however, significantly elevated in the remote symptomatic group (SMR 3.7 [95% CI=2.9,4.6]) and in the acute symptomatic group (SMR 3.0 [95%CI=2.0,4.3]).

Table 4. All cause mortality in patients with definite epilepsy according to aetiology.

Aetiology	At risk	Number of deaths			
		Obs	Exp	SMR	(CI95%)
Idiopathic/cryptogenic	346	34	25.8	1.3	(0.9, 1.9)
Remote Symptomatic	119	81	22.1	3.7	(2.9, 4.6)
Acute symptomatic	83	31	10.3	3.0	(2.0, 4.3)
Congenital deficit	16	3	0.1	25	(5.1, 73)

The commonest causes of death in patients under the age of 50 years were primary brain tumours, neoplasms other than primary brain tumours and lung neoplasms. Ischaemic heart disease, cerebrovascular disease and pneumonia accounted for most deaths in people over the age of 50 although SMRs were not significant in the ischaemic heart disease group. In the definite seizures group, cause specific SMRs were higher with wider CIs than the combined group (Table 5). Mortality from all causes other than malignant neoplasms, cerebrovascular disease and pneumonia was still higher than in the standard population (SMR 1.2; 95%CI=0.96-1.6; p=0.097) but the slightly higher risk was confined to women even in those

with definite epilepsy (women SMR 1.9 [95%CI=1.2-2.7], men SMR 1.1 [95%CI=0.6-1.7]). There was one death consistent with the criteria for sudden unexpected death in epilepsy (SUDEP) and one death due to status epilepticus. Burns sustained during a seizure (1), a bathtub drowning (1) and a fall resulting in a broken neck (1) were other causes of seizure related mortality. One patient committed suicide.

Table 5. Selected causes of death for the combined group with definite and probable epilepsy, patients with definite epilepsy and the subgroup with idiopathic/cryptogenic epilepsy.

	Number of Deaths											
	In first 7 years				In second 7 years				Overall – 14 yrs			
Cause of Death	**Obs**	**Exp**	**SMR**	**(95%CI)**	**Obs**	**Exp**	**SMR**	**(95%CI)**	**Obs**	**Exp**	**SMR**	**(95%CI)**
Definite and probable epilepsy (n=792)												
Malignant Neoplasms including primary brain tumour	47	13.5	3.5	(2.5,4.6)	9	7.8	1.2	(0.5,2.2)	56	21.3	2.6	(1.9,3.4)
Malignant Neoplasms excluding primary brain tumour	33	13.3	2.5	(1.7,3.5)	6	7.5	0.8	(0.3,1.8)	39	20.7	1.9	(1.3,2.6)
Neoplasms of Lung	10	3.3	3.0	(1.4,5.5)	4	1.8	2.3	(0.6,5.8)	14	5.1	2.7	(1.5,4.6)
Ischaemic Heart Disease	16	15.6	1.0	(0.5,1.7)	9	7.8	1.2	(0.5,2.2)	25	23.4	1.1	(0.7,1.6)
Cerebrovascular disease	28	7.5	3.7	(2.4,5.4)	7	3.6	1.9	(0.8,4.0)	35	11.1	3.2	(2.2,4.4)
Pneumonia	25	3.5	7.2	(4.6,10.7)	14	3.2	4.4	(2.4,7.4)	39	6.6	5.9	(4.1,8.0)
Other*	34	20.6	1.7	(1.1,2.3)	10	11.8	0.9	(0.4,1.6)	44	32.4	1.4	(0.9,1.8)
Definite epilepsy (n=564)												
Malignant Neoplasms including primary brain tumour	43	8.9	4.8	(3.4,6.5)	7	5.3	1.3	(0.5,2.7)	50	14.3	3.5	(2.6,4.6)
Malignant Neoplasms excluding primary brain tumour	30	8.8	3.4	(2.3,4.9)	4	5.1	0.8	(0.2,2.0)	34	13.9	2.4	(1.7,3.4)
Neoplasms of Lung	10	2.3	4.3	(2.0,7.9)	2	1.3	1.6	(0.2,5.7)	12	3.6	3.3	(1.7,5.8)
Ischaemic Heart Disease	10	9.9	1.0	(0.4,1.9)	6	5.2	1.2	(0.4,2.5)	16	15.1	1.1	(0.6,1.7)
Cerebrovascular Disease	19	5.0	4.4	(2.6,6.8)	5	2.2	2.3	(0.7,5.4)	24	6.5	3.7	(2.3,5.5)
Pneumonia	18	1.9	9.6	(5.6,15.1)	9	1.8	5.0	(2.3,9.5)	27	3.7	7.3	(4.8,10.6)
Other*	24	12.2	2.0	(1.2,2.9)	8	1.2	1.2	(0.5,2.4)	32	13.4	1.7	(1.1,2.4)
Idiopathic/cryptogenic epilepsy (n=346)												
Malignant Neoplasms including primary brain tumour	8	3.9	2.0	(0.8,4.0)	1	3.0	0.3	(0.0,1.9)	9	7.0	1.3	(0.6,2.5)
Malignant Neoplasms excluding primary brain tumour	5	3.8	1.3	(0.4,3.0)	1	2.9	0.3	(0.0,1.9)	6	6.8	1.3	(0.3,1.9)
Neoplasms of Lung	0	1.0	0	(0.0,3.6)	1	0.7	1.4	(0.0,7.8)	1	1.8	0.6	(0.0,3.2)
Ischaemic Heart Disease	1	3.9	0.3	(0.0,1.4)	3	2.8	1.1	(0.2,3.2)	4	6.7	0.6	(0.1,1.5)
Cerebrovascular disease	1	1.5	0.6	(0.0,3.6)	2	1.1	1.8	(0.2,6.5)	3	2.7	1.1	(0.2,3.3)
Pneumonia	6	0.6	10.1	(3.6,21.8)	2	0.9	2.3	(0.2,8.2)	8	1.5	5.4	(2.3,10.7)
Other*	8	4.6	1.7	(0.7,3.4)	2	3.3	0.6	(0.0,2.2)	10	8.0	1.3	(0.6,2.3)

*Causes of death other than those listed above. These included ruptured aortic aneurysm, pneumoconiosis, accident, old age, duodenal ulcer, cardiomyopathy, cirrhosis, septicaemia, fracture neck of femur, Alzheimer's disease and not known (1). There were 5 directly epilepsy related deaths (Sudden unexpected death in epilepsy or SUDEP=1, status epilepticus=1, burns=1, cervical fracture=1, drowning=1).

3.1.2.4 **Mortality according to time since diagnosis**

Mortality for each year of follow-up is shown in Table VI. SMR was highest in patients with definite epilepsy (SMR 6.6 [95%CI=4.8,8.7]), and slightly lower in the combined probable and definite epilepsy group (SMR 5.01[95%CI=3.7,6.4]) during the first year of follow-up. This halved during the subsequent 3 years, and then halved again after 3 further years. Excess mortality fell below significant levels after 4 years from the index seizure but then increased again to significant levels after 9 years (SMR 1.6 [95%CI=1.1,2.2]).

Similar results were obtained with period of exposure to seizures (defined as the interval from the first seizure). Among those with a history of seizures for less than 2 years, the SMR was 5.0 (95%CI=3.9,6.3). It then declined to 2.2 (95%CI=1.5,3.1) in those having a history of between 2 and 4 years of seizures, and to 1.4 (95%CI=1.1,1.7) in those with a history of more than 4 years of seizures.

Table 6. Mortality for each year of follow-up from index seizure in the combined group with definite and probable epilepsy, patients with definite epilepsy and patients with idiopathic/cryptogenic epilepsy.

Yrs after index seizure	No. at risk	No. of Deaths			
		Obs	Exp	SMR	(CI95%)
Definite and probable epilepsy (n=792)					
0-1	792	59	11.9	5.0	(3.7,6.4)
1-2	733	24	9.9	2.4	(1.5,3.6)
2-3	709	18	8.8	2.1	(1.2,3.2)
3-4	691	20	8.1	2.5	(1.5,3.9)
4-9	671	46	35.8	1.3	(0.9,1.7)
9-14	625	32	20.4	1.6	(1.1,2.2)
Definite epilepsy (n=564)					
0-1	564	49	7.4	6.6	(4.8,8.7)
1-2	515	16	6.1	2.6	(1.5,4.2)
2-3	499	13	5.7	2.3	(1.2,3.9)
3-4	486	16	5.1	3.1	(1.8,5.1)
4-9	470	33	21.6	1.5	(1.0,2.1)
9-14	437	22	12.3	1.8	(1.1,2.7)
Idiopathic/cryptogenic epilepsy (n=346)					
0-1	346	6	2.8	2.2	(0.8,4.7)
1-2	340	3	2.5	1.2	(0.2,3.5)
2-3	337	5	2.3	2.2	(0.7,5.2)
3-4	332	5	1.9	2.7	(0.8,6.3)
4-9	327	11	9.4	1.2	(0.6,2.1)
9-14	316	4	7.0	0.6	(0.1,1.5)

3.1.3 *The Cox proportional hazards analysis*

The Cox model was used to examine the possible influence of baseline characteristics on mortality. In view of the expected influence of age and sex on mortality, these two variables were entered into the initial Cox model, and the remaining variables then selected stepwise (p to enter = 0.10; p to remove = 0.15). Enhanced mortality was associated with older age at index seizure, cerebrovascular disease, alcohol-related seizures, malignant neoplasms and congenital neurological deficits (Table 7). One or more seizures before the index seizure appeared to be associated with reduced mortality.

When patients with idiopathic/cryptogenic (no known cause) epilepsy with generalised tonic clonic seizures were analysed separately, they were found to have a significantly increased risk of mortality, although the confidence intervals were wide (hazard ratio 6.2 [95%CI=1.4-27.7; p=0.049]).

Table 7. Cox model analysis of mortality in definite and probable epilepsy.

	n (%)	Hazard ratios (95%CI)	p (n=792)
Age at index seizure(per decade)		1.9 (1.7,2.0)	<0.001
Aetiology of epilepsy			
Cerebrovascular disease	111 (14)	2.4 (1.7,3.4)	<0.001
Alcohol	38 (5)	2.9 (1.5,5.7)	=0.004
Tumour	40 (5)	12.0 (7.9,18.2)	<0.001
Congenital neurological deficits	16 (2)	10.9 (3.2,36.1)	=0.003
Number of seizures before index seizure			
One or more	428 (54)	0.6(0.4,0.8)	<0.001

A hazard ratio >1.0 indicates enhanced risk of mortality for a patient with the associated risk factor by comparison with one without it. The hazard ratio of 0.6 indicates a reduction in the risk of mortality for a patient with one or more seizures prior to the index seizure by comparison with a patient for whom the index seizure is the first.

3.1.4 ***Time-dependent co-variate analysis***

The Cox model with time-dependent co-variates was used to examine the influence of events that occurred during the follow-up period. The time-dependent co-variates were those described earlier (and presented in Table 8); each has been adjusted for the baseline characteristics listed in Table 6.

As is evident from Table VIII, neither seizure recurrence nor AED treatment appeared to be associated with mortality. The analysis of cumulative seizures and cumulative AED treatment in particular, gives a tight confidence interval around a hazard ratio of one. (The hazard ratios are unchanged whether the time dependent co-variates are analysed singly or together).

There was also a suggestion that the achievement of remission (particularly short term) may enhance survival though these results do not reach significance at p=0.05 and the confidence intervals are wide. In an analysis restricted to patients with primary or secondary generalised seizures tonic clonic seizures, seizure recurrence was associated with increased mortality although this did not reach significant levels (hazard ratio 1.79 [95%CI 0.98 – 3.06]).

