THE EPIDEMIOLOGY OF EPILEPSY: REMISSION, MORTALITY, SECULAR TRENDS, AND ECONOMIC COST

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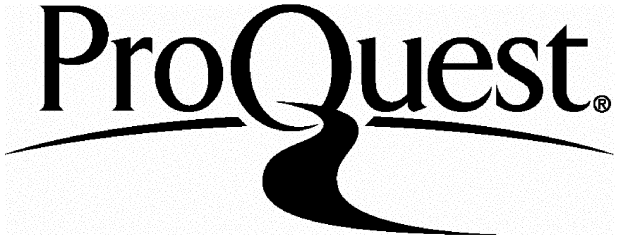

Abstract

The work in this thesis is concerned with five major areas of epilepsy epidemiology: remission, mortality rates, mortality risk factors, economic cost, and secular trends.

The National General Practice Study of Epilepsy (NGPSE) is a prospective population-based cohort study which identified patients with newly diagnosed patients between 1984-87. 1091 patients with suspected seizures were identified, and follow up has continued to date on the 564 patients with definite, and the 228 with possible seizures. Follow up was continued for up to 9 years. The aim of the study was to determine the prognosis of epilepsy (remission and morality). The overall rate of remission was 85.7% for a three year, and 68.1% for a five year remission. The figures for terminal remission were 10% less. Aetiology, age of onset, and seizure type did not have a major influences on the chances of achieving remission, neither did early seizure pattern or treatment.

The early mortality rate of patients with epilepsy was high, and was over two times that expected. The death rate was highest in the first year after diagnosis and was highest in patients with symptomatic epilepsy. Nevertheless the death rate of idiopathic epilepsy was still raised, suggesting that epilepsy itself carries an increased death risk.

The causes of the increased deaths due to strokes, cancer and pneumonia were examined in case controlled study. No significant differences were found for the level of smoking, drinking, blood pressure, or body mass index suggesting that these factors are not significant contributors to the death rate in patients with epilepsy.

A population of 6000 persons was identified in a GP surgery in Kent, and compared to a similar analysis performed ten years previously. The aims of the study were to examine secular trends in the prevalence, incidence and prognosis of epilepsy. The most striking finding was that the incidence of epilepsy in children had fallen over the last decade, and the incidence of epilepsy in the elderly had correspondingly risen.

The economic cost of epilepsy was estimated from the NGPSE cohort and compared to a cross sectional cohort of patients with established epilepsy.

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AUTHOR'S CONTRIBUTION

The National General Practice Study of Epilepsy (NGPSE)

The author was the co-ordinator of this study during the period 1992-1994. He was responsible for all aspects of planning, administration and execution of the study. Day to day running of the study was co-ordinated and run by the author who ensured that follow up was complete, deaths registered and the cause of death determined. He was responsible for all the data handling and carried out the statistical work in conjunction with Dr AL Johnson of the MRC Biostatistics Unit, in Cambridge.

The economic cost of epilepsy

The author was responsible for all aspects of the data handling and analysis from the NGPSE and from the data already obtained from the National Epilepsy Survey by Dr YM Hart.

The Risk Factor Study

The author was wholly responsible for the design, planning and execution of the study. Statistical help was carried out in conjunction with Miss S Gupta of the Neuroepidemiology Unit at the National Hospital.

The Prevalence study

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INTRODUCTION

Epilepsy is one of the most common of the serious neurological conditions. It has an estimated incidence of between 50-122/100,000 cases per year, the prevalence of active epilepsy is 5 - 8 /1000, and the lifetime prevalence is 3 - 5 % of the general population. (Goodridge & Shorvon, 1983, Sander & Shorvon, 1987) In the United Kingdom it has been estimated that there are over 300,000 persons with active epilepsy and over 1 million persons with a history of seizures. (Duncan & Hart, 1993) Descriptions of patients with epilepsy can be traced to man's earliest recorded history with one text from Akkadia in 2000 BC giving an account of a convulsion. Epilepsy was often thought to be a manifestation of evil spirits, or an expression of divine displeasure whose visitation took no account of time or status. For instance, there is an interesting description of the death of Charles II of England, which suggests that he died in status epilepticus, although the attendance of his physicians may have hastened his demise with frequent blood lettings. (Swinyard, 1980) The modern concept of epilepsy owes much to Hughlings Jackson, who characterised a seizure as a sudden, excessive discharge of grey matter, (Taylor, 1931) and to Gowers was another important figure in the developing years of modern neurology and contributed a wealth of data on the clinical features of the various forms of epilepsy, and was one of the first investigators to address the issues of treatment and prognosis. (Gowers, 1885)

Epidemiology is one of the key disciplines in neurology. Incidence, mortality, and prevalence studies provide crucial measures of disease burden and give a broad picture of disease patterns and this enables service provisions to be planned. Longitudinal prospective epidemiological studies allow natural history and prognosis to be ascertained, and neuroepidemiology can advance the knowledge of a disease by determining risk factors and calculating attack rates. Much of the early work in the epidemiology of epilepsy was bedevilled by methodological problems concerning the diagnosis and classification of epilepsy, as well as inappropriate reliance on hospital-based studies. Ideas about the prognosis of epilepsy reached a watershed in 1969 with the publication by Rodin of his observations on his own patients, as well as a comprehensive review of all previous work. (Rodin, 1968) An important tenet of his study was that most patients with epilepsy have a chronic condition that needs lifelong treatment, which was hardly different to Gowers' views almost a century prior to this.

Rodin also recognised that epilepsy could be a life-threatening condition with a considerably reduced life expectancy. This was a departure from much of the early work, and Gowers who was one of the first to examine the mortality of epilepsy in any detail, thought that, in contradistinction to the poor chances for remission, the chances for a normal life span appeared to be favourable. (Gowers, 1885)

In the last 15 years the pessimistic view of remission has been almost completely reversed, whereas views on the mortality of epilepsy have remained much unaltered. The change from hospital-based studies to studies that are more population-based has shown that good outcome is the norm rather than the exception. This is exemplified in two studies, one from Rochester, USA and the other from Tonbridge in the United Kingdom (UK). In the USA study a population based retrospective analysis of 457 patients with up to a 20 year follow up found that the eventual chances for remission were very good with about 70% of patients achieving a 5 year remission. This was similar to the UK study which also examined remission in a retrospective population based cohort of 122 patients, and found rates for 4 year remission of nearly 80%. However, the old outlook is often repeated, even in standard textbooks of neurology, for example "epilepsy is a chronic disorder with recurrent symptoms or seizures". (Lorenzo, 1990) Although there have been numerous other studies of the prognosis of epilepsy many have serious methodological problems and there is still a dearth of prospective population-based studies that have followed patients from the first seizure. Also, there are only a handful of studies that have satisfactorily looked at the mortality of epilepsy, even in retrospective populations, and the mechanisms of the increased mortality remains speculative.

Another aspect the epidemiology of epilepsy, is whether it has changed over the years. Since the first drugs for epilepsy were developed the treatment has altered dramatically with better treatment of status epilepticus, improved ideas about when to start and when to stop antiepileptic drugs (AEDs), as well as advances in the diagnosis and treatment of meningitis, tumours and other cerebral disorders that cause epilepsy. Despite these advances there is considerable uncertainty about whether epilepsy is becoming more or less common, and whether the outcome has actually improved. The only clue to any changes is a possible falling incidence of epilepsy in childhood that has been reported in the Rochester series. (Hauser & Kurland, 1975)

One aspect of the prognosis of epilepsy which has been consistently neglected, is the economic outcome. The economic cost of caring for patients with epilepsy has been increasing out of all proportion to the capability (or willingness) of, even the richest economies, to finance it. There have never before been so many new expensive AEDs, new investigations, or such demand for surgery, rehabilitation, or special training. All these new developments incur costs greatly in excess of their older replacements, and if nations are to improve the care and treatment of their patients with epilepsy so maximisation of resources is vital. In 1991 the Office of Health Economics calculated that the cost of epilepsy to the UK was £109 million ($255 million US). (Griffin & Wiles, 1991) In the USA a study carried out in 1975 calculated a total cost to the economy of $10.3 billion US (updated figure). (US Commission for the control of Epilepsy, and its consequences., 1978) A more recent study in the USA, which modelled the total costs of epilepsy over a lifetimes treatment, found that the total lifetime cost of a patient who enters remission soon after initial diagnosis was about $4000, whereas the cost for a patient with intractable seizures was over $130,000. (Begley, Annegers, Lairson, Reynolds & Hauser, 1993) One of the problems with assessing the economic impact and prognosis of epilepsy is the basis of the economic method which different studies have used, and this has accounted for considerable differences in the conclusions from different studies. There is thus a pressing need for economic analysis in the field of epilepsy.