Table 8. Effect of seizure recurrence and AED treatment during follow-up (time-dependent co-variates) in patients with both definite and probable epilepsy adjusted for the characteristics in Table 6.

*Time dependent co-variates	Hazard ratios (95% CI)
Seizure recurrence (yes/no)	1.30 (0.84,2.01)
Cumulative seizures	1.02 (0.99,1.05)
AED Treatment (yes/no)	0.97 (0.67,1.38)
Cumulative AEDs	1.00 (0.98,1.02)
6 month remission	0.70 (0.46,1.07)

*for definitions see methods section.

This analysis excludes deaths during the first 3 months of follow up.

3.2 THE DYNAMICS OF THE TREATMENT OF EPILEPSY

3.2.1 **Follow-up**

Out of 564 patients with newly diagnosed definite epilepsy, only 17 were lost to follow-up at the end of the study in 1997 (the median follow-up was 11.8 years [25th and 75th centiles 10.6 and 12.7 years respectively] a total of 11,400 person years). The causes of loss to follow-up in these 17 cases were emigration (4), entry into the armed forces (5; medical details of serving personnel are not made available by government decree), withdrawal of consent (3) and unknown (5).

3.2.2 **Overall treatment**

433 (77%) were started on drug treatment. Of the 131 (23%) who did not start therapy, 41 had suffered acute symptomatic seizures; 42 died within the first 6 months due to underlying pathologies.

3.2.3 **Treatment of the first seizure**

Of the 252 cases in whom the index seizure was also the first seizure, only 38 (15%) were prescribed medication after the first seizure. Due to high rate of seizure recurrence in these patients however, almost 70% were eventually treated. Initial therapy was prescribed by a hospital physician in 303 (70%) cases whilst a GP initiated therapy in the remainder (although often on the advice of a specialist).

3.2.4 **Choice of antiepileptic drug**

433 (77%) patients were started on therapy. Phenytoin was started in 161 (29%), carbamazepine in 154 (27%), valproate in 84 (15%), phenobarbital in 14 (2%) and other drugs including benzodiazepines and ethosuximide in 20 (4%).

3.2.5 **Duotherapy**

Of these, 426 (98%) were started on single drug therapy and 7 (2%) patients were started on duotherapy, 3 with phenytoin and phenobarbital, and 4 patients with phenytoin and carbamazepine.

3.2.6 **Treatment according to seizure type**

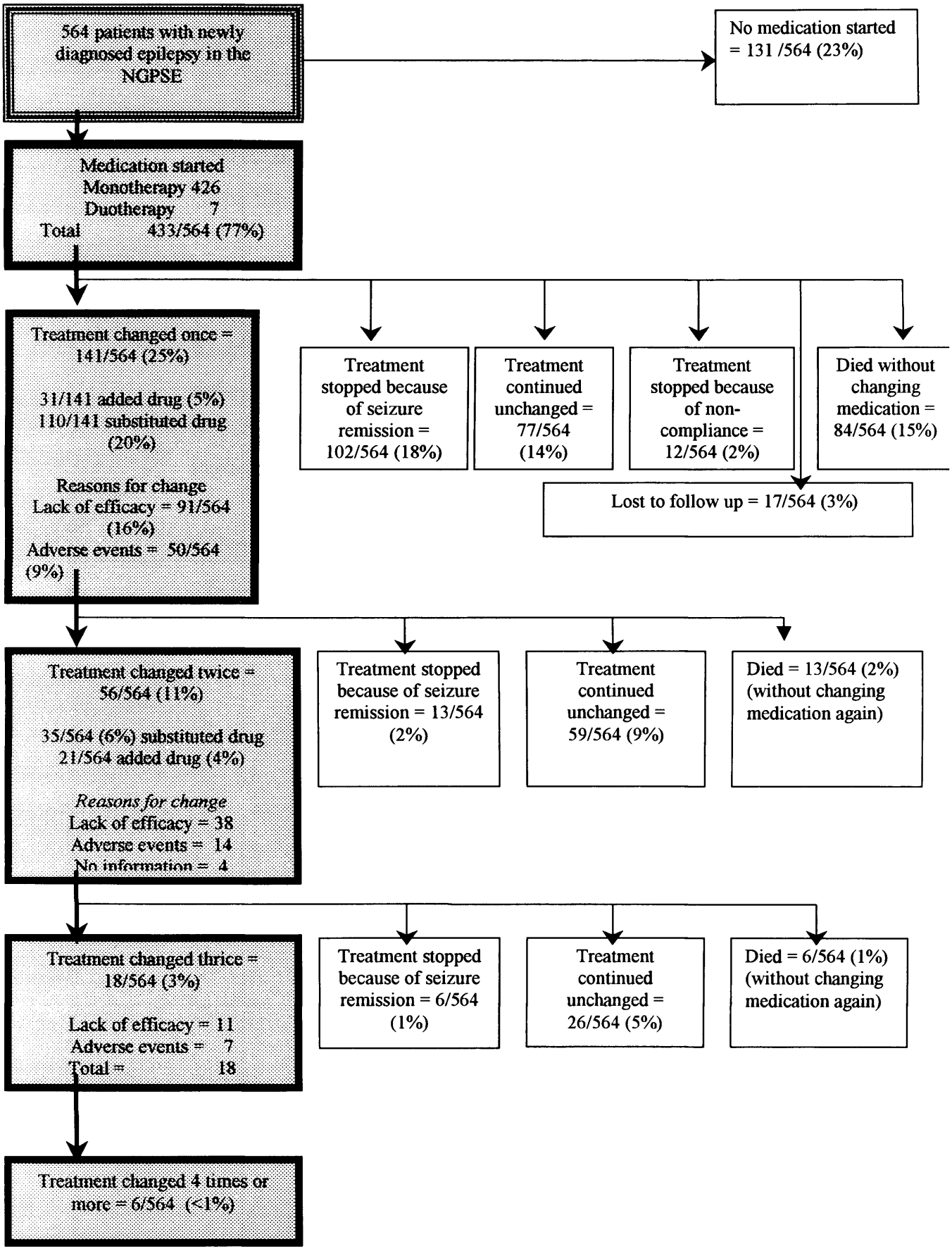
Of 292 patients with partial seizures with or without secondary generalisation, 236 (81%) received treatment. Of these, 105 (45%) patients were prescribed carbamazepine, 90 (38%) phenytoin, 27 (11%) valproate and 14 (6%) received other drugs. Of the 160 out of 221 patients with generalised seizures who received treatment, phenytoin was the most frequently preferred drug in 59 (37%) patients followed by valproate in 48 (30%), carbamazepine in 44 (28%) and other drugs in 9 (5%). Carbamazepine was prescribed initially in 9 patients who had absence and/or myoclonic seizures in addition to generalised tonic-clonic seizures. Of 36 patients with unclassified seizures, phenytoin was the most frequently preferred drug (36%) followed by valproate (25%), carbamazepine (19.5%) and other drugs (19.5%).

3.2.7 **Treatment changes and treatment retention**

A life table survival analysis (Fig.4) of patients shows that patients changing therapy usually do so early in the course of their history. The sequence of treatment events is illustrated in Fig.3. 91/564 (16%) patients changed medication for the first time because of lack of efficacy. Of these 91, 29 (32%) patients have now achieved 2 year terminal remission and 21 (23%) have achieved 5 year terminal remission. 5% (30) of all patients went on to change medication for the second time for the same reason, and of this group 9 patients (30%) achieved 2 year terminal remission and only 5 (17%) have achieved 5 year terminal remission. Of the 50/564 (9%) patients who changed for the first time due to adverse events, only 4 did so

again for the same reason. 39/564 patients (7%) have not switched to any other drug despite failure to attain even 2-year terminal remission from seizures.

Fig.3 Treatment dynamics over 11-14 years (median 11.8 years) in a community based cohort with newly diagnosed epilepsy.



3.2.8 **The use of new antiepileptic drugs**

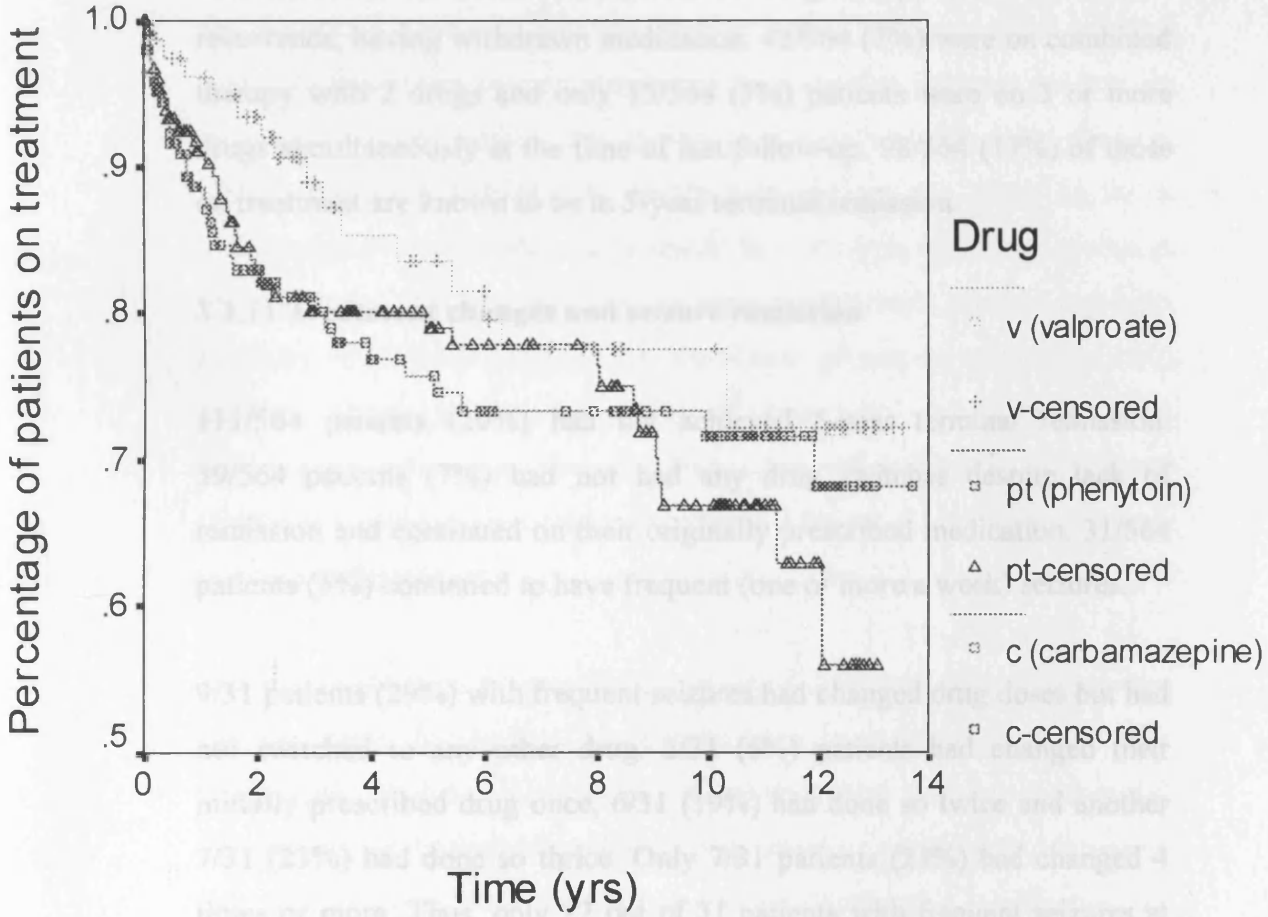
A new antiepileptic drug such as gabapentin, lamotrigine, vigabatrin or topiramate was used in only 25 (11%) treatment changes in 17 patients with recurrent seizures, out of a total of 221 treatment changes in the whole cohort (11%). The most commonly used new antiepileptic drugs were lamotrigine and vigabatrin (11 patients each), followed by gabapentin (2 patients) and topiramate (1 patient).

3.3.9 **The time course of treatment changes**

Kaplan Meier survival analysis estimated the time course of treatment changes (addition or substitution of antiepileptic drugs) in the cohort (Fig.4) Of the 433 treated patients, 15% changed their initially prescribed medication for the first time within 2 years and a further 20% did so in the next 12 years. Approximately 18% of patients on phenytoin and carbamazepine changed medication in the first 2 years compared to 7% on valproate (Fig.4).

Fig. 4 Time taken to first treatment change

(addition or substitution of drug to existing treatment)



+censored = patients who added or substituted drugs

3.3.10 **Current cohort characteristics**

209/564 patients (37%) were on drug therapy for epilepsy at the time of last follow-up. 168/564 patients (30%) stayed continuously on medication and another 41/564 patients (7%) restarted drug therapy because of seizure recurrence, having withdrawn medication. 42/564 (7%) were on combined therapy with 2 drugs and only 15/564 (3%) patients were on 3 or more drugs simultaneously at the time of last follow-up. 98/564 (17%) of those on treatment are known to be in 5-year terminal remission.

3.3.11 **Treatment changes and seizure remission**

111/564 patients (20%) had not achieved 5-year terminal remission. 39/564 patients (7%) had not had any drug switches despite lack of remission and continued on their originally prescribed medication. 31/564 patients (5%) continued to have frequent (one or more a week) seizures.

9/31 patients (29%) with frequent seizures had changed drug doses but had not switched to any other drug. 2/31 (6%) patients had changed their initially prescribed drug once, 6/31 (19%) had done so twice and another 7/31 (23%) had done so thrice. Only 7/31 patients (23%) had changed 4 times or more. Thus, only 22 out of 31 patients with frequent seizures at the time of follow-up (4% of the study population) changed medication more than once in order to achieve better seizure control.

4. DISCUSSION

Despite its strengths, the NGPSE has been criticised for its methodology. An important criticism is the inclusion of first seizures, a feature of this study that runs contrary to the definition of epilepsy with its requirement for "recurrent" seizures. This argument is largely based on older, hospital based studies where seizure recurrence rates for first seizures are low. In community-based studies, the majority of first seizures recur (Sander 1993). We have argued that single seizures are not likely to be a biologically distinct entity and probably represent one end of the spectrum of disease severity. The inclusion of acute symptomatic seizures has been similarly criticised because of the significant proportion of patients with alcohol related seizures. Analyses of data with and without acute symptomatic seizures in the prognosis (Cockerell and others, 1997) and seizure remission studies (Hart and others, 1994) in the NGPSE show no significant differences.

The epilepsies are a heterogeneous group of disorders. Whilst inferences can be drawn for several broad categories in epilepsy, such as with aetiological classes, numbers are insufficient for deriving meaningful information on individual epilepsy syndromes or aetiologies. Moreover, the NGPSE was designed before the International Classification of Epilepsies, Epilepsy Syndromes and Related Disorders was proposed.

A major difficulty with the continuation of the NGPSE has ironically been its longevity. Ethics approval obtained in 1983 at the conception of this study is no longer deemed sufficient in many general practices and obtaining approval with a vast number of individual local ethics committees is not practical. This was becoming increasingly evident in 1997 and 1998 during the collection of data for this thesis and in the subsequent years has resulted in the cessation of all data collection.

4.1 MORTALITY

Although recent reports on the long-term prognosis of seizure disorders have made observations on mortality (Sillanpaa, and others 1998), there have been no specific, long-term community based studies of mortality in epilepsy since the Mayo Clinic study in 1980 (Hauser, and others 1980) and certainly none that have been prospectively reported in patients with newly diagnosed epilepsy. Recent retrospective, long-term mortality studies (Nilsson L, and others 1997; Shackleton DP, and others 1999) have included large numbers of patients but their focus on hospital populations is likely to exaggerate mortality in general and epilepsy related deaths in particular (Nashef L and Shorvon SD 1997). The limitations of older studies based on cohorts derived from insurance registers, hospital clinics and institutions are well recognised (Cockerell, and others 1994a; Hauser, and others 1980). Many previous studies have suffered from the unreliability of death certificates used to ascertain causes of death, a large proportion of which do not mention epilepsy as cause or contributor to mortality (Zielinski JJ 1974a; Hauser, and others 1980). The design of the NGPSE (Hart YM, and others 1989; Sander, and others 1990), large patient database (1091 patients), cohort characteristics similar to that of an incident population with epilepsy (Cockerell, and others 1997b), long follow-up and efficient system of data collection (2% lost to follow up), provides an ideal opportunity to study mortality in epilepsy. It is also representative of the current population of a developed country, in which significant demographic changes in the incidence of epilepsy have occurred in the last few decades (Everitt and Sander 1998). The category of "probable seizures" recognises initial difficulty in the diagnosis of some epileptic disorders and allows analyses that would otherwise not account for patients who later turn out to have seizure disorders (Hart YM, and others 1989; Sander, and others 1990).

4.1.1 Overall mortality

All cause mortality in the whole cohort analysed up to 14 years from index seizure was significantly elevated to twice that of the age-matched general population. This finding is similar to that noted at 8 years (Cockerell, and others 1994a) and in other studies (Hauser, and others 1980; Zielinski JJ 1974a) although expectedly lower than those noted in recent, more hospital based populations (Nilsson L, and others 1997; Shackleton DP, and others 1999). It confirms previously made observations that mortality is significantly elevated above that of the general population in patients who suffer from epilepsy.

4.1.2 Mortality and time trends

Initial mortality in the cohort was very high but halved over the subsequent 3 years and dropped below significant levels after 4 years. A late, significant rise in mortality occurred again after 9 years. Epilepsy related deaths were few and the late increase in mortality is not easily explained. In an earlier community based study, a late increase in mortality, thought to be directly caused by epilepsy, occurred only in the 3rd decade (Hauser, and others 1980). In this cohort, further follow-up beyond 15 years is required to confirm this trend.

The cause of the initial high mortality is a consequence of underlying serious brain pathologies such as primary and secondary brain tumours as well as major cerebrovascular events. The seizures were thus agonal seizures arising as a direct consequence of these pathologies, and the raised mortality probably reflects the mortality inherently associated.

The late rise in mortality in this cohort is not explainable and may be artefactual. The late increase seen in the Mayo report (Hauser, and others 1980) encouraged speculation that this reflected direct epilepsy related deaths although, in this cohort, there were only 5 deaths attributable to epilepsy throughout the period of follow-up, two of which occurred early.

4.1.3 SUDEP and epilepsy related mortality

Three epilepsy related deaths were noted in the second decade of follow-up in addition to the two (one burns death and one death due to a fall) reported in the first 8 years of follow-up (Cockerell, and others 1994a). These included one death consistent with sudden death in epilepsy (SUDEP) (Lhatoo SD, and others 1999), one due to convulsive status epilepticus in a patient with brain tumour, and one drowning after a seizure. Data from this study suggests that SUDEP is an infrequent occurrence in the community with only one death having occurred in 11,400 person years of patient follow-up. This compares with one death per 2500 person years of patient follow-up in another community based study (Medical Research Council Antiepileptic Drug Withdrawal Study Group 1991) and up to 1 death per 200 patients in a tertiary referral centre. (Nashef, and others 1995a)

4.1.4 Mortality and seizure duration

Mortality was significantly elevated in patients who had suffered seizures for more than 4 years, was even higher in patients who had suffered seizures for 2-4 years and highest in patients who had suffered seizures for less than 2 years. This is consistent with mortality trends in other studies (Hauser, and others 1980; Shackleton DP, and others 1999) and reflects the greater representation of people with epilepsy due to serious pathologies such as tumours and cerebrovascular disease who tend to die soon after presentation.

4.1.5 Multi-variate analysis of mortality

Cox regression analysis of baseline variables showed that older age, cerebrovascular disease, alcohol, malignant neoplasms and congenital neurological deficits were associated with significantly increased mortality in patients with newly diagnosed seizures. The occurrence of one or more seizures before the index seizure, however, was associated with a significantly decreased mortality. This is partly explained by the presence in

this group of patients with less severe seizure disorders such as absence seizures and cryptogenic partial seizures that come to medical attention later. These seizure disorders may not be associated with increased mortality (Hauser, and others 1980; Nilsson L, and others 1997).

4.1.6 Time dependent co-variate analysis –

4.1.6.1 The effects of seizure recurrence

Neither recurrent seizures or cumulative seizure recurrence were found to be significant factors in cohort mortality. Reports that frequent, recurrent seizures are an independent risk factor (Hendriksen B, and others 1970; Sperling MR, and others 1999) for mortality may not hold true in unselected populations with epilepsy. Seizure recurrence may not significantly influence mortality in a community-based cohort due to the inclusion of absence seizures and mild cryptogenic partial seizures, for example, which may not have an increased risk of mortality even if occurring frequently in patients. Seizure recurrence may have a more serious connotation in a hospital-based cohort in which patients tend to have more disabling epilepsy, as is evident from the high SMR obtained from a recent comparison of patients with seizure remission and patients with continuing, frequent seizures in a post-epilepsy surgery cohort (Sperling MR, and others 1999). Similarly, high mortality has been noted in an outpatient cohort with refractory, disabling seizures in a tertiary referral centre (Nashef L, and others 1995a). The relative non-homogeneity of seizure types and epilepsy syndromes with different prognoses in a community-based cohort may be masked in analysis, thus creating the impression that seizure frequency is unimportant in mortality analysis. This is partly confirmed in this cohort by the observation that in patients with primary or secondary generalised tonic clonic seizures, seizure recurrence appeared to increase mortality although not significantly so. Larger studies could potentially surmount these differences to provide a more discerning picture of mortality in individual epilepsy syndromes although the logistical implications are considerable. Despite the exclusion of 33 deaths that

occurred within the first 3 months after the index seizure as those most likely to have occurred due to underlying pathologies, mortality in the first year was high. Seizure remission, and short term remission in particular, was associated with decreased mortality, although this did not reach significance.

4.1.6.2 The effects of antiepileptic drug treatment

AED treatment was also found not to influence mortality. High mortality in the 1st year may have influenced this finding as patients dying of serious underlying pathologies would not be expected to have their risk of mortality improved by AEDs. Conversely, there is no evidence to suggest that AEDs worsen mortality risks either. These findings are consistent with studies that have suggested a seemingly ambiguous role played by AEDs in the prognosis of epilepsy in other community-based populations (Sander JWAS and Sillanpaa 1997).

4.1.7 Mortality and age

Mortality was most marked in the 50-59 year age group and this reflected the high incidence of both CNS and non-CNS neoplasias. SMRs were significantly raised, although comparatively much lower in the >70 years age group despite a high absolute number of deaths due to increased age-related mortality in the corresponding age bands in the general population.

4.1.8 Mortality and idiopathic/cryptogenic generalised epilepsy

Idiopathic/cryptogenic epilepsy, a category that included all epilepsies with no obvious cause as well as idiopathic generalised epilepsy had a slight but not significantly increased long-term mortality. When patients with generalised tonic clonic seizures in the idiopathic/cryptogenic group were analysed however, mortality was significantly increased. This suggests that tonic clonic seizures may be an independent risk factor for mortality.