In this thesis I will report on five separate areas, based on three separate studies. The first is the National General Practice Study of Epilepsy (NGPSE) which is the first population based prospective study of newly diagnosed epilepsy. I will address two important aspects of prognosis based on the NGPSE: the chances of achieving a remission lasting 3 and 5 years and the early mortality of epilepsy. The second area of study will be into the mechanisms that underlie some of the causes of increased mortality in patients with epilepsy, both at a community and a institution level, looking at the risk factors for vascular death, pneumonia, and cancer in patients with epilepsy compared to the general population. The third study will re-examine all patients with epilepsy in a population covered by a Tonbridge general practice population of 6000 persons, which was first examined in 1982. (Goodridge & Shorvon, 1983) And by doing so, to discern any secular changes in the epidemiology of epilepsy, with an emphasis on possible changes in the incidence, prevalence and prognosis. The fourth area

will examine the economic impact of epilepsy based on data from the NGPSE, and comparing this to a cross-sectional population of patients with established epilepsy called the National Epilepsy Survey.

SECTION 1

A CRITICAL REVIEW OF THE LITERATURE

1.1. THE PROGNOSIS OF EPILEPSY

The outcome, or prognosis, of a disease is one of the most fundamental measures in epidemiology. In epilepsy there are a number of important end points that comprise outcome: the risk of recurrence after the first seizure, the chances for remission after more than one seizure, and the prospect of an increased risk of premature death. The measurement of these endpoints, and the effect various factors have on them, forms the basis for an understanding of the prognosis of epilepsy.

1.1.1. The recurrence of seizures after the first non-febrile seizure

The overall risk of recurrence after the first seizure has already been studied in the NGPSE, (Hart, 1992, Sander & Shorvon, 1989) and so does not form a part of this thesis. Nevertheless, this aspect of prognosis is important, especially with regard to the nature of epilepsy itself and the distinctions that are often between epilepsy and single seizures. I will briefly discuss the main points.

1.1.1.1. The rate of recurrence

Previous studies have reported rates of between 16-81% for the risk of recurrence following a single non-febrile convulsion. (Blom, Heijbel & Bergfors, 1978, Camfield, Camfield, Dooley, Tibbles, Fung & Garner, 1985, Cleland, Mosquera, Steward & Foster, 1981, Costeff, 1965, Elwes, Chesterman & Reynolds, 1985, Goodridge & Shorvon, 1983, Hart et al., 1990, Hauser, Anderson, Loewenson & McRoberts, 1982, Hopkins, Garman & Clarke, 1988, Thomas, 1959, van Donselaar, Geerts & Schimsheimer, 1991) The variation in these results is large and is largely explained by methodological differences between studies. (Hart et al., 1990) Many of the differences are similar to those encountered in studies of remission, which will be discussed later.

The studies that have reported rates of less than 50% have often been in specific populations of patients with an a priori reason for a low recurrence rate, or there has usually been some other obvious methodological difficulty. The commonest reason for a low recurrence is that the study was retrospective, and /or was in patients who attended special epilepsy clinics, or some other hospital department. (Camfield et al., 1985, Cleland et al.,

1981, Costeff, 1965, Saunders & Marshall, 1975, Thomas, 1959) Patients attending electroencephalography (EEG) departments, for instance, only form about 65% of patients with a seizure disorder, and patients who attend hospital clinics are more likely to have more frequent, or complicated seizures and be of a younger age. (Hart, 1992) The retrospective nature of many of these studies also means that patients who are better controlled or poorly compliant tend not re-attend clinics, so that their follow up will more likely be incomplete. It is also more problematic to ensure complete follow up data retrospectively, making later data analysis difficult. Patients attending hospital clinics might be expected to have higher rates of recurrence because of their severity, but the study design often operates to exclude patients who have had an early recurrence. For instance, two studies only included patients with an isolated seizure presenting to a hospital clinic, so that patients who had already suffered a seizure were not analysed. (Cleland et al., 1981, van Donselaar et al., 1991) The delay in being seen in a clinic is critical as most seizure recurrences occur within the first few weeks and months, (Hart et al., 1990) and will lead to considerable under estimation of recurrence risks.

As iterated above, prospective studies are generally preferable to retrospective analyses. However, studies which only recruited patients attending hospital clinics are also likely to result in low recurrence rates for the reasons discussed above, and rates of between 27-71% have been found. (Blom et al., 1978, Elwes et al., 1985, Hauser et al., 1982, Hopkins et al., 1988) This differences in rates between such similar populations are again due to differences in study design. For instance, Hauser reported a particularly low rate, of 27% by 3 years, but patients were excluded who had 2 or more seizures prior to presentation, and there was non random selection of patients for AED treatment. (Logan & Hart, 1983)

There have been a few population based studies of seizure recurrence with recurrence rates of between 56% and 81%. (Annegers, Shirts, Hauser & Kurland, 1986, Goodridge & Shorvon, 1983, Hart et al., 1990) The advantage of using population based methods is the improvement in case ascertainment and therefore the reduction of bias due to missing certain types of patient. Both the Tonbridge and Rochester studies were retrospective with the problems these types of study entail, nevertheless recurrence rates were of a similar order, with more complete ascertainment and the inclusion of provoked seizures in the Tonbridge study accounting

for the higher rate. The NGPSE is the only prospective descriptive study reporting on the risk of recurrence following a seizure with an overall rate of 67% by 1 year and 78% by 3 years. (Hart et al., 1990)

1.1.1.2. Factors affecting the rate of recurrence

A higher risk of seizure recurrence might be expected where there was an identifiable cause. Hauser found that 37% of patients with head trauma, compared to 28% of idiopathic cases, experienced a second seizure. (Hauser et al., 1982, Hauser, Rich, Annegers & Anderson, 1990) Annegers compared patients who had a remote cause such as a tumour or stroke against idiopathic cases, with a rate of 45% (by 5 years) for idiopathic, versus 77% for remote seizures. (Annegers et al., 1986) This was not confirmed by Hopkins who only found this to be true in patients with tumours. (Hopkins et al., 1988) Hart with the NGPSE cohort found that patients with acute causes had a lower recurrence rate, (Hart et al., 1990) whereas there was little difference between the vascular, tumour and idiopathic groups. Factors predictive of a higher rate of recurrence are neurological deficits at birth, (Annegers et al., 1986, Hart et al., 1990) age less than 16 years, (Blom et al., 1978, Costeff, 1965, Hart et al., 1990, Hirtz, Ellenberg & Nelson, 1984) age over 65 years, (Hart et al., 1990) and partial seizures (Annegers et al., 1986, Blom et al., 1978, Goodridge & Shorvon, 1983, Hart et al., 1990, Hirtz et al., 1984) Although patients with generalised spike wave EEG discharges also have high recurrence rates. (Blom et al., 1978, Cleland et al., 1981, Hauser et al., 1982, van Donselaar et al., 1991)

1.1.1.3. Effect of AED on recurrence rate after initial seizure

In descriptive studies there is no attempt to control for AED treatment effects, so that patients with more severe seizures are more likely to be treated. Thus both Hauser and Hirtz found no affect of treatment on risks of recurrence. (Annegers et al., 1986, Hauser et al., 1982, Hirtz et al., 1984), although other descriptive studies have found the risk for recurrence to be lower for patients on treatment (Hopkins et al., 1988) An important study has recently been reported from Italy which randomised patients to treatment or no treatment after the first seizure. (First Seizure Trial Group, 1993) Although there were some deficiencies in the study design, such as lack of randomisation and exclusion of patients with early recurrences, it was the first study to systematically assess the effect of early treatment. The

risk of relapse among treated subjects was 25% by 24 months and 51% for untreated subjects, and they calculated that the risk of a second seizure was 2.8 times higher in the untreated group.

1.1.2. The remission of epilepsy

The remission of epilepsy is the seizure free period experienced by a patient who has had one or more seizure. Remission is important as it is a marker for the end of the disease, and is the ultimate goal of both clinician and patient. Remission may be permanent or temporary and the seizure free period may be defined for variable lengths of time. There are a number of factors which affect the chances of a patient entering remission, and also of relapsing from it. I will first discuss the historical aspects, then the influence of study design on our understanding of remission, and then review the current literature on remission.