4.1.9 Mortality and aetiology

Epilepsy due to acute symptomatic causes was significantly more likely to be associated with increased mortality and this reflects the large number of patients who died in the first 2 years after entry due to acute underlying conditions. Mortality was most marked in the remote symptomatic group, which had a high proportion of primary brain tumours and cerebrovascular disease. In patients with symptomatic epilepsy, acute or remote, the increased mortality almost certainly reflects serious underlying causes of epilepsy rather than the epilepsy itself. Patients with congenital neurological deficits causing epilepsy also had comparatively high mortality rates although confidence intervals were very wide.

Pneumonia had the highest cause-specific mortality rates in patients with definite epilepsy as well as in the combined definite and probable group, as noted previously (Cockerell, and others 1994a). This is more likely to reflect overrepresentation of pneumonia as a terminal event in the elderly during hospital admissions for concurrent illnesses rather than the seizure disorder itself or antiepileptic drug treatment (Cockerell, and others 1994a). Cancer related mortality was also significantly elevated and whilst more readily explained in the group with primary brain tumours, it is not so in those who died of lung and other non-CNS tumours. Antiepileptic drug treatment has been implicated, although no association between any particular drug and neoplasia-related mortality was noted in this study. Mortality due to cerebrovascular diseases was significantly elevated. This does not directly implicate epilepsy as a cause of death in these patients who had cerebrovascular disease although it may imply that patients who have cerebrovascular disease and subsequent seizures have a worse prognosis than those without seizures. This may be more true of patients with acute symptomatic seizures than those who present with remote symptomatic seizures due to cerebrovascular disease.

SUMMARY AND CONCLUSIONS

- The long-term mortality in a population based cohort of patients with newly diagnosed epilepsy was found to be twice that of the age-matched general population.

- Patients with symptomatic epilepsy and epilepsy due to congenital neurological deficits had significantly increased mortality rates whilst patients with idiopathic/cryptogenic epilepsy did not.

- Patients with generalised tonic clonic seizures appeared to have an increased risk of mortality although this did not reach significance. Short-term remission on the other hand appeared to reduce mortality although this also did not reach significance.

- Baseline factors that significantly enhanced mortality were vascular and tumour etiologies, congenital neurological deficits and older age at index seizure. On the other hand, one or more seizures before index seizure significantly reduced mortality, possibly suggesting milder epilepsy in such patients.

- Seizure recurrence, cumulative seizure recurrence, AED treatment and cumulative AED treatment had no effect on mortality, a possible reflection of the heterogeneity of the different types of seizure disorders analysed in which frequent seizures do not always imply severe epilepsy.

4.2 THE DYNAMICS OF THE TREATMENT OF EPILEPSY

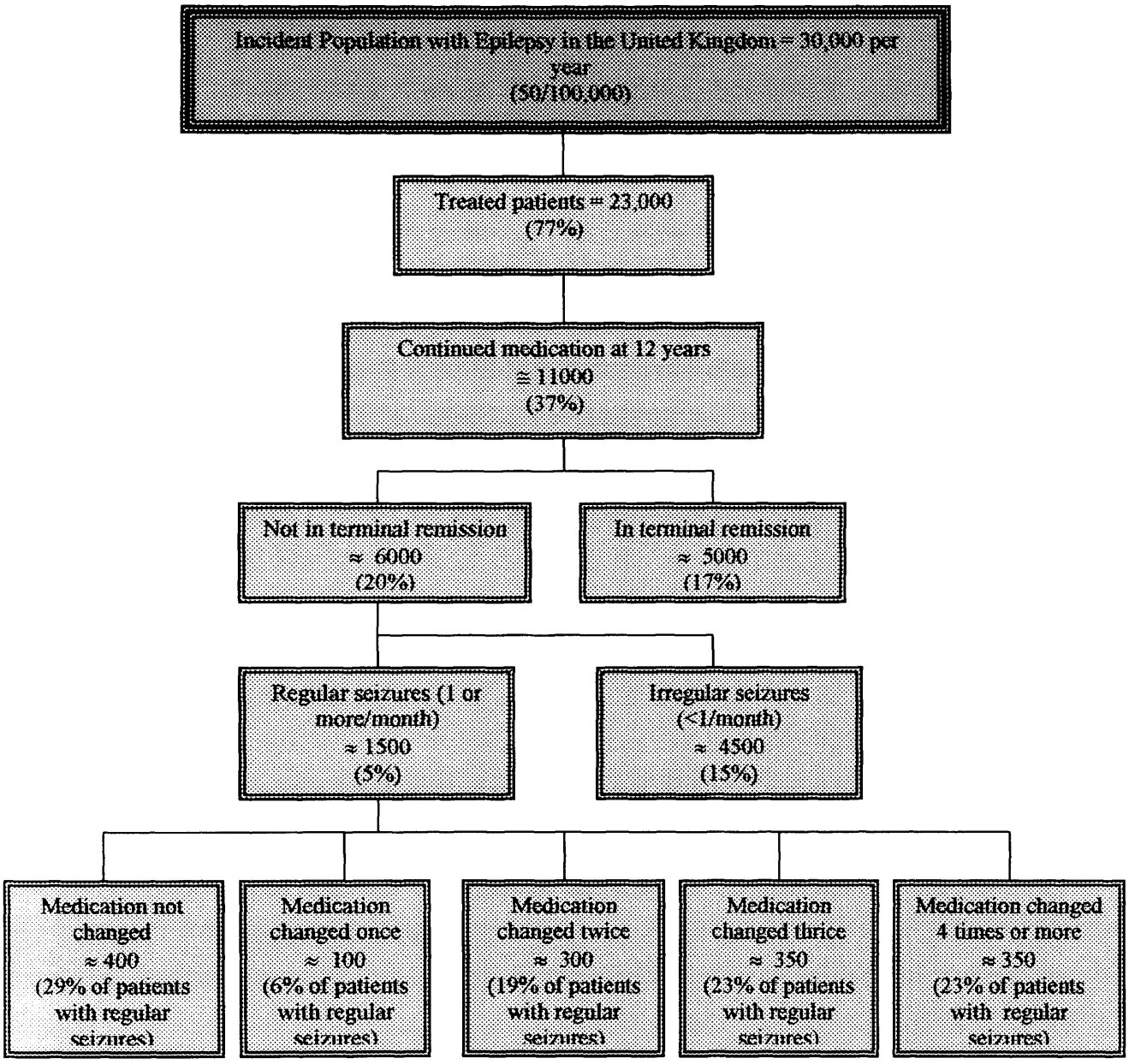
This study provides a useful overview of the dynamics of treatment and treatment changes, as they occur in routine practice throughout the United Kingdom. This data is valuable for targeting health service provision and identifying areas for raising clinical standards. This analysis of treatment dynamics in the NGPSE reveals several interesting findings that provide a picture of the patterns of treatment of epilepsy in the general population during the period 1984-1997, a pattern of treatment which is quite different from that observed from hospital clinics of chronic, often intractable cases. We found that 77% of patients receiving a diagnosis of epilepsy are started on therapy. The hospital physician (clinic and accident and emergency) initiated therapy in over 2/3rds of cases. Furthermore, it is likely that in many of the cases in which therapy was started by the GP, the advice of the hospital was taken. This appears to be a change in practice over the past decade (Hart YM and Shorvon SD 1995), and is an improvement in line with current guidelines, which emphasise the importance of obtaining specialist advice before initiating antiepileptic drug therapy.

4.2.1 **Treatment changes and treatment retention**

The study allowed us to track treatment over the 12-year period from the initiation of therapy. Overall, about one third of patients continued long term therapy (i.e. were still on treatment at the time of last follow-up, a mean of 12 years). The yearly incidence of epilepsy is about 50/100,000 in the UK or 30,000 patients per year. Thus, about 11,000 newly diagnosed patients each year continue to be on medication for a mean of 12 years after the initiation of therapy (Fig.5). Of these, about 5000 continue on drug therapy despite long-term remission from seizures whilst about 6000 do so because of unsatisfactory seizure control. The majority of the latter group have infrequent seizures although approximately 1500 patients have seizures at least once a month. Of these, surprisingly, 400 patients will not have done so despite frequent seizures. Of the patients having more than

one seizure a week, one third are still taking their initial antiepileptic drug. Only about 400 patients may have tried 4 or more drugs, alone or in combination, in addition to the initial medication for seizure control. When one considers the fact that these are annual, recurring figures in each year's incident population, it is probable that there are large numbers of people in the prevalent "pool" of chronic epilepsy patients who have not been adequately treated. The lack of change and the slowness to change are an indictment of current practice, and suggest that too often an insouciant attitude is taken to early epilepsy. How many of the 20% of patients with continuing epilepsy would have benefited from a more aggressive approach to treatment is not possible to say, but almost certainly some medical and social complications could have been avoided, and perhaps even mortality.

Fig.5 A model of long-term treatment patterns in epilepsy in the United Kingdom



Note: These figures/percentages are approximations

4.2.2 Treatment changes and seizure remission

The outcome of those who do make treatment switches is not necessarily good. 91 patients (16%) switched medication because of poor control on the first drug of whom 38 (41%) failed to gain control on the second. This is similar to the findings of Kwan and Brodie in which epilepsy was not controlled by first medication in 248 patients, of whom treatment was still ineffective with second or more drug changes in 113 patients (46%). (Kwan and Brodie 2000) Furthermore, only $1/6^{th}$ of those who switched because of poor control on the second drug obtained lasting control on the third. Whilst it is possible that alternative drug changes would have helped some of these patients, the majority are likely to be resistant to all antiepileptics. The first switch was usually within 2 years of initiating therapy. These are the types of patients who develop chronic epilepsy. As the first drug change is usually in the first 2 years after diagnosis, our findings imply that the patients at risk of chronicity can be identified early in the course of their epilepsy. In most but not all patients, the failure of initial monotherapy is predictive of chronicity as has been noted before (Shorvon 1984). The identification of reliably predictive clinical factors at this stage would be of great importance, but to date none have been found. More research is needed to identify these drug resistant cases earlier, as more aggressive therapy or much earlier surgical intervention would be appropriate in many.

4.2.3 Treatment of the first seizure

About a quarter of patients with newly diagnosed epilepsy did not receive medication for their seizures, most commonly those with serious or progressive underlying pathology. Only 15% of patients whose index seizure was also their first seizure received medication after the first seizure. This reflects a more conservative approach to single seizure

management in the UK in contrast to approximately 70% of such patients in the USA who are given drug treatment (Hauser, and others 1982); which is the most appropriate approach is controversial. However, because of high rates of subsequent seizure recurrence, the ultimate number who received antiepileptic medication was more than 70%. Preliminary analyses in the MESS study suggest that there are significantly fewer recurrences for patients immediately allocated to treatment. (Hazard ratio 1.4; 95% CI 1.2-1.7) (Marson and others, 2004)

4.2.4 Duotherapy and polytherapy

The vast majority of patients were prescribed initial monotherapy. This is in accord with current guidelines (NICE guidelines 2004; SIGN guidelines 2003). Therapy with more than one drug has been recommended in the past (Yahr MD, and others 1952), although the lack of evidence supporting this has been pointed out (Shorvon, and others 1978). Duotherapy no longer appears to be common practice as only 7 patients were simultaneously started on 2 drugs. With continued drug treatment, polytherapy was more common although less than 3% continued on 3 or more drugs. Less than a tenth of all patients continued on 2 drugs, suggesting that this is a relatively infrequent practice in an unselected population with epilepsy, contrary to observations in more selected populations with uncontrolled seizures (Mattson 1992).

4.2.5 Choice of treatment

The choice of drug for initial therapy in this study is a useful reflection on overall practice in the UK between 1984-1987. Phenytoin and carbamazepine were the most frequently preferred first line drugs and were used in over a third each of the treated cohort; valproate was used in a fifth and phenobarbital in only a minority. The comparatively infrequent use of phenobarbital is probably due to increased awareness of its frequent adverse events and the availability of better drugs, and this is a change in practice from that a decade earlier. Carbamazepine was the most

commonly used first line drug in partial seizures, consistent with current advice (Sillanpaa 1996; NICE guidelines 2004; SIGN guidelines 2003). Only a slightly smaller number however, were prescribed phenytoin, suggesting this is also a popular first choice drug. In the case of generalised seizures, phenytoin was most often prescribed. Only a quarter of treated patients with generalised epilepsy were prescribed valproate first, contrary to its current status as first line therapy (Bruni J 1996; Mattson, and others 1992; NICE guidelines 2004; SIGN guidelines 2003). Furthermore, carbamazepine was used in 9 patients who had idiopathic generalised epilepsy and absence and/or myoclonic seizures. In such situations, carbamazepine is a contraindication because of the risk of exacerbating seizures (Snead OC and Hosey LC 1985). Almost all the patients with childhood absence epilepsy were prescribed ethosuximide. Although this remains effective therapy for the condition, valproate is probably a more favoured first line option by many specialists nowadays (Bruni J 1996).

4.2.6 Reasons for treatment changes

Most patients who change therapy due to adverse events or lack of efficacy appear to do so in the first 2 years (Fig.4). Valproate (7%) appeared to be less commonly discontinued at 2 years than carbamazepine (18%) or phenytoin (19%) (Fig.4). Less than a tenth of the cohort patients changed medication for the first time because of adverse events, suggesting that this is not an overly frequent cause of failed drug retention (Fig.3). This figure is similar to another study of drug therapy in newly diagnosed epilepsy although only hospital referred patients with 2 or more seizures were considered over a 3-year period (Heller A, and others 1995). Only 4 patients subsequently changed therapy again because of adverse events to the second drug and repeated discontinuation of medication due to adverse events seems uncommon in the general population. Lack of efficacy is the commonest cause for change of therapy and 16% of the cohort did so for the first time for this reason. A third of these patients went on to change therapy again for the same reason, suggesting more refractory seizures in

these patients. 47 patients restarted medication after seizure recurrence during the course of follow-up; in all cases returning to the discontinued drug. These patients were not considered to have changed medication during analysis if they continued on the same drug until further seizure remission, mortality or loss to follow-up.

Even at the stage of the first treatment change, several patients had medication added rather than substituted. Substitution however, was 4 times more frequent. Current practice is to advise that monotherapy with the conventional antiepileptic drugs should be tried sequentially before trying combination therapy.

4.2.7 The use of new antiepileptic drugs

Only 11% of treatment changes involved a new antiepileptic drug (lamotrigine, vigabatrin, gabapentin and topiramate). This is unsurprising as most drug changes took place in the first two years of entering into the study, which was before these antiepileptic drugs were widely available. The situation is probably gradually changing now.

4.2.8 Treatment retention

38% of patients who continued on therapy did so despite 5 or more years of terminal remission. Driving considerations, fear of seizure recurrence and lack of specialist advice on drug discontinuation may account for this. Of the 111 patients not in 5 year terminal remission, 31 (28%) had one or more seizures a week at the time of last follow-up and although a high frequency of drug changes would be expected in this group, a third had only tried a single drug. Only a quarter had changed their medication 4 or more times. This may suggest poor specialist input in this group as more than a third were not under regular hospital follow-up despite frequent seizures.

SUMMARY and CONCLUSIONS

- This study allows us to determine to what extent the pattern of therapy in the population follows accepted clinical guidelines. Practice in some areas is acceptable; for instance, the widespread use of initial monotherapy and substitution rather than addition of the second drug; hospital referral for initial treatment advice; restriction of initial monotherapy to conventional cheaper drugs; and a general reluctance to treat the first seizure. Other aspects of practice are below acceptable standards; for instance, lack of change of medication in the face of continuing seizures; lack of specificity in the choice of drugs; reluctance to use newer antiepileptic drugs in patients with resistant epilepsy.
- There also seems to be a lack of correlation between seizure occurrence and the decision to continue or withdraw therapy.
- Some patients may have benefited from the newer antiepileptic drugs although it is probable that only a small proportion of patients in the general population require these drugs and this is in marked contrast to those in hospital clinics.
- These findings indicate that there is considerable scope for improving the care of patients with epilepsy, that treatment is not changed fast or often enough in those with continuing seizures. This lack of urgency will inevitably result in less good medical and social outcomes for people with epilepsy. Whilst it is clear that some aspects of therapy are better than in previous surveys, others are not, and there is probably considerable room for improvement in the provision of epilepsy treatment in the UK.

Appendix 1

The International Classification of Epileptic Seizures

I. PARTIAL SEIZURES (seizures beginning locally)

A. Simple partial seizures (consciousness not impaired)

1. With motor symptoms
2. With somatosensory and special sensory symptoms
3. With autonomic symptoms
4. With psychic symptoms

B. Complex partial seizures (consciousness impaired)

1. Beginning as simple partial seizures and progressing to impairment of consciousness

   a. With no other features
   b. With features as in A.(1-4)
   c. With automatisms

2. With impairment of consciousness at onset

   a. With no other features
   b. With features as in A.(1-4)
   c. With automatisms

C. Partial Seizures secondarily generalised

II.GENERALISED SEIZURES (Bilaterally symmetrical and without focal onset)

A. Absence Seizures

1. Typical absence seizures
2. Atypical absence seizures

B Myoclonic Seizures

C. Clonic Seizures

D. Tonic Seizures

E. Tonic Clonic Seizures

F. Atonic Seizures

III. UNCLASSIFIED EPILEPTIC SEIZURES (inadequate or incomplete data)

Appendix 2

INTERNATIONAL CLASSIFICATION OF EPILEPSIES, EPILEPTIC SYNDROMES AND RELATED DISORDERS

1. LOCALISATION RELATED (focal, local, partial)

Idiopathic (Primary)

1.1 Benign childhood epilepsy with centro-temporal spikes
Childhood epilepsy with occipital paroxysms
Primary reading epilepsy

Symptomatic

1.2 Temporal lobe epilepsies
Frontal lobe epilepsies
Parietal lobe epilepsies
Occipital lobe epilepsies
Chronic progressive epilepsia partialis continua of childhood
Syndromes characterised by seizures with specific modes of precipitation

Cryptogenic

1.3 Defined by

Seizure type
Clinical features
Etiology
Anatomical Localisation

2. GENERALISED

2.1 Benign neonatal familial convulsions
Benign neonatal convulsions
Benign myoclonic epilepsy in infancy
Childhood absence epilepsy
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsies with grand mal epilepsy on awakening
Other generalised idiopathic epilepsies
Epilepsies with seizures precipitated by specific modes of activation

Cryptogenic or symptomatic

2.2 West syndrome
Lennox Gastaut syndrome
Epilepsy with myoclonic-astatic seizures
Epilepsy with myoclonic absences

2.3.1 Non specific etiology

Early myoclonic encephalopathy
Early infantile epileptic encephalopathy with suppression bursts
Other symptomatic generalised epilepsies

2.3.2 Specific syndromes

Epileptic seizures complicating many disease states

3. UNDETERMINED EPILEPSIES

3.1 With both generalised and partial seizures

Neonatal seizures
Severe myoclonic epilepsy in infancy
Epilepsy with continuous spike waves during slow wave sleep
Acquired epileptic aphasia
Other undetermined epilepsies

3.2 Without unequivocal generalised or focal features

4. SPECIAL SYNDROMES

4.1 Situation related seizures

Febrile convulsions
Isolated seizures or isolated status epilepticus
Seizures occurring only when there is an acute or toxic event due to factors such as alcohol, drugs, eclampsia,
non-ketotic hyperglycemia

Appendix 3

Some important studies of epilepsy treatment in the community

Crombie et al, 1960.

A survey of the epilepsies in general practice: a report by the research committee of the College of General Practitioners.

1957-8 survey of patients with seizures identified by 134 general practitioners from 67 practices. 182 patients with first seizures (including febrile and acute symptomatic seizures) identified: 46% of those with "major" and 58% with "other" seizures referred to hospital. 1209 with chronic epilepsy identified: 6% with "major" fits and 10% with "other" fits referred to hospital during study year, with 4% admitted for treatment of epilepsy or respite care. 44% with chronic epilepsy with "major" and 32% with "other" seizures completely controlled during study year.

Zielinski, 1974c.

Epileptics not in treatment.

Study of 2 groups with epilepsy: (A) Random sample of 10% of people with epilepsy known in 1969 to specialty facilities, re-examined 1971-3 (312 patients), (B) 98 patients with epilepsy found during field survey (structured interview of 15000 Warsaw residents subsequently examined by neurologists). Epilepsy if >2 spontaneous seizures. Convulsions with fever, intoxication or hypoglycaemia excluded. Nearly ¼ of patients known to specialist facilities, and 2/3 of patients identified in field survey were on no medication. Most known to have epilepsy had themselves stopped treatment in 3 years preceding examination, and 2/3 of those on medication had previously attempted withdrawal. More than 1/3 identified in field survey had never received treatment.

Hopkins and Scambler, 1977.

How doctors deal with epilepsy

Adults with>1 non-febrile seizure, >=1 seizure in 2 years preceding prevalence day and/or on continuing anti-convulsants for >1 previous non-febrile seizure, and not in long-term institutional care identified from lists of 17 general practitioners in 5 London group practices using Second National Morbidity Study records, diagnostic indices, or scrutiny of notes. 94/108 (87%) interviewed. Study population 42339, prevalence 3.4/1000. 18% unaware they had epilepsy. 95% referred to hospital (86% to hospital with consultant neurologist on staff); 86% of these had EEGs. 10 (11%) (5 with <=1 generalised seizure/year) were under continued hospital surveillance. 32% of 74 patients questioned had seen GP in past month, 49% in past 2 months, 65% in past 6 months, and 85% in past year. 3 (4%) had not seen their doctor for >+2 years. 5/94 were taking no medication, a sixth was taking only oral diazepam. Phenobarbital and phenytoin most frequently used drugs.

Zander et al, 1979.

Audit of care for epileptics in a general practice.

Record review of 64 patients with epilepsy in general practice of 8500 identified from morbidity register. 12 had died or left practice, giving prevalence 7.6/1000. 29 had active epilepsy (seizures or medication in preceding 2 years), 4 were under regular hospital surveillance, and 96% had hospital diagnosis (compared with 83% of 23 with inactive epilepsy). 66% with active epilepsy, and 48% with inactive epilepsy had had EEG. Only 3/21 with active epilepsy not under hospital surveillance, and who were reviewed, had had fit during previous year. ¾ attending hospital had intractable seizures, the fourth insisted on hospital follow-up despite being fit-free 30 years. Patient education or satisfaction not mentioned.

Lloyd Jones, 1980.

Medical audit of the care of patients with epilepsy in one group practice.