1.1.2.1. Historical aspects

Gowers was the first to systematically examine the prognosis of epilepsy in patients he had observed at the Hospital for Nervous diseases. (Gowers, 1885) He wrote that "...the spontaneous cessation of seizures is an event too rare to be anticipated in any given case" and that "each attack facilitates the occurrence of another". (Gowers, 1885) This rather gloomy opinion on prognosis was reinforced by Habermas who reported a remission rate of only 10%. (Habermas, 1901) Even in those early days treatment was available, and Gowers observed that Bromides were effective in reducing seizure frequency. The effectiveness of this early treatment was demonstrated by Turner who reported good seizure control in 33% of his patients using Bromides. (Turner, 1907)

After the war in the 1950s a more rigorous approach to the investigation of the prognosis of epilepsy was adopted, with larger numbers of patients studies and with more prolonged follow up. In one study in which patients were followed up for over 5 years Alstrom calculated a total 5 year remission rate of 29.2% for idiopathic seizures and only 14% for patients with a known underlying cause. (Alstrom, 1950) A number of other authors found that patients with neurological deficits or EEG abnormalities tended to fare significantly worse. (Arief, 1942, Brain, 1951, Strobos, 1959) Later, the beneficial properties of the newer AEDs were reported in a large study by Juul-Jensen. (Juul-Jensen, 1964) This study was also the first to

document the effect of AED withdrawal, which increased the risk of relapse, even after a period of prolonged remission. (Juul-Jensen, 1964)

The watershed in our understanding of the remission of epilepsy came in 1968 when all the work up to that date was reviewed by Rodin, who then added his own observations. (Rodin, 1968b) His study comprised three retrospective studies: a study of 32 patients less than 10 years old and seen more than 5 years previously at the Michigan Epilepsy Centre, USA, 222 patients, also at the Michigan Centre, but without an age limitation, and 122 patients attending the Laffayette clinic, who were followed for more than 2 years, and up to 7 years. Only 32% of the 222 were seizure free for more than 2 years, and 17% were seizure free for more than 5 years. There was a worse prognosis for psychomotor seizures, if patients had more than one seizure type, a history of status epilepticus, or if patients had an abnormal EEG. In the 122, only 26% achieved a remission of more than 6 months after 2 years. Rodin concluded by echoing the sentiments of Gowers with a pessimistic view of the prognosis of epilepsy, stating epilepsy was "a chronic condition characterised by a tendency to seizure relapse". This early work is summarised in table form (table 1).

Table 1 *Studies of epilepsy prognosis prior to 1968*

Study	Number	% in remission	Duration of remission
Habermas, 1901	937	10	2
Turner, 1907	212	33	2
Kirstein, 1942	174	22	3
Alstrom, 1950	897	22	3
Strobos, 1959	228	38	1
McNaughton, 1954	257	30	1
Kiorbie, 1961	130	32	4
Trolle, 1961	437	42	1
Juul-Jensen, 1964	969	32	2
Kuhl, 1967	173	34	4
Rodin, 1968	222	32	2

1.1.2.2. Methodological problems and considerations

Understanding study design is crucial before the results of the epidemiology of epilepsy can be interpreted. I will therefore examine the problems that have been encountered in the past and the way this has affected ideas about the remission of epilepsy.

1.1.2.2.1. Patient selection

1.1.2.2.1.1. Definition and classification of epilepsy

Epilepsy is a symptom with many causes, and in order to examine prognosis studies require clear definitions and a comprehensible classification system. For instance, there are a number of studies of epilepsy prognosis that have not stipulated the criteria used for the definition of epilepsy. (Juul-Jensen & Foldspang, 1983, Wagner, 1983) Lack of such definitions has lead to inability to interpret results, and makes comparisons with other studies difficult. For example, the recurrence of seizures is thought to be a sine qua non of the definition of epilepsy, however, much of the more recent work on the prognosis of single seizures has shown that single seizures themselves have a high likelihood of recurring, so that the distinction between epilepsy and an isolated seizure is probably artificial. (Chadwick, 1991, Hart et al., 1990) The need for a unified system of epilepsy definitions which would enable researchers and clinicians to work to a common standard lead to a number of attempts at classification. The present and most widely accepted classification of epilepsy based on the syndromic type of epilepsy, was produced by the International League Against Epilepsy (ILEA). (Commission on Terminology and Classification of the International League Against Epilepsy, 1989a) This was designed, not only to be workable, but also comprehensive, with classification giving a guide to prognosis. In a clinical setting the syndromic ILEA classification can be difficult to apply, and one study which assessed this in a normal out-patient population found a reliability of about 50% (Fetski, Kaamugisha, Sander, Gatti & Shorvon, 1991) The ILEA classification also came too late to be used by most earlier studies. Modifications of the ILEA seizure classification system have been used in some prognosis studies. (Goodridge & Shorvon, 1983, Okuma & Kamashiro, 1981)

1.1.2.2.1.2. Difficulty of diagnosis

There are considerable problems in diagnosing patients with epilepsy and patients with epilepsy may even conceal the diagnosis. (Beran, Hall &

Michelazzi, 1985, Cockerell, Sander & Shorvon, 1993) The diagnosis rests on a clinical description of the seizure and therefore there is little room for improving the diagnostic validity without some form of gold standard test. Inter-observer reliability is also low, even among trained neurologists, with a Kappa value of 0.58 reported in one study. (Van Donselaar, Geerts, Meulstee, Habbema & Staal, 1989) In a psychiatric hospital population of epileptics, 20% of patients originally diagnosed as having epilepsy did not have epilepsy after a more detailed examination. (Betts, 1983) In the Rochester study, the time from first seizure to diagnosis took more than 6 months in over 50% of patients, and in 30% the delay was over 2 years. (Hauser & Kurland, 1975) In another study the median time to treatment was over 6 months. (Goodridge & Shorvon, 1983) In the NGPSE at 6 months there were 224 patients who still had a diagnosis of possible or probable epilepsy. (Sander, Hart, Johnson & Shorvon, 1990) The difficulty of making a diagnosis, and the time this often takes, means that if studies do not include patients with possible seizure disorders there will be tendency to exclude specific subgroups of patients in whom the diagnosis is particularly difficult. For instance, patients with infrequent seizures, or patients who live alone, such as the elderly. All these patients have a lower chance of having one of their seizures witnessed and therefore achieving an accurate and early diagnosis. All the studies to date have largely ignored this problem, apart from the NGPSE, and have often just selected patients with a diagnosis of definite epilepsy. (Annegers et al., 1986, Blom et al., 1978, Cleland et al., 1981, Goodridge & Shorvon, 1983)

1.1.2.2.1.3. Patient population characteristics

Unless heterogeneous populations are used there will be problems concerning the wider applicability of such studies. Numerous studies have only included patients referred to university hospitals or special epilepsy clinics. (Collaborative Group for the Study of Epilepsy, 1992, Kuhl, Kiorboe & Lund, 1967, Okuma & Kamashiro, 1981, Strobos, 1959) Not all patients with seizures attend hospital, and in the UK many patients will be seen by other specialists, such as general physicians. (Crombie, Cross, Fry, Pinsent & Watts, 1960, Hart, 1992) This introduces bias due to selection of a particular type of patient, with under representation again of the elderly and the less severely affected. The Rochester studies, which were in a population-based population, may also have their deficiencies. (Annegers, Hauser & Elveback, 1979, Hauser & Kurland, 1975) The Rochester population is a homogenous, mainly white, middle class population whose

ancestors were from Scandinavia and central Europe, and so evidence from this population may not be applicable outside Rochester itself. (Dorn, 1950) Other studies have been limited to even narrower populations, such as insured patients, (Livingston, 1963) or service personnel. (Johnson et al, 1972)

1.1.2.2.1.4. Inclusion / exclusion criteria

The exclusion of particular types of patients will have an obvious effect on the remission rates, and, for example, the exclusion of patients with high relapse rates will increase the overall remission figures. As described above, the criteria for the definition of epilepsy used is crucial, and depends upon the authors conception of what constitutes epilepsy. Single seizures are usually not considered to be epilepsy per se, and thus most studies of epilepsy prognosis have not included patients with single seizures, (Annegers et al., 1979, Hauser & Kurland, 1975, Ross, Peckham, West & Butler, 1980) whilst others have. (Cooper, 1965, Goodridge & Shorvon, 1983) Eliminating such patients will lower the remission rates, as such patients have a better outlook. (Elwes, Johnson & Reynolds, 1988) In a large Italian study patients were excluded who had an obvious treatable cause for their epilepsy, such as a metabolic disturbance, or if there was a cause that would increase the relapse rate such as a brain tumour. (Collaborative Group for the Study of Epilepsy, 1992) It also only included patients who had been started on AEDs, thereby leaving out patients who were perceived (by themselves or their physician) to have a less serious disorder. One study actually excluded patients who did not have an abnormal EEG on at least 2 occasions, (Strobos, 1959) stringent criteria that many patients with epilepsy don't meet. In one of the Rochester studies patients were only selected who had EEGs performed, and no attempt was made to explain any bias that might result from excluding patients who were probably less severely affected or who had poorer access to such facilities. (Shafer, Hauser, Annegers & Klass, 1988) Febrile convulsions are a separate sub-group of patients with epilepsy with a generally favourable prognosis so that most studies have not included them with the analysis of epilepsy , however this is not a consistent approach and was not done in one study. (Holowach, Thurston & O'Leary, 1972)

1.1.2.2.2. Temporal aspects

A critical factor in delineating the prognosis of epilepsy is the point in time from which the patient is followed. Some studies have taken a cross section of patients with established epilepsy, and then calculated the overall prognosis of epilepsy. (Kuhl et al., 1967, Rodin, 1968a) This however will give a distorted view. Most patients enter long term remission soon after the time of diagnosis, and cross sectional studies will mostly be composed of patients with chronic epilepsy with a much lower rate of remission. In the Rochester study the net probability of achieving remission within 10 years was 65%, but patients who were not in remission 5 years after diagnosis had a lower chance of achieving remission of only 33%. (Annegers et al., 1979) Thus, unless patients are followed from the time of diagnosis the remission rates will be significantly underestimated. (Shorvon, 1984)