Audit of care given to 47 patients with epilepsy in group practice of 8607, prevalence 5.5/1000. Patients identified through prescriptions over four

months. Untreated patients excluded, handling of patients with single seizures unclear. 45/47 patients participated in structured interview and examination. Most having <3 seizures/year. 29 (64%) remembered being given diagnosis. 91% had seen hospital specialists, all these had had EEG. 36% continued to attend hospital. 27 (60%) had not seen any doctor during preceding year. 4 had not seen any doctor to discuss seizures within previous 10 years. 38% were on monotherapy. Few patients advised about avoiding potentially dangerous situations, management of seizures, inheritance of epilepsy or British Epilepsy Association.

Taylor, 1980.

A job half done.

Audit of patients with epilepsy in Doncaster practice of 6498 in which efforts made to improve management in previous year. 37 with active epilepsy, prevalence 5.8/1000. 3 children aged <16. Extent of hospital referral not given. 70% had had EEG, 92% had been seen by doctor within previous year. 4 untreated, 17 on monotherapy. 21 (57%) were "seizure-free" (duration not stated). Only 2 were in long-term remission.

White and Buckley, 1981.

The management of epilepsy – an audit of two practices.

Structured interview of patients with epilepsy in 2 practices, list size 20043, identified through repeat prescriptions. Handling of single seizures not stated: untreated patients excluded. 38 in one practice and 26 in other, prevalences 3.4/1000 (practice A), and 2.3/1000 (practice B). 58% in practice A and 30% in B under hospital supervision; >90% in each practice seen in hospital at some time. 42% had 2 or more seizures during year preceding study, while 42% seizure-free during this time. Patient education not mentioned.

Fry, 1982.

Epilepsy.

96 patients with epilepsy or convulsions (including febrile) identified from general practice 1955-75 and still at practice assessed 1981 (cumulative incidence over 20 years 10.5/1000). 21/96 had febrile convulsions (none developed epilepsy). Prevalence treated patients 1981 3/1000, 73% of these having >=1 attack in previous year. 80% with seizures starting under age 1 seizure-free for 3 years at follow-up, and 75% with attacks beginning aged 1-14.

Goodman, 1983.

Auditing care of epilepsy in a group practice.

36 patients with recurrent spontaneous afebrile seizures identified from practice morbidity register (list size 8743), prevalence 4/1000. Extent of hospital referral unclear, but hospital care described as unsatisfactory, with lack of continuity of supervision: "patients saw a different doctor at each attendance, and most of the follow-up was performed by junior hospital doctors". No comment made about general practice follow-up. 33% on monotherapy, 67% taking 2-3 drugs. 58% had <4 seizures/year.

Goodridge and Shorvon, 1983.

Epileptic seizures in a population of 6000

122 patients with history of definite seizures identified by scrutiny of 3000 male, 3000 female consecutive records in Tonbridge general practice. Single and acute symptomatic seizures included. 71 (58%) seen by neurologist, 22 (18%) by paediatrician. 73% known to have had EEG, result unknown in 18%. 8% had CT. 10% continuing to attend hospital clinic. 39% of total were receiving medication, 68% monotherapy. A further 40% had previously taken drugs. Nearly half of those with active epilepsy were not receiving anti-convulsants, others were receiving inadequate or inappropriate treatment unchanged despite continuing fits.

Taylor, 1983.

Improving the outlook for patients with epilepsy.

Records from practice audited in l980 were re-audited in l981. 37 (95%) had history of tonic clonic seizures, of whom 20% had evidence of focal onset or associated partial seizures. Only 10 had tonic clonic seizures in past year, though 33% continued to have recurrent partial seizures. 46% were seizure-free. Polypharmacy had been reduced, with 59% now on monotherapy.

McCluggage et al, 1984.

Anticonvulsant therapy in a general practice population in Northern Ireland.

Study of 300 patients with epilepsy (>1 non-febrile seizure, on anti-convulsants at time of study, over 6 months old, and living at home) identified through repeat prescriptions in 9 general practices, population 75200, in Belfast, 1979-81. Prevalence of treated epilepsy 4/1000. 247 participated, of whom 5 found not to have epilepsy and excluded. Proportion referred to hospital not stated. EEG mentioned in practice records in 72%. Approximately equal numbers of patients had partial and generalised seizures. 59% treated >=10years, and 36% for >=20 years. 30% seizure-free in preceding year.

Cooper and Huitson, 1986.

An audit of the management of patients with epilepsy in thirty general practices.

Patients aged >=12 with treated epilepsy on lists of 30 general practitioner members of research group (total list size 100,000) identified over 3 months through surgery attendance or repeat prescription, or sometimes by diagnostic register. Patients interviewed by GP, and patient and doctor completed matching questionnaires, and were being compared. 377 took part, prevalence 3.8/1000. Mean age 46 years. 71% had generalised tonic clinic seizures. 69% had <1 seizure per three months. 39% saw GP at less than three monthly intervals. No comment about hospital referral. 54% on monotherapy. Considerable discrepancy between answers of doctors and patients, particularly regarding effect of epilepsy on patient's home life.

Hall and Ross, 1986.

General practice study of the care of epileptic patients.

39 patients with epilepsy identified through repeat prescriptions over six months from list of 8000, prevalence 4/1000. 32/39 interviewed. Most had generalised tonic clonic seizures only. All knew they had epilepsy, except one child whose parents did not want him told. 58% had seen GP within previous 6 months: 19% >1 year earlier. Except for advice about precipitating factors, special risks, and driving, which were discussed with > ½ patients, patients' recollection of advice was sketchy. No information given about hospital referral.

Taylor, 1987.

Epilepsy in a Doncaster practice: audit and change over eight years.

The same Doncaster practice, list size now 7500, re-audited in 1986. Patients with active epilepsy (seizures in past 2 years, or previous seizures and current mediation) identified from disease register, checked through repeat prescriptions over 6 months. Single and febrile seizures excluded. Prevalence of active epilepsy 6.1/1000. One of original 37 patients excluded as having febrile convulsions only; 2 recorded as having been in remission. 61% had seizures of partial origin. 89% seen at early stage by specialist, usually neurologist or paediatrician, EEG performed on all of these. CT performed on 24% of patients. 67% under GP care alone, 22% "shared are", and 11% solely under specialist. 41% seizure-free, 15% had <3 seizures/year. 67% on monotherapy or no medication. No comment made about patient education.

Clinical standards advisory group (CSAG) study into epilepsy services in the United Kingdom 1999.

The CSAG committee was commissioned by competitive tender as a national research project to provide a comprehensive report on epilepsy services in the UK and to make recommendations that would improve the care of patients with epilepsy in the United Kingdom. Evidence and data

were sought from a postal questionnaire distributed to 4620 patients (52% responded), another to 731 clinicians (72% responded), a tape recorded interview of 79 patients, consultations with professionals, patients and organisations, telephone surveys of all UK Trusts and postal enquiries of neurosurgical and neurophysiological facilities. It was found that only 30% of patients had attended hospital in the last 12 months. Half of those with severe epilepsy, for example had not attended hospital in the last year. Access and waiting times for consultation and investigations were unduly long. Various recommendations were made and the need for patients to expect the highest standards of care was emphasised. In the same vein, recommendations for the provision of services and facilities were made at the primary, secondary and tertiary care levels.

Appendix 4

Selected Studies of mortality

(Zelinski, 1974c)

An important study which was population based study and carried out in Warsaw. Patients with epilepsy were ascertained as part of a wider study into the epidemiology of epilepsy in Warsaw using patient record review and house to house survey. 218 patients with epilepsy died in 1969 giving an SMR of 1.8 which was much higher in patients under 50 years. Epilepsy was the cause of death in 14% of patients and this was 20% in institutionalised patients. Other important causes of death were cancer, pneumonia and heart disease. The lot of the patient with epilepsy resident in Warsaw in 1969 is illustrated by a high suicide rate.

(Terrence Jr, Wisotzkey & Perper, 1975)

Thirty-seven cases of unexpected, unexplained death in epileptic patients were recorded by the Allegheny County Coroner's Office during the years 1969 through 1973. In no case was there anatomic or chemical evidence at autopsy sufficient to explain death. All patients had a duration of epilepsy greater than a year. All but two had less than one seizure per month. Blood levels of anticonvulsants at autopsy revealed only three patients with therapeutic levels of the drugs. Almost 50 percent of the cases studied had no demonstrable anticonvulsant. It was suggested that inadequate levels of anticonvulsant drugs were a significant factor associated with unexpected, unexplained death in epileptic patients.

(Annegers, Elveback, Labarthe & Hauser, 1976)

The records of a cohort of patients with epilepsy in Rochester, Minnesota were reviewed to ascertain their rates of occurrence of ischaemic heart disease. The results did not show any relative decrease in the incidence of

mortality rates due to ischaemic heart disease among men or women with epilepsy. The number of ischaemic heart disease incidence and mortality cases were 25 and 15, respectively, relative to corresponding expected values of 15.0 and 15.7 new and fatal events. The use of anticonvulsant medications did not appear to influence the rates of ischaemic heart disease among the patients with epilepsy. Subgroups of the epilepsy patients, by aetiology and types of epilepsy, were not found to account for a disproportionate share of the ischaemic heart disease. The survivorship of epilepsy patients after the initial manifestations of ischaemic heart disease was comparable to that expected among all ischaemic heart disease patients.

(Bowerman, Levisky, Urich & Wittenberg, 1978)

A good early study looking at the factors predictive of SUD. Eleven autopsy cases from a Colorado coroner's service were presented in which post-mortem levels of anticonvulsant drugs were subtherapeutic. Scene investigation or medical history, or both, revealed evidence of epilepsy in all eleven cases. Five of the deaths (three drowning and two with aspiration of gastric contents) occurred during a suspected seizure. The six remaining deaths were attributed to asphyxia associated with terminal seizures. Because anatomic evidence of epilepsy is often minimal and non-specific, the authors though that levels of anticonvulsant drugs should be determined in cases of sudden unexpected death with a history of epilepsy, and that these eleven deaths were preventable with better patient motivation and compliance with the physicians' orders.

(Chevrie & Aicardi, 1978)

Mortality and neurological and mental outcome were studied in infants 28 days to 1 year of age with afebrile seizures not due to an acute postnatal injury. Cases were divided into four seizure types: infantile spasms: status epilepticus; and "others" (patients without spasms or status), generalised and partial. Mortality was studied in 334 cases. Mortality

was higher and mental and neurological sequelae were more common in symptomatic than in cryptogenic cases. The highest mortality and greatest number of neurological defects were in status epilepticus and in "others" partial groups. Severely retarded subjects were more common in infantile spasms and "others" partial. The proportion of mentally normal patients, however, was no different according to ictal type. Mental and neurological prognosis was less unfavourable when the first seizure occurred at or over 6 months.

(Iivanainen & Lehtinen, 1979)

An interesting paper which examined the causes of death in institutionalised epilepsy patients at the Vaajasalo Hospital in Finland. During the years 1900-1076, 179 inpatients in Vaajasalo Hospital had died; 12% of all inpatients. The most common causes of death were pneumonia in 40 cases, seizures in 34 cases (single seizure in 18 and status epileptics in 16), drowning in 29 cases, stroke in 10 cases and heart infarct in 9 cases. Chronic intoxication caused by phenytoin and/or phenobarbital was a common supplementary factor leading to death in patients who died of pneumonia or seizures. Thirteen deaths were recorded as suicides or suspected suicides (11 by drowning and 2 by strangulation). This study will be best remembered for the large numbers of death by drowning which was due to the close proximity of a lake where the residents often bathed.