1.1.2.2.3. Definition of remission

It has often been difficult to compare the remission rates between different studies because different definitions of remission have been used. Hauser considered the best measure of remission to be a seizure free period of 5 years without AED medication at the time of the latest follow up, although he did also provide figures for 2 year remission, and for remission whilst on treatment. (Hauser & Kurland, 1975) This may be a valid definition, as it is only when patients are off medication that the stigma of having epilepsy, and risks of side effects, are removed. However, most authors would not consider the AED status as a criteria for remission, and Annegers and Hauser in their extended observations of the same cohort were later to redefine remission as a 5 year period free from seizures regardless of AED treatment. (Annegers et al., 1979) Some authors have used terminal remission, (Goodridge & Shorvon, 1983) which is the number of patients in remission at the time of the survey. Terminal remission will only be equal to the other measures of remission if there are no relapses after a period of remission has been entered. Comparing terminal and non-terminal remission will therefore give an idea of the relapse rates, and it is most helpful if both can be given. In some studies no definition of remission is given at all. (Juul-Jensen & Foldspang, 1983)

1.1.2.2.4. Retrospective versus prospective studies

Retrospective studies are easier to undertake, but less reliance can be placed on their results. With a prospective cohort the classification, end-points, and inclusion or exclusion criteria can be clearly defined from the start of the

study, which is difficult to do retrospectively. It is also more difficult to detect a source of bias when this is done retrospectively. The changing habits of doctors over the years means that certain details may become more or less likely to be recorded by routine. This must be more problematic when the age of the retrospective sample becomes very old. For instance the Rochester cohorts go back to 1935, (Annegers et al., 1979, Hauser & Kurland, 1975) and it is hard to believe that the methods of clinical application and the recording of clinical information have been totally uniform over all these years.

1.1.2.2.5. Length of follow up

Rodin noted that the prognosis of epilepsy is inversely proportional to the length of follow up. (Rodin, 1968b) This is probably because his patients were drawn from hospital clinics and were weighted towards a worse prognosis. Studies of newly diagnosed patients followed for just one year have given excellent prognostic figures with 80% remission rates. (Feely, O'Callaghan, Dugan & Callaghan, 1980, Ramsay et al., 1983b, Turnbull, Rawlins, Weightman & Chadwick, 1982) In a large Italian multi-centre study, the average length of follow-up was 21.6 months (range 2-40), and seizure relapse occurred in 52% of cases during follow-up (36% by 3 months, 43% by 6 months, and 49% by 12 months). (Beghi & Tognoni, 1988) As discussed, the meaningful measurements of remission are of at least two years, and so the outcome after just one year is an inadequate measure, and is not much better with just two years follow up. Longer follow up might be expected to decrease the rates proportionally, but as many of the more prolonged follow up studies were population based, the reverse effect is seen because there are much higher proportions of less severely affected individuals, which will therefore tend to increase the remission rates. (Annegers et al., 1979)

1.1.2.2.6. Lost patients

The inability to comment on a group of patients because of lost follow up can seriously damage the validity of a study. A comment on lost follow up was made by a famous epidemiologist called Dorn, who said that the only way to deal with it was "not have any". (Callaghan, O'Callaghan, Dugan & Feely, 1978) Researchers have to justify the numbers of non-responders and how these may have affected results. (Kahn & Sempos, 1989) In a Japanese study over 42% of patients were not followed up, but an attempt was made

to explain how this would affect the results, claiming that the lost patients did not differ substantially from the patients under observation. (Okuma & Kamashiro, 1981) The remission of lost patients is included in actuarial analysis, although if too many have been lost, a falsely pessimistic figure will result. (Beghi & Tognoni, 1988) The Rochester study was apparently able to follow up all but 18 of the 618 patients and claimed that the data obtained was complete, even though this may have been collected over the telephone, or by speaking to relatives. (Annegers et al., 1979) Interestingly, a later study on the same population was not able to trace 172 out of the 732 patients ascertained. (Shafer et al., 1988)

1.1.2.2.7. Statistical analysis

Most patients relapse from remission early in the course of the illness. Therefore a simple proportional analysis of the percentage of patients with epilepsy in remission is of little value unless the time of onset of the epilepsy is taken into account. Kuhl examined the remission rate in a population of patients with seizures but no attempt was made to measure the rate against time of onset, thus a patient with epilepsy for 20 years would have been included with new onset cases making the results meaningless. (Kuhl et al., 1967) This was a similar problem in other studies. (Wagner, 1983)

Life table methods provide an convenient method of analysing cohorts of patients as they progress over time. It has a facility for including patients recruited at different times, and has been established for many years. However there are problems with its usage in studies of epilepsy prognosis. The life table needs an end point for each patient such as relapse of seizures. After that, the patient is excluded from analysis, so that, for instance, should the patient go into another remission he will not be included in the at risk group. This may not be a major distortion as only about 12% of patients have such an intermittent pattern, (Goodridge & Shorvon, 1983) and if both cumulative and terminal remission is calculated such differences can be assessed.

1.1.2.2.8. Treatment as a biasing factor

To accurately gauge the prognosis of epilepsy it is necessary to have an unbiased set of factors operating on the whole cohort and the effect of various treatments may compromise this. For instance, in a study of newly diagnosed patients, all were started on AEDs, but there was no

randomisation, meaning that patients may have entered remission or not entered remission because of correct or incorrect drug treatment. (Beghi & Tognoni, 1988) Withdrawal from treatment is an important stimulus for relapse. (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991) In Rochester about two thirds of patients who relapsed were not on treatment suggesting that this may have been causal, but more detailed information on this was not given. (Annegers et al., 1979) All modern trials have included a sizeable group on treatment, but unless details are given it is difficult to assess the role of treatment compared to the natural history of the condition.

1.1.2.3. Natural History

One of the most important aspects of remission is the natural history of the condition unaffected by treatment. We have already seen that treatment may bias study results and so an idea of what happens in the natural setting would be an important piece of evidence. Information on the natural history has come from two areas of study:

1.1.2.3.1. Drug naive data from the developed world

The availability of effective anticonvulsant treatment since the 1850s, with the introduction of Bromides, has made it unethical to follow up patients with epilepsy who have had treatment withheld, and so all studies refer to the treated form of the disease. Although in some studies there are a small percentage of patients who were not treated it is difficult to extrapolate information from an untreated group into any unbiased conception of the natural history of untreated epilepsy. In a retrospective study carried out in eastern Finland, 33 out of 1375 patients were identified as never having been treated, (Keranen & Riekkinen, 1993) and the probability of achieving a 2 year terminal remission was 42% at 10 years, and 52% at 20 years. In another study over 30% of patients never receiving medication were in 5 year remission. (Gudmundsson, 1966, Zielinski, 1974) This suggests that untreated epilepsy may run a benign course, although other reasons for not treating patients, such as less severe seizures, were probably operating.

1.1.2.3.2. Incidence and prevalence studies in the developing world

The cumulative incidence of a disease is the total number of cases of a condition that have ever arisen in a population in a lifetime. The cumulative

incidence of epilepsy in Europe and the USA is between 10-30 per 1000 whereas the prevalence of active epilepsy is between 2-4 per 1000. (Kurland & Molgaard, 1981) This disparity between the figures suggests that the prognosis for patients developing epilepsy is relatively good with most patients entering a period of prolonged remission. In the developed world one could speculate that this was due to the wide spread usage of AEDs.

In the third world the resources for the treatment of epilepsy often do not exist and many patients with epilepsy have never been treated. If AEDs really do influence the natural history of epilepsy, then we might expect that the prevalence of active epilepsy would be much higher in the third world. The populations of untreated patients therefore gives an opportunity to look at the natural history of epilepsy and to test whether wider availability of AEDs in the developed world has lead to a lower prevalence of active epilepsy, and whether there is the same difference between cumulative incidence and prevalence in the third, as there is in the developed world.

The first studies did suggest that there was a higher prevalence of epilepsy in the third world, however these studies were in small selected samples with particular reasons for their high prevalence rates such as high rates of parasitic disease. (Osuntokun, Adeuja & Nottidge, 1987, Sander & Shorvon, 1987) Generally, data from other third world countries give very similar prevalence rates to the developed world, with prevalence rates of active epilepsy being 0.53% in Nigeria, (Jilek-Aal, 1965) 0.52% in Ethiopia, (Placencia, Paredes, Cascante, Sander & Shorvon, 1992) with similar figures from India, (Li, Schoenberg & Bolis, 1985) and China. (Tekle-Haimanot, Forsgren & Adebe, 1990) Assuming that the incidence and death rates are similar in the developed compared to the third world, this data shows that patients in the third world who usually are not treated, have the same chances of entering remission as patients in the developed world.

In a recent and thorough epidemiological study in Ecuador, a well validated case ascertainment method was applied to a population of 75,000 people. (Placencia et al., 1992) The cumulative lifetime incidence was 1.9% compared to a prevalence rate of active epilepsy of 0.67%, suggesting that at least 50% of people developing epilepsy go into long term remission regardless of treatment. A similar conclusion was reached in a study that ascertained 460 patients with epilepsy in Malawi. (Watts, 1992) It was found that as the duration of active epilepsy increased, the number of

patients having epilepsy of a given duration decreased. Possible explanations for this result, such as an increasing incidence of epilepsy or a high mortality rate, were thought to be unlikely. The distribution of patients with epilepsy of differing duration was similar to the Tonbridge study, (Goodridge & Shorvon, 1983) where the number of patients in remission was found to increase over time. It was postulated that the observed distribution reflects remission, and that spontaneous remission of epilepsy is a frequent occurrence, independent of AED treatment.

1.1.2.4. Overall remission rates from hospital-based studies (post 1968)

1.1.2.4.1. Retrospective

As we have discussed, the combination of retrospective study and hospital populations, even if all patients are than analysed, is liable to bias on two counts. However a number of large studies have been reported since the work of Rodin (see table 2). The Group for the Study of Prognosis of Epilepsy in Japan looked at 1,868 patients who had been seen in 20 neurological institutions between 1964 and 1974. (Okuma & Kamashiro, 1981) As noted above they encountered considerable problems with follow up and 1,868 represents only 42% of the patients who had attended the hospitals. The remission rates surprisingly showed little difference when examined at 3, 5, and 10 years, which were about 58%. A similar study from Denmark examined the seizure status of 1,505 patients who had been registered at diagnosis by means of a card system used by all the specialist and general hospitals in a specified region around the town of Aarhus. (Juul-Jensen & Foldspang, 1983) The prognostic figures were given as a crude percentage of patients who were seizure free, without mention of length of follow up, and varied from 47% for patients with primary generalised epilepsy, to 28% for patients with complex partial seizures. An almost identical study, also in Denmark, from outside Copenhagen, was reported, and although attempts were made to ascertain patients in the community, this was incomplete, missing at least 10% according to the authors, and probably many more. (Wagner, 1983) Again, remission rates were given as crude percentages at last follow up, and 31% were in remission of over 3 years.

1.1.2.4.2. Newly diagnosed

There are a number prospective studies of newly identified or untreated patients with epilepsy presenting to hospitals and special clinics. (Beghi & Tognoni, 1988, Bharucha & Bharucha, 1988, Collaborative Group for the Study of Epilepsy, 1992, Elwes, Johnson, Shorvon & Reynolds, 1984, Feely et al., 1980, Juul-Jensen & Foldspang, 1983, Mattson, Cramer & Collins, 1992, Okuma & Kamashiro, 1981, Ramsay et al., 1983b, Richens, Davidson, Cartlidge & Easter, 1994, Shorvon & Reynolds, 1982, Turnbull et al., 1982, Wagner, 1983, Yahr, Sciarra, Carter & Merritt, 1952) Many of these studies of prognosis have been in the context of drug trials undertaken to test the efficacy of particular AEDs, (Callaghan et al., 1978, Camfield, Camfield, Smith & Tibbles, 1985, Feely et al., 1980, Ramsay et al., 1983a, Ramsay et al., 1983b, Richens et al., 1994) nevertheless they do provide information on the short term prognosis of treated epilepsy in a hospital population, bearing in mind that generally none of the modern AEDs have been shown to be any more effective than each other, and the limitations of using hospital populations as a standard for epilepsy as a whole. Also, most of the AED trials addressed their enquiry to patients with previously untreated seizures rather than new onset seizures per se. Patients with newly diagnosed or previously untreated seizures may still have had seizures for many years, and as we have already seen the prognosis of epilepsy is closely related to the time from onset. Some of these trials were also in small numbers of patients and follow up was often only up to one or two years, the outcomes measures being ratings such as "complete seizure control" with no definition of remission attempted.

Two small studies from Ireland tested the efficacy of carbamazepine in 13 patients, (Feely et al., 1980) and phenobarbitone in another 13. (Ramsay et al., 1983b) Both AEDs achieved over 80% remission with a variable period of follow up, between 7-32 months, (Feely et al., 1980) and 8-13 months. (Ramsay et al., 1983b) A larger study compared valproate with carbamazepine in 88 newly diagnosed adult epileptic patients. (Turnbull et al., 1982) Remission rates over 12 months were 71% for phenytoin and 83% for valproate. A more definitive comparison was made in two American double blind studies (Mattson et al., 1992, Yahr et al., 1952) One recruited 87 patients and treated half with either phenytoin or carbamazepine with limited follow up for between 7-24 months, and achieved 81.5% complete control with carbamazepine and 85.8% with phenytoin. (Yahr et al., 1952)

In the other study carbamazepine was compared with valproate in a large double blind study of 480 previously untreated or under-treated patients. (Mattson et al., 1992) When assessed at 12 months 34% of the carbamazepine and 30% of the valproate treated patients were rendered seizure free. These figures are worse than other studies of AED efficacy because of the cross-sectional design which included many patients who had chronic epilepsy, nearly half having received previous AEDs, or were even still taking them. A recent trial compared valproate against carbamazepine in newly diagnosed adult patients seen in a specialist clinic. (Richens et al., 1994) 149 patients received valproate and 151 received carbamazepine. After 3 years of follow up 80% of patients had achieved a one year remission and 60% a two year remission. Interestingly the rates were similar for the two drugs, and also for partial as well as primary generalised epilepsy.

A more complete understanding of the prognosis for seizure control in newly diagnosed patients presenting to an adult neurology clinic comes from the Kings College Group. (Elwes et al., 1984, Shorvon & Reynolds, 1982) They recruited 106 patients who presented to the adult neurology clinic with two or more tonic-clonic seizures, or enough partial seizures to warrant treatment, and either began treatment with carbamazepine or phenytoin. In the first report they looked at the prognosis over a follow up period of a mean of 32 months. (Shorvon & Reynolds, 1982) 57% of patients were seizure free throughout the study at 12 months, and this only fell at 36 months to 50%. Further analysis was presented after a median of 66 months, and 26% of patients were still seizure free since the onset of treatment. (Elwes et al., 1984) Actuarial analysis showed that the proportion who had a remission of 3 years from the start of treatment had risen to 73% at 4 years, and 82% at 8 years.

A multi-centre prospective study was carried out in Italy on a population of newly referred patients seen in specialist hospital clinics. (Beghi & Tognoni, 1988, Collaborative Group for the Study of Epilepsy, 1992) In the more recent report, 280 patients (mysteriously, there were 283 in the earlier report) were identified. Patients of all ages and types of epilepsy were included, but the definition of epilepsy was rather loose: "previously untreated afebrile seizures", and it was not clear if single seizures had been excluded. Also, patients with an increased risk of seizures (e.g. CNS tumours) were excluded. This is conceptually unsatisfactory as tumours are

often diagnosed late, and presumably patients with dysembryoblastic neuroepithelial tumours or even mesial temporal sclerosis were included, but they certainly have a greatly increased risk of seizures. Even by 1992 the numbers followed up for useful lengths of time were small, even though case collection took place between 1982-85. 228 patients (81%) were followed for 2 years and 81 (28.9%) for 5 years. 77% of patients had a 1 year remission at some time over the follow up, and 70% had a 1 year terminal remission. 78% of patients had a 3 year remission at some time by 5 years. These optimistic results are in broad agreement with the Kings group, however, the populations were different, and the Italian study included children, and, as discussed, excluded patients with symptomatic epilepsy.

1.1.2.5. Population-based studies

One of the first population based studies of epilepsy was carried out in 1960 by the Royal College of General Practitioners. (Crombie et al., 1960) 134 GPs were surveyed over one year and asked to record any patient with a fit or convulsion of any kind. Out of 44% of patients with chronic grand mal epilepsy 42% had no seizures over the one year period.

The GP primary health care system was used in a more detailed analysis of seizures in a population of 6,000 people from a single general practice in Kent. (Goodridge & Shorvon, 1983) 6,000 medical records were examined retrospectively for a history of at least one non-febrile seizure of all types and aetiologies, and the patients later interviewed After 1 year from the onset of the first seizure half the patients still had active epilepsy, and at 5 years from onset, over 50% had entered a remission of 2 or more years, and slightly less entered a remission of 4 or more years. At 15 years from onset nearly 70% had achieved a 2 year remission.

There have been three important studies looking at the prognosis of epilepsy in Rochester, USA. (Annegers et al., 1979, Hauser & Kurland, 1975, Ramsay et al., 1983a) In 1975 Hauser reported on the prognosis of 516 patients who had been seen in one of the Mayo linked clinics between 1935 and 1967. (Hauser & Kurland, 1975) After 10 years from diagnosis 40% had achieved a 2 year terminal remission, which rose to 49% at 15 years and 55% at 20 years. These observations were extended and expanded by Annegers to include 102 further patients who had been seen up to 1974. (Annegers et al., 1979) For all the 457 patients followed for 5 years or more 65% were in a 5 year remission within 10 years and 76% within 20 years.