(White, McLean & Howland, 1979)

Over 2000 epileptic patients admitted to the Chalfont Centre for Epilepsy between 1931 and 1971 and taking anticonvulsants were followed up to the end of 1977. Mortality between 1951 and 1977 was greatly in excess of that in the general population of England and Wales in that period allowing for age and sex. Some of the excess was directly attributable to epilepsy, but there were also more deaths from suicide and circulatory, respiratory, and malignant disease than would be expected. Apart from

the brain and central nervous system, no particular site had a significant excess of tumours. In particular, there were no liver tumours (and only one gallbladder carcinoma). The authors concluded that it was unlikely that the liver tumours produced on feeding phenobarbital to mice are indicators of major human risk.

(Hauser, Annegers & Elveback, 1980)

This was another important study to come from the Rochester series. 516 patients with epilepsy were identified over a 32 year period. Single seizures, provoked seizures and febrile seizures were excluded. The SMR for this period of follow up was 2.3, and 1.8 for idiopathic epilepsy. Patients with absence seizures and complex partial seizures had a normal life expectancy. The SMR was highest in the early years after diagnosis and then progressively declined.

(Kurokawa, Fung, Hanai & Goya, l982)

This study followed 385 patients with epilepsy beginning under age 15. 22 (5.7%) patients had died during the first 10 years after the onset of epilepsy and another 11 (2.9%) between 11 and 24 years. Mortality was significantly high in cases with the following clinical features: (1) epilepsy with onset before the first birthday (mortality being 25.5%), (2) symptomatic epilepsy in aetiology (17.2%), (3) infantile spasms (40.7%), tonic epilepsy (33.3%) or myoclonic epilepsy (33.3%) as compared with grand mal (5.9~%) in seizures type and (4) developmental retardation at the first visit (25.5%). The authors highlighted a lack of seizure control in 31 out of 33 patients at the time of death. The causes of death were status epilepticus or convulsion in 10, pneumonia in 5, severe emaciation in 3 "cerebral palsy" in 5, and drowning, suffocation, traffic accidents or acute lymphocytic leukaemia, in one each, and unknown in 6. Most of the patients died at home.

(Annegers, Hauser & Shirts, 1984)

In this later study all-cause and heart disease mortality and ischaemic heart disease incidence among patients with an initial diagnosis of epilepsy while residents of Rochester, MN, from 1935 through 1979 were determined. Death rates from heart disease were slightly elevated for persons with epilepsy. The increased death rate from heart disease was confined to persons less that 65 years of age. The incidence of ischaemic heart disease and of sudden cardiac death as the initial manifestation of ischaemic heart disease was significantly increased in persons with epilepsy, but the increase was primarily limited to those with symptomatic epilepsy attributed to cerebrovascular disease. The occurrence of ischaemic heart disease and sudden cardiac death was not related to anticonvulsant medication status. There was a failure in this study to differentiate the different sub-types of sudden death and many of the sudden cardiac deaths may have been SUDs.

(Leestma, Hughes, Teas & Kalelkar, 1985)

This paper, by an authority on the subject, reviewed the factors predisposing patients with epilepsy to sudden unexpected deaths, and discussed the following: they are most commonly encountered by the forensic pathologist rather than the clinician. Such deaths may represent 1-1.5% of all "natural" deaths certified by the medical examiner or coroner. The typical victim is a black male about 30 years of age who tends to abuse alcohol, with a history of generalised epilepsy for more than 1 year and likely for more than 10 years. There are a lack of obvious anatomic causes for the death at autopsy, but 60-70% of cases will have a lesion in the brain (most commonly old trauma) to explain the epilepsy. Most victims have no blood levels of anticonvulsant medications at the time of death.

(Lund & Gormsen, 1985)

In a small study of sudden unexpected death in treated epileptic patients. One or more of the anticonvulsants phenobarbital, phenytoin and carbamazepine were found in subtherapeutic drug levels in half of the cases and "lethal" concentrations, mainly of phenobarbital, in one third of the cases. The results suggested that non-compliance was a predisposing factor for SUD in epilepsy.

(Massey & Schoenberg, 1985)

Average annual age-adjusted mortality rates for epilepsy from 33 countries for 1967-1973 were calculated and compared to earlier data (when available) from the 1950s. Rates during 1967-1973 ranged from 0.6 deaths/100,000/year (Denmark) to 4.0 deaths/100,000/year (Portugal). Countries in Latin America generally had higher rates. With few exceptions, epilepsy morality rates have declined over time. For each country studied, the rates were higher for males.

(Muuronen, Kaste, Nikkila & Tolppanen, 1985)

This study looked at mortality rate from heart disease in patients with epilepsy and the elation to AEDs. All patients with epilepsy in a specific hospital-based population, known to be taking AEDs who died during 1978-80 were studied. Of 1399 deaths of anticonvulsant users, 258 (18.4%) were caused by ischaemic heart disease. This was significantly less (p less than 0.001) than the 382 deaths from ischaemic heart disease (27.3%) observed among paired controls matched for sex, age, and date of death. The total cardiovascular mortality was also lower among patients with epilepsy than among controls (p less than 0.02) despite there being more deaths due to cerebrovascular disease among patients. The difference in mortality from ischaemic heart disease was significant for both sexes and was not accounted for by excess deaths due to any other single cause. Users of phenytoin, carbamazepine and barbiturates (alone or in combination) showed 29% less mortality due to ischaemic heart disease than respective controls (p less than 0.001).

(Neuspiel & Kuller, 1985)

This study examined all the sudden non-traumatic deaths in persons aged 1 to 21 years in a defined population. In nine years, the 207 deaths in this group (4.6/100,000 population/per year) comprised 22% of non-traumatic mortality. Age-specific rates were highest between 1 and 4 years (mainly infections and undetermined causes) and 14 and 21 years (mainly cardiovascular, epilepsy, intracranial haemorrhage, and asthma). Most epilepsy deaths were unwitnessed and had absent or low anticonvulsant levels.

(Barraclough, 1987)

This study reviewed evidence from follow-up studies concerned with the mortality of epilepsy which suggested that the suicide rate is increased. The risk of suicide was higher for temporal lobe epilepsy, for epilepsy with a greater degree of handicap and in the early years of the condition.

(Luhdorf, Jensen & Plesner, 1987)

All patients in a clinic-based population who were over the age of 60 who experienced seizures between 1979-83, were registered. The numbers of deaths was registered until July 2, 1985. 162 patients were on no anti-epileptic drugs prior to the study period, and 87 patients had established epilepsy. The number of deaths among previously untreated patients significantly exceeded expectation. Mortality did not correlate to the severity of epilepsy. In patients with brain tumours all but one died within the first year. Mortality among patients with post apoplectic seizures was significantly higher than expected being especially during the first year. Numbers of deaths among patients with seizures of unknown cause did not differ from the expected, neither did causes of death. Numbers of deaths in

patients with established epilepsy at the time of admission was significantly higher than expected although none had malignant tumours and only 4 had post-apoplectic seizures thus illustrating the influence of selecting patients with chronic active epilepsy. Eleven patients died suddenly and unexpectedly of unknown cause, which was more than expected. These patients were found dead under circumstances compatible with death occurring during a seizure. The authors pointed out that epilepsy was mentioned on the death certificate in only once case, indicating that the frequency of sudden, unexpected death among epileptics could easily be underestimated.

(Wolfersdorf & Froscher, l987)

This paper reviewed other work in this area. The proportion of suicide in the overall mortality of epilepsy patients was about 8%, about four times more frequent than in the general population. An affective disorder leading to suicide may be caused reactivity, pharmaco-genically, or by the epileptic function disorder itself or by an underlying cerebral disease. The paper said that for prophylaxis of suicide, it is especially important to be informed about pharmaco-genetic depressive moods, which occur in phenobarbital treatment. Help is often possible by change of medication.

(Satishchandra, Chandra & Schoenberg, l988)

This report utilised data from the National Centre for Health Statistics which recorded all conditions mentioned on each death certificate for the entire US population. Using a case-control study design, all the associated conditions at the time of death in patients with epilepsy for the year l978 wee analysed. Association between epilepsy and the following conditions reached statistical significance: mental retardation, cerebral palsy, cerebrovascular disease, myocardial ischaemia, dementia, foreign body in pharynx and larynx, pneumonia, alcoholism and cirrhosis of liver. The meaning of all these associations was not explicit, but the authors then

said that early recognition and proper management of these factors could significantly reduce the mortality and morbidity in epileptic patients.

(Kelling & Knowles, 1989)

This study looked at all sudden natural deaths between the ages of 2 and 20 years which occurred during a 20-year period, identified from mortuary records of a specific population. Necropsy reports and histological sections were reviewed; 169 sudden natural deaths were identified amongst 1012 deaths in that age group. Ninety-two sudden deaths occurred to children with recognised disorders; and as well as congenital heart disease, and asthma, epilepsy was one of the commonest problems identified.

(Leestma, Walczak, Hughes, Kalelkar & Teas, 1989)

This study is important as it attempted to estimate the risk of SUD in patients with epilepsy at the population level. Sudden unexpected deaths were monitored by the Office of the Medical Examiner of Cook County (Chicago), Illinois in a year-long prospective study. It was revealed that victims of this complication of epilepsy were most commonly black males averaging 35 years of age who had infrequent generalised seizures and usually some structural lesion in the brain responsible for their seizures. They tended to abuse alcohol and have poor compliance with anticonvulsant medication. The electroencephalograms displayed considerable variability from record to record. At autopsy the heart, lung, and liver weights were heavier and the brain weights were lighter than expected. The authors speculated on the mechanisms involved that may include autonomically mediated cardiac arrhythmia alone or in combination with sudden "neurogenic" pulmonary oedema and "backward" cardiac failure.

(Dasheiff, l991)

This report reviews the number of deaths that occurred in a population of patients on a pre-surgery programme. Seven patients died a sudden unexpected death. This incidence of sudden unexpected death was five times higher than the 1-2/1000 per year reported in the general epilepsy population. The authors pointed out that SUD shares some of the characteristics associated with sudden cardiac death, which kills 300.000 people in the United States each year. A cardiac arrhythmia, usually ventricular fibrillation, is the most common terminal event for sudden cardiac death and the authors speculated that it is also the leading candidate as the mechanism for sudden unexpected death.

(Earnest, Thomas, Eden & Hossack, 1992)

This study examined 44 cases of SUD for details of seizure history, treatment, medical and psychological history, events at the time of death, and post mortem findings. Cases of status epilepticus, drowning or other identifiable causes of death were excluded. Two groups emerged: five children with uncontrolled seizures receiving multiple AEDs and good compliance with medications, and 39 adults with less frequent seizures, often receiving monotherapy, but noncompliant with medications. Four children (80%) but only one adult (3%) had fully therapeutic post-mortem AED levels. Sixty-three percent of adults recently had experienced an unusually stressful life event. Investigation of the circumstances at the time of death suggested two possible m odes of death: (a) a seizure with an immediately fatal arrhythmia, or, (b) a seizure, recovery, then delayed secondary respiratory arrest or arrhythmia.

(Klenerman, Sander & Shorvon, 1993)

The causes of death in a group of patients with severe epilepsy in long term residential care over a period of 11 years were assessed and standardised mortality rate (SMR) determined. A total of 3392 patient-years were surveyed.

One hundred and thirteen deaths were recorded in the period which gave an SMR of 1.9. Most deaths were due to cancer (26%), bronchopneumonia (25%), circulatory disease (24%), were seizure-related (12%) or due to sudden unexpected death (6%). The highest SMRs in the neoplasm sub-group were due to cancers of the pancreas (SMR = 6.2) and hepatobiliary tumours (SMR = 17.6). Twenty per cent of patients died of epilepsy or epilepsy related causes. One in every 480 patients died due to a sudden unexpected death. This study in a highly selected population seems to confirm suggestions that mortality rates are higher in patients with epilepsy than in the general population.