The 5 year terminal remission rates were 61% at 10 years and 70% at 20 year. Both studies excluded patients with isolated single seizures, febrile seizures, and acute symptomatic seizures. The latest report analysed 306 patients diagnosed up to 1978, with the probability of reaching 20 years and having a five year seizure free period equal to 75%. (Ramsay et al., 1983a)

Table 2 *Studies of epilepsy prognosis after 1968*

Study	Population of study	Number	% in remission	Remission (years)
Currie, 1971	Hospital*	666	40	1
Janz, 1976	Hospital	396	72	2
Blom et al, 1978	Hospital	43†	56	1
Annegers et al, 1979	Community	618	70	5
Okuma et al, 1981	Hospital	1838	58	3
Sofijanov, 1982	Hospital†	512	42	4
Shorvon & Reynolds, 1982	Hospital	94	83	-
Schmidt, 1984	Hospital*	82	22	-
Camfield et al, 1985	Hospital†	82	59	-
Goodridge & Shorvon, 1983	Community	112	70	4
Brorson & Wranne, 1987	Hospital†	194	78	3
Shafer et al 1988	Community	306	75	5
Elwes et al, 1988	Hospital	106	82	2
Beghi et al, 1988 & 1992	Hospital	283	78	5
Sillanpaa, 1993	Hospital†	178	74	5

* TLE only

† Children only

1.1.2.6. Drug withdrawal

It is not possible to carry out placebo controlled trials of AED treatment of epilepsy, because of the ethical concern. Although up to 80% of patients with epilepsy who are started on AED therapy enter remission, it is possible that this reflects the natural history of certain types of epilepsy rather than any beneficial treatment effect. One way at looking at the effect of treatment is to study the relapse rate after drug withdrawal. Studies of the prognosis of epilepsy have usually included a proportion of patients who withdraw from treatment, either due to poor compliance or under the direction of their physician. (Annegers et al., 1979, Goodridge & Shorvon, 1983) Most patients in the USA are started on AEDs when they develop seizures and Annegers reported that two thirds of the patients who relapsed were not on AEDs, suggesting that this may have been a factor in causing the relapse, although the temporal relationships between relapse and stopping were not always consistent. (Annegers et al., 1979) Other studies of early prognosis have shown relapses are often due to poor compliance or withdrawal for other reasons. (Bharucha & Bharucha, 1988, Ramsay et al., 1983b) However, this observational data is not conclusive as there are many other factors which prompt drug withdrawal, for instance, young patients with well controlled seizures are more likely to be non compliant, whereas patients with intractable seizures with other associated neurological problems are more likely to be maintained on treatment.

As most patients enter a sustained remission there are risks of continuing treatment because all the AEDs have associated side effects. (Shafer et al., 1988) This makes drug withdrawal a reasonable and ethical option to consider in patients who have been seizure free for ascertain length of time. The effect of AED withdrawal has been tested in a number of studies. These have been in two main patient groups: covering all ages, and those only including children.

1.1.2.6.1. Studies including all age groups

One of the first studies to systematically tackle this subject was by Juul-Jensen. (Juul-Jensen, 1964) He recruited 200 patients who had been seizure free for at least 2 years and attempted slow discontinuation of AEDs over 2-3 months. In 2 years 35% relapsed, with 3 patients relapsing after 2 years. The frequency of relapse did not seem to be related to the rate of withdrawal or type of epilepsy, or indeed to any other variables apart from

certain EEG abnormalities. Juul-Jensen's conclusion that "withdrawal of anticonvulsant therapy should only be contemplated in very suitable cases" has not been greatly improved upon, in spite of a major flaw in the study design, which was the absence of a control group. The same error was made in two further studies. One study enrolled 92 patients who had been seizure free for 2 years, (Schmidt, 1982) and the other from Holland, which enrolled 62 patients who had been seizure free for 3 years. (Callaghan, Garrett & Goggin, 1988) The range of relapses were from 39% to 66% with no prior predictors of outcome, even between children and adults. The differing rates can probably be explained by different length of follow up, and in the Dutch study the age range of patients recruited was between 18-60 years. (Callaghan et al., 1988)

Arguably the best study of AED withdrawal has recently been carried out by the Medical Research Council. (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991, Overweg, Binnie, Oosting & Rowan, 1987) 1013 patients who had been seizure free for two years were randomised to continued treatment or slow withdrawal. Interestingly the group which continued treatment still had a significant relapse rate of 22% by 2 years, making the results of the non randomised studies described above virtually worthless. However, the relapse rates of patients on slow withdrawal of 41% were even worse. The study group later tested variables for their predictive value and found that age over 16 years, polytherapy, a history of seizures after starting AED treatment, a history of tonic-clonic seizures, myoclonic seizures, and an abnormal EEG, were all indicators of a higher chance of relapse after withdrawal. (Overweg et al., 1987)

1.1.2.6.2. Studies confined to children

The situation in children with epilepsy should provide a more favourable environment for AED withdrawal because of the excellent natural history of many childhood epilepsies, with may entering natural remission in late childhood or adolescence. (Gram, 1990) This good outcome has been confirmed in a number of studies with relapse rates between 19.5% and 31%, depending on the length of follow up and criteria for withdrawal, which is usually a seizure free period of 2 or 4 years. (Arts et al, 1988, Emerson, D'Souza, Vining, Holden, Mellitis & Freeman, 1981, Hollowach, Thurston & O' Leary, 1972, Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993, Shinnar et al, 1985, Thurston, Thurston,

Hixon & Keller, 1982, Todt, 1984) Adverse factors were found in some studies, such as abnormal EEGs, family history, grand mal seizures, and presence of neurological deficits, but not in all, (Hollowach et al., 1972) Earlier age of withdrawal was favourable in most, but not all studies. (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1993) Again none of these studies compared the withdrawal group with a group on continued treatment, probably because of the ethical difficulties of doing this, as withdrawal appears to be a favourable outcome in most children with epilepsy.

1.1.2.7. Factors affecting prognosis

So far the overall prognosis for all patients with epilepsy has been examined and I have not commented on factors that exert an influence on outcome. Epilepsy is not a single disease but rather the clinical expression of a large number of differing brain disorders. To talk about the overall prognosis for epilepsy may be misleading. For instance, the prognosis for a child with benign Rolandic epilepsy is better than that for a patient with a progressive degenerative neurological condition. Therefore the factors affecting the prognosis of different types of patient with epilepsy are probably of even more interest than figures which give overall remission rates.

1.1.2.7.1. Age

1.1.2.7.1.1. As a dependent variable in studies which have included all ages

The majority of studies have found that youth is a predictor of a better outcome. (Annegers et al., 1979, Hauser & Kurland, 1975, Ramsay et al., 1983a) Although this was not always confirmed. (Collaborative Group for the Study of Epilepsy, 1992, Goodridge & Shorvon, 1983) There is no adequate explanation for this discrepancy. All the studies included about 20% under the age of 16 years, and no explanation is forthcoming when the method of statistical analysis, or the type of study, i.e. prospective versus retrospective, or population versus hospital based, is compared.

1.1.2.7.1.2. Studies of prognosis in children

There has been considerable interest in assessing the prognosis of epilepsy in children. Unfortunately many of the difficulties in examining this aspect of outcome, as discussed above, have been especially apparent in studies of children. The frequency of different classifications and their application has

been a source of confusion in studies of children, and relating the results of one study to the next can be difficult. Also, all the studies, whether retrospective or prospective, have been in hospital based populations with all the pitfalls of selecting patients with necessarily worse epilepsy.

Studies including all seizure types- A number of studies have looked at the prognosis of an unselected population of children with all types of epilepsies, usually attending a specialist paediatric epilepsy clinic. Sofijanov followed 512 patients retrospectively, aged 2 months to 14 years for between 4 to 10 years. (Sofijanov, 1982) Patients were included regardless of the chronicity of their seizures and new and old onset cases were analysed together making interpretation of his results difficult. Nevertheless, there were rather similar remission rates to adult studies described above with 50.6% entering a 2 year terminal remission and 42.2% entering a 4 year terminal remission. Bad prognostic factors were early age of onset and generalised seizures. A better prognosis was found by Brorson and Wranne who made a concerted attempt to identify all childhood seizures occurring in a defined population in Uppsala, Sweden. (Brorson & Wranne, 1987) This accounts for overall figures for children with normal neurology and intellects, with only 11% after 12 years of follow up still having active epilepsy (defined as one or more seizures occurring in the previous 3 years). For children with neurological deficits, only 3% after the first year entered a remission. Less informative studies have also reported on the remission rates. One recruited a cross sectional sample of children and compared their treatment with carbamazepine alone against polytherapy. (Bouma, Peters, Arts, Stijnen & Rossum, 1987) After a mean follow up period of 7 years 74% of the CBZ monotherapy patents were seizure free for more than 3 years. Camfield recruited 82 newly diagnosed children and started them on various AEDs. (Okuno et al, 1989) He found that 41% had recurrent seizure in the first 6 months, but after this no patients who were controlled had a later relapse, although follow up of these patients was inadequate with a mean of 19 months.

Absence epilepsy- The earliest concepts about the prognosis of absence seizures (AS) were very favourable with the belief that patients with absence seizures did not develop grand mal seizures or mental retardation. (Camfield et al., 1985) However this changed when studies began to utilise EEG diagnosis and it was found that some patients had persistent attacks or developed other seizure types. (Friedmann, 1915, Janz, 1955, Paal, 1957)

One of the largest studies was reported in 1969 by Dalby on a retrospective series of 436 patients that had EEGs done at the Aarhus Municipal Hospital. (Dalby, 1969) Patients were selected on the basis of spike and wave EEGs, and patients with typical and atypical EEGs were included, as well as children with abnormal EEGs but without epilepsy. The total risk of relapse after one year free of seizures, was 7% for patients with pure "petit mal", and for cases complicated by focal discharges, or other seizure types, the relapse rate was higher at 30.8%. Dalby found that the worse prognostic factor was the development of grand mal seizures, far outweighing the effects of brain damage or the EEG appearance. This outcome was confirmed by a prospective prognostic study which recruited 52 patients seen in a specialist neurology unit. (Sato, Dreifuss & Penry, 1976) After 6-8 years from diagnosis over 90% of patients with uncomplicated AS had become seizure free, although "seizure free" was not defined, 19 patients did not have any seizures for more than 5 years. When AS was accompanied by mental retardation or abnormal background EEG activity, the outlook was worse with most patients continuing to have seizures. A less favourable outcome was recorded by Loiseau in a later study, who obtained retrospective information on 90 patients followed for more than 15 years. (Loiseau, Pestre, Dartigues, Commenges, Barberger-Gateau & Cohadon, 1983) He found that only 57.7% experienced a remission of seizures, although patients with simple AS only, faired better than this with a 70% remission rate. The reason for the different remission rates in such studies is not always clear. The retrospective nature of some studies may mean that there is a tendency to miss patients with less severe or frequent seizures. The main reason is that absence seizures are a seizure type, and may occur in the context of the benign self-limiting absence epilepsies, or may occur with other seizure types in patients with more malignant cryptogenic generalised epilepsies, with the differing composition of each kind of patient in each study accounting for the different results.

Other seizure types and situations- The idiopathic localisation related seizures almost exclusively occur in children. (Gram, 1990) Both Rolandic epilepsy and Occipital epilepsy have an excellent prognosis with the majority of patients entering adolescence free of seizures and off any treatment. (Gram, 1990, Loiseau, Dartigues & Pestre, 1983, Panayiotopoulos, 1989)

The primary generalised epilepsies also occur more commonly in childhood or adolescence. Of these Juvenile Myoclonic Epilepsy is one of the more

commonly recognised syndromes representing up to 5% of all epilepsies. (Gram, 1990) Again the prognosis is good with most patients showing a response to valproate. (Holowach, Thurston & O'Leary, 1062) However withdrawal of valproate is often associated with relapse and so treatment may have to be lifelong. (Gram, 1990)

Seizures starting in the first year of life are particularly difficult to define and so studies of prognosis have been problematic. (Anonymous, 1985) Overall the prognosis in the first year is bleak. Even patients with cryptogenic seizures have a high risk of developing mental retardation in the order of 70% (Covanis, Gupta & Jeavons, 1983) When other syndromes or situations are encountered such as West's syndrome, Lennox Gastaut, or status epilepticus, the mortality is high and most patients go on to have further seizures, and/or, mental retardation. (Covanis et al., 1983) Intractable seizures in children carry as grave a prognosis as in adults, if not worse with most continuing to suffer with epilepsy and other problems. (Huttenlocher & Hapke, 1990) Children with partial epilepsy may have a less favourable outlook than other childhood epilepsies. (Anonymous, 1980, Lindsay, Ounsted & Richards, 1979, Lindsay, Ounsted & Richards, 1980) Lindsay et al recruited 100 children with temporal lobe epilepsy in a population based study and followed them into adult hood. (Lindsay et al., 1979, 1980) They found that one roughly third of the sample ended up seizure free, one third with seizures and or on AEDs, and the other third requiring long term care form parents or institutions.

1.1.2.7.2. Sex

It would be surprising from a neurobiological viewpoint if sex had any significant effect on the prognosis of epilepsy. This is born out in most studies. (Collaborative Group for the Study of Epilepsy, 1992, Okuma & Kumashiro, 1978) Hauser found a slightly better 2 year terminal remission for males versus females, but this did not reach any level of significance. (Hauser & Kurland, 1975) In the later Rochester analyses, although Annegers did find that initially females faired slightly better, the remission curves came together after 10 years had elapsed. (Annegers et al., 1979)

1.1.2.7.3. Seizure type

We have already seen in children that absence seizures (when they occur in isolation), and the occipital epilepsies have a good prognosis, with up to

90% remission rates. However, it is not the type of seizure but rather the underlying aetiology that is the critical factor, and analysis of the seizure type as an independent variable is not generally helpful. For instance, Annegers found that in patients with idiopathic epilepsy the remission rate after 20 years from diagnosis was only slightly less for patients with tonic clonic compared with AS, and that for patients with complex partial seizures the rate was still relatively favourable at 65%. (Annegers et al., 1979) Later analysis using multivariate proportional hazard models did show that never having had a tonic-clonic seizure did improve the chances of achieving remission, but this is probably a reflection of a higher likelihood of serious cerebral impairment rather than an independent risk factor. (Ramsay et al., 1983a) Interestingly this paper reported that patients with complex partial seizures had a similar outcome to patients with other seizure types, differing from the general conception of a worse prognosis for patients with this seizure type. (Rodin, 1972) However, the primacy of underlying aetiology is again seen because when the early onset cases (before 16 years of age) were examined, the non idiopathic complex partial seizures did have a poorer prognosis (presumably due to the presence of chronic lesions such as tumours and mesial temporal sclerosis). Other studies have also shown a slightly worse prognosis for partial seizures. (Goodridge & Shorvon, 1983, Okuma & Kamashiro, 1981)

1.1.2.7.4. Aetiology

In comparison to the seizure type the aetiology is of paramount importance in predicting the prognosis. This was partly one of the aims of the ILEA in producing a syndromic classification system which would also be a guide to outcome. (Commission on Classification and Terminology of the International League Against Epilepsy, 1989b) The classification of epilepsy has advanced over the years with improved phenomenology, investigations, and refinement of our understanding of pathogenesis, thus earlier studies are generally less helpful than later ones.

From first principals it might reasonably be expected that epilepsy that was associated with an identifiable cause would have a worse prognosis. This, however, has generally not been substantiated. Annegers reported that the probability of attaining a 5 year remission after 20 years was 74% for patients with idiopathic epilepsy, compared to a slightly lower rate for symptomatic epilepsy in the early years, but which evened out later on.

(Annegers et al., 1979) Patients with neurological dysfunction present at birth did, however, do badly and only 46% achieved remission after 20 years. When Shafer used Cox modelling on the extended cohort an unknown aetiology was a favourable factor in univariate analysis, but complex interactions with other variables such as seizure type makes this affect difficult to quantify. (Shafer et al., 1988) In 3 hospital based studies conflicting evidence is given. Okuma and Shorvon were able to show a significantly better outcomes for the idiopathic groups, (Okuma & Kumashiro, 1978, Shorvon & Reynolds, 1982) whereas the Italian Multi Centre study did not. (Collaborative Group for the Study of Epilepsy, 1992) It should be remembered, as discussed above, that the Italian study excluded patients with symptomatic causes that would lead to an increased risk of convulsions. The other important population-based study from Kent also was not able to find any differences for the outcome of symptomatic versus idiopathic epilepsy. (Goodridge & Shorvon, 1983) The explanation for the differences between these findings may be that those studies that have classified and investigated patients better report more favourable outcomes for the idiopathic group because patients with uncontrolled seizures are more likely to have an underlying cause diagnosed. Also, when studies are more population-based there are many more benign forms of epilepsy, of both idiopathic and symptomatic aetiologies, which then tends to obscure any differences that may occur between more severely affected patients.

1.1.2.7.4.1. Neurological or neuropsychiatric deficits

Most studies have found that remission rates are very much lower in the presence of significant neurological or neuropsychiatric deficits. (Okuma & Kumashiro, 1978, Shorvon & Reynolds, 1982) This reflects the grave prognosis found in patients with underlying cerebral damage, and is equivalent to the Rochester findings in patients with neurological dysfunction present at birth (see above).