(Cockerell OC et al, 1994)

This was an important study, the first report on mortality from the NGPSE and the first to report mortality prospectively in a truly community based cohort. The SMR for the whole cohort was 2.5 (95% CI 2.1-2.9) and 3.0 (95% CI 2.5-3.7) for patients with definite epilepsy. The SMR for idiopathic epilepsy was 1.6 (1.0-2.4), for remote symptomatic epilepsy 4.3(3.3-5.5) and acute symptomatic epilepsy 2.9(1.7-4.5). The commonest causes of death were pneumonia (SMR 7.2), cancer (3.5) and stroke (3.7).

(Nilsson L et al, 1997)

This Swedish hospital based study looked at 9061 patients over the age of 15 years and over a 53520 patient year period in which 4001 deaths were observed. This yielded an SMR of 3.6 (95% CI 3.5-3.70. SMR was significantly increased in all age groups. Excess mortality was due to a wide range of causes including malignancy (SMR 2.6; 2.4-2.8), ischaemic disease (SMR 3.1; 3.0-3.3) and respiratory disease (SMR 4.0; 3.6-4.5). This confirmed the increased mortality in patients with epilepsy noted in previous studies.

Appendix 5

List of General Practitioners currently participating in the NGPSE

Dr. K.N. Addey
Dr. S. Ahmad
Dr. H. W. Aitken
Dr. M. Al-Saleem
Dr. S.m. Amin
Dr. N. Amin
Dr. J. C. Anderson
Dr. D. I. Anderson
Dr. Y. Anthony
Dr. D. P. Archer
Dr. N. Arnott,
Dr. S. M. Ashby
Dr. Y. C. Au
Dr. S. Bailey
Dr. J. W. Baker
Dr. R. Baker
Dr. F. C. Ballinger
Dr. B. R. Bannar-Martin
Dr. D. Clare
Dr. P. M. Barrie
Dr. S.K. Bassi
Dr. Beazer
Dr. D.J. Bell
Dr. S.J. Bellamy
Dr. R. B. Bennet
Dr. R. B. Bennet
Dr. E. N. Nenson
Dr. R. Bertram
Dr. Bhanja
Dr. M. A. Bielenky
Dr. C. E. Birchall
Dr. K. Biswas
Dr. F. J. Borchardt
Dr. P. Bosworth
Dr. G. M. P. Boyes
Dr. B. H. Boyle
Dr. J. G. Bradbrooke
Dr. P. Bradley
Dr. D. Brodie
Dr. P. G. Brown
Dr. Bryant
Dr.B. S. Bryant
Dr. R. J. Buckle
Dr. R. Bull
Dr. A.J. Burch
Dr. K. Burch
Dr. S. Burcombe
Dr. S. Burgoyne
Dr. R. H. Burton
Dr. R. H. Burton
Dr. D.F. Burwood
Dr. S. Butcher
Dr. Butcher,
Dr. D. N. Greig

Dr. J. R. Bywater
Dr. M. F.A. Cahill
Dr. G. R. Caird
Dr. Calder
Dr. G. E. Clavert
Dr. P. D. Campion
Dr. C. Campion-Smith
Dr. W. Drysdale
Dr. T. J. Cantor
Dr. S. Carne
Dr. T. A. Carney
Dr. J. Carrol
Dr. B. E. Carter
Dr. P. M. Carter
Dr. R. J. s. Cave
Dr. G. J. Charlwood
Dr. D. A. Chidwick
Dr. J. D. Churcher
Dr. Elsby
Dr. R. C. Clare
Dr. P. Claydon
Dr. C. Clayton-Payne
Dr. A. Coggan
Dr. R. W. Coles
Dr. M. Collins
Dr. P.H. Cook
Dr. A. Cook
Dr. H. Corcoran
Dr. D. J. Corlett
Dr. H. Cotton
Dr. P. Cottrell
Dr. E.J. Coutinho
Dr. H. L. Coysh
Dr. D. Craig
Dr. P. J. Craven
Dr. J. A. Cree
Dr. N. R. Crossley
Dr. I. D. Cruickshank
Dr. M. Cunningham
Dr. M. T. Cwynarski
Dr. J. Czauderna
Dr. M. D'Souza
Dr. S. L. Davidson
Dr. F. Davidson
Dr. H.C.R. Davies
Dr. A. W. Davies
Dr. P. H. Davison
Dr. S. C. Davoodbhoy
Dr. F. W. Debney
Dr. A. R. Del Mar
Dr. C. I. Dellaportas
Dr. P. J. Dennis
Dr. A. Dhesi,
Dr. P. Jeavons

Dr. L. H. Dhiya
Dr. G. A. Dinnis
Dr. J. B. Donald
Dr. R. R.Donmall
Dr. S. Dove
Dr. J. Dowell
Dr. M. Doyle

Dr. A. R. Duke
Dr. Dunn
Dr. R. J. Dunstan
Dr. A. J. Dutton
Dr. Dyer
Dr. L. Dyson
Dr. N. E. Early
Dr. M. P. Eddington
Dr. D. A. Edmonds
Dr. Elder

Dr. A. R. Emerson
Dr. H. Enright
Dr. P. R. Evans
Dr. K. G. Evans
Dr. D. J. Fairclough
Dr. T. M. Farley
Dr. A. Farmer
Dr. G. Fletcher
Dr. B. A.Flintan
Dr. R. Fosket
Dr. I. L. Foster
Dr. R.D. Fouracre
Dr. P. M. Francis
Dr. A. Frazer
Dr. G.K. Freeman
Dr. A. French
Dr. A. R. Gall
Dr. B Geffin
Dr. D. Gelipter
Dr. R. L. Gibbins
Dr. J. S. Gibson
Dr. J. R. Gilbert
Dr. B. V. Gill
Dr. S. C. Gillam
Dr. J. B. Glass
Dr. J. D.Goddard
Dr. D.M.G. Goodridge
Dr. D.Gordon
Dr. J. Granger
Dr. G. R. Green
Dr. R. W. Green
Dr. D.J. Green
Dr. R. M. Greenfield
Dr. E. D. Gregson
Dr. M. McBride

Dr. S.K. Griffith
Dr. H. G. Gunton
Dr. P. E. Haddon
Dr. J. L. Hadley
Dr. S. A. Hall
Dr. W. Hall
Dr. I. Hamilton
Dr. R. A. Hamlin
Dr. C.H. Hand
Dr. M. C. Hannan
Dr. M. Harland
Dr. D. W. Harley
Dr. A. Harris
Dr. J. J. Harris
Dr. R. G. Harrison
Dr. K. R. Harrison
Dr. E. A. Harrison
Dr. R. Harrod
Dr. Hassan
Dr. M. Hassenfuss
Dr. Hassey
Dr. T. Hatch
Dr. Hawkins
Dr. J. L. Haworth
Dr. K. A. Heatley
Dr. G. D. Heaton
Dr. I. N. Hempshall
Dr. F. Hennessey
Dr. C.Henry
Dr. J. Hewlett
Prof Higgins
Dr. F. Higgs
Dr. S. Highton
Dr. A. P. Hill
Dr. S. Hilton
Dr. I. M. Hiscock
Dr. S. J. Hogg
Dr. R. Hollands
Dr. R. Holloway
Dr. S. G. Holmes
Dr. D.H. Hood
Dr. P. Hopkins
Dr. P. Horsfield
Dr. B. Hourihane
Dr. T. R. Howard
Dr. A. Howe
Dr. I. E.Hughes
Dr. M. E. Hughes
Dr. D. Hughes
Dr. C. Hulbert
Dr. M. H. Husain
Dr. W. Isherwood
Dr. M. Jackson
Dr. N. R. Jackson
Dr. P. W. James
Dr. I. Jamieson
Dr. R. J. Jarvis
Dr. L. G. Posser
Dr. D. J. Poulton
Dr. P. Preston
Dr. J. M. Jones
Dr. K. J. Jones
Dr. M. R. Jones
Dr. B. Jones
Dr. W. M. Jordan
Dr. J. F. Judge
Dr. A. Jumaily
Dr. J. Kane
Dr. J. F. Kedward
Dr. M. R. Kennedy
Dr. I. S. Kewley
Dr. S. J. King
Dr. R. H. King
Dr. K. N. Kini
Dr. R.N. Kirby
Dr. P Kirk-Smith
Dr. S. Kitson
Dr. J. Kloer
Prof. J. D. Knox
Dr. Koppel
Dr. M. G. Kremer
Dr. J. M. Lakeman
Dr. D. C. Langley
Dr. M. J. Latham
Dr. J. Launer
Dr. D. Law
Dr. D. Lawton
Dr. C. Lay
Dr. Lean
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Appendix 6

THE NATIONAL GENERAL PRACTICE STUDY OF EPILEPSY ANNUAL GP FOLLOW UP FORM

NATIONAL GENERAL PRACTICE STUDY OF EPILEPSY AND EPILEPTIC SEIZURES
(NGPSE)
FORM 5 – YEARLY FOLLOW UP

This is a follow up about a patient you notified to the NGPSE. Please could you arrange to see the patient to complete the questionnaire, (if the patient has changed practices, please provide as much detail as you can, so that the patient may be traced or followed up elsewhere). PLEASE FILL IN ALL GREY SHADED BOXES (in as much detail as possible) and feel free to make any comment you wish which may amplify answers or reflect any difficulties you encounter when completing the questionnaire.

PLEASE RETURN THE COMPLETED FOR TO: Dr. S.D. Shorvon
FREEPOST
Chalfont Centre for Epilepsy
Chalfont, St. Peter, Bucks. SL9
7BR

1. General Practitioner 2. Patient

If patient has changed address or general practice, please insert new address/general practice. (If not known please give as much information as possible, indicate area etc.).

New Address New General Practice

___If patient has died please give details (date, cause of death etc.)

A MOST IMPORTANT AIM OF THE STUDY IS TO OBTAIN FULL INFORMATION ABOUT SEIZURE RECURRENCE – PLEASE ANSWER IN THE GREY SHADED BOXES IN AS MUCH DETAIL AS POSSIBLE.

3. SEIZURES

Date of entry to study:

Date of first seizure:

The last follow-up was on:

At last follow-up, details of recurrence were:

The seizures were described as:

3.i Number of seizures since last follow-up

3.ii Date of these seizures

3.iii Timing (Asleep/awake/asleep and awake/don't know)

3.iv If seizure type has changed, or if further information is available concerning seizure recurrence, please give full details below:

We have the following information regarding

Aetiology

Circumstances/precipitating factors

4.iv If these have changed, please amend in as much detail as possible:

4. Have there been ANY NEUROLOGICAL, MEDICAL ANDPSYCHOLOGICAL DEVELOPMENTS? If so, please give further details:

5. DRUG TREATMENT

The drug treatment previously notified was:

Drug Dosage per day

6.i If any drug change has occurred since the last follow up, please specify:

6.ii Present anticonvulsant treatment:

6. Is the patient attending a hospital clinic because of the seizures?

Yes/No/Don't know

If yes please give details:

Hospital

Address

Consultant/Clinic

7. We have classified the patient as follows

DEFINITE EPILEPSY	( )
DEFINITELY NOT EPILEPSY	( )
PROBABLE/POSSIBLE EPILEPSY	( )
DON'T KNOW	( )

Is this correct? Yes/No/Don't know

Comment re: diagnosis

Other Comments

Form completed by:

Date:

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