1.1.2.7.4.2. Strokes

Cerebrovascular disease is the commonest cause of epilepsy in the elderly. (Dodge, Richardson & Victor, 1954) After acute strokes seizures occur in between 4.4- 5.7% of patients, and this is more frequent with cerebral haemorrhage than infarction. (Kilpatrick, Davis, Tress, Rossiter, Hopper & Vandendriesen, 1990) Most seizures associated with strokes are partial and occur within 24 hours. (Kilpatrick et al., 1990) The mortality rate of strokes is not influenced by the development of seizures, but rather the extent of the

cerebral insult. (Davalos, Cendra, Genis & Lopez-Pousa, 1988, Kilpatrick et al., 1990) It is not totally clear from the literature whether seizures after acute strokes are predictive of later epilepsy, and the reported rates vary form 0-39%. (Fish, Miller, Roberts, Blackie & Gilliatt, 1989, Shinton, Gill, Melnick, Gupta & Beevers, 1988) Secondary epilepsy may be more likely if the patient has had the seizure more than two weeks after the stroke. (Fish et al., 1989, Shinton et al., 1988)

1.1.2.7.4.3. Post-traumatic

Seizures after non-missile head injury substantially increase the probability of future epilepsy with an overall risk of about 5% (Dodge et al., 1954, Jennett, 1974, Miller & Jennett, 1968, Weiss & Caveness, 1972) Seizures which occur soon after the injury, in less than a week, are less likely to recur, and seizures after a week are more likely. (Annegers, Grabow, Groover, Laws, Elveback & Kurland, 1980, Jennett, 1974) The risk increases with any identified cerebral injury or a depressed skull fracture. (Annegers et al., 1980, Miller & Jennett, 1968)

1.1.2.7.5. EEG findings

EEG is an inexpensive and readily available tool and there has been a lot of interest in using the early EEG findings to predict outcome. However, the EEG is subject to the usual constraints of any investigation, with a limited validity and reliability. Some studies have actually required the EEG to be abnormal as an inclusion criteria. (Dalby, 1969, Sofijanov, 1982, Strobos, 1959) There has also been no agreement as to the type of EEG criteria which are important. Most studies have found that an abnormal EEG is an accurate predictor of poor prognosis. Rodin found that focal sharp waves and theta activity indicated a poor outcome. (Rodin, 1978) Okuma also found that paroxysmal frontal or anterior temporal activity augured badly, (Okuma & Kumashiro, 1978) and Strobos found that bilateral synchrony was a favourable factor. (Strobos, 1959) In Rochester the EEG findings of generalised epileptiform activity was the most significant adverse EEG factor, and this could occur at any time in the course of the epilepsy. Focal EEG findings actually had a good outcome, probably due to the inclusion of patients with Rolandic epilepsy, the prognosis of which is very favourable. (Loiseau et al., 1983, Loiseau, Duche, Cordova, Dartigues & Cohadon, 1988) Rather like the seizure type as a predictive variable, the EEG is a

1.1.2.8. The patterns of remission and relapse

The patterns of seizure activity have been examined in two studies. (Goodridge & Shorvon, 1983, Shorvon & Sander, 1986) In both studies the seizure histories were taken and patients classified into one of four categories (remission was defined as a seizure free interval of two years): "burst" pattern was repeated attacks followed by a remission continuing to the time of the survey, "intermittent pattern" was repeated attacks occurring with at least one period of remission interposed, "continuous" which was repeated seizures with no remission, and "single" seizures. In the population-based study of 122 patients, (Goodridge & Shorvon, 1983) 18% had single seizures, 49% burst, 22% continuous, and 12% intermittent. The majority of patients experienced less than 10 seizures (68%), and had a short seizure history followed by remission. A minority of patients had intermittent seizures, and in those that did, there was usually a provoking cause for the relapse such has drug withdrawal or pregnancy. Patients with partial seizures or patients experiencing multiple seizure types were more likely to enter a continuous pattern, but interestingly other characteristics such as aetiology, were not more likely to produce any particular pattern.

These ideas were extended on the 108 patients from the earlier study that one of the authors had personally seen, and also 181 patients with active epilepsy seen in a specialist epilepsy clinic. (Shorvon & Sander, 1986) The 181 patients contrasted with the population-based sample because of the low numbers of patients who entered any remission and had an intermittent pattern (22%), the majority of patients having continuous seizures. By comparing the two groups the authors speculated that there were two distinct populations of patients with epilepsy: patients who experienced a few seizures and rapid remission, and patients without remission in whom, even if remission was attained was often followed by a relapse. The possibility that AEDs could influence these patterns early on in the course of the history was discussed. Of note was the failure to predict eventual long term remission by analysis of seizure type, age, aetiology etc., and the best prediction was made by examining the early temporal pattern in the first 5 years. Patients who failed to achieve early remission usually failed to achieve remission at all, and this supports the ideas of other workers in relation to the early pattern of epilepsy which was discussed above. (Elwes et al., 1984, 1988, Reynolds, 1987)

mirror to abnormal cerebral functioning and this should be remembered when attempting to use EEG data in prognostic studies.

1.1.2.7.6. The effect of the early seizure pattern on eventual remission

There is some evidence that the prognosis of epilepsy becomes established soon after its presentation. Gowers believed that seizures beget seizures and Rodin said that the more seizures a patient experienced the less chance there was of future control. (Rodin, 1968b) Camfield found that the majority of new onset patients were easily controlled and did not then relapse, however if seizures continued despite treatment, remission was a much rarer event. (Okuno et al., 1989) Other studies have addressed this aspect more thoroughly. In the King's cohort, if seizures continued in the first 2 years despite AED therapy, the likelihood of subsequent control declined by half, (Elwes et al., 1984) and this poor outcome was also related to the number of seizures prior to treatment. (Shorvon & Reynolds, 1982) Elwes extended these ideas to an analysis of the number of tonic-clonic seizures experienced before treatment and the relation to longer-term prognosis. (Elwes et al., 1988) An accelerating seizure rate was often found, with the time between seizures progressively shortening which suggested that there was an accelerating disease process in the early stages. In the Kent population-based study, patients could be divided up into burst, intermittent, continuous, and single seizures. (Goodridge & Shorvon, 1983) Those patients who had a continuous pattern from the start of treatment were more likely to remain with unremitting seizures, often unresponsive to treatment. The response to treatment in most patients with newly diagnosed epilepsy and the good long term outcome suggests that it is the AEDs that are influencing prognosis. As discussed above it is not possible to carry out trials without treatment, however studies in third world countries on patients with long-standing epilepsy are interesting. In one study from Kenya, patients who had never received AEDs were started on phenobarbitone. (Cavazutti, Ferrari & Lalla, 1984) An excellent response was found, both in patients with newly diagnosed epilepsy as well as in patients who had active epilepsy for many years. This argues against the Gowers theory that seizures induce further seizures and also that AEDs have any long term prognostic effect.

1.1.3. The Mortality of epilepsy

1.1.3.1. Introduction

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, 1963, Schwade & Owen, 1954) it is now generally accepted that patients with epilepsy have a higher death rate than the general population. (Annegers, Elveback, Labarthe & Hauser, 1976, Annegers, Hauser & Shirts, 1984, Hauser, Annegers & Elveback, 1980, Klenerman, Sander & Shorvon, 1993, Massey & Schoenberg, 1985, Zielinski, 1974) In this section I will review the current literature on the mortality of epilepsy.

1.1.3.2. Historical perspective

Gowers in his observations of patients at the National Hospital for the Paralysed and Epileptic thought that "the danger to life of patents with epilepsy was not great" and that the main risk was one of drowning. (Gowers, 1885) Spratling, in 1907, in figures from the Craig's Colony for Epileptics, USA, drew attention to the sudden and unpredictable nature of death in 5% of epileptics. (Spratling, 1902) A more comprehensive analysis of the mortality rate in 2,732 patients with epilepsy, also from Craig's Colony, was published in 1910 by JF Munson. (Munson, 1910) Sudden death was a major cause of death in young patients, as was pulmonary disease, and status epilepticus. Although it was realised that patients with epilepsy might die as a result of having epilepsy, accurate quantification of this was lacking. In 1928 Munsken, reviewing the work to date, echoed Gowers, saying that the "immediate danger to life of an epileptic fit was not great" (cited by Rodin (Rodin, 1968b)). Two studies in the 1950's appeared to confirm this optimistic view and reported that the death rate in patients without neurological deficits was no different from the general population. (Alstrom, 1950, Livingston, 1963, Schwade & Owen, 1954) However, Rodin in his monograph on the prognosis of epilepsy, which also summarised the current literature, compared the median age of death of patients with epilepsy against the normal population and concluded that the life expectancy of epilepsy was significantly reduced. (Rodin, 1968a) Although there is some evidence that the mortality rate for epilepsy has changed over the decades, the rate, if anything, has probably declined, (Massey & Schoenberg, 1985) and there is no reason to suspect that Rodin's observations were due to a worsening of the mortality rate of epilepsy.

1.1.3.3. Methodological considerations

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, 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 & Sempos, 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%-29% of patients with epilepsy do not have epilepsy included on the death certificate. (Massey & Schoenberg, 1985, Silfvenius & Olivecrona, 1988) Where available, this information is often supplemented with data from post-mortems, hospital records and other sources, 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 for what constitutes epilepsy. Inclusion or exclusion of potentially benign or malignant categories, such as isolated single seizures or agonal symptomatic seizures, will result in major bias. Hauser, for instance, defined epilepsy as the state of having two or more seizures, (Hauser et al., 1980) but this is not uniform practice. Studies employing proportional mortality rates calculated from death certificates (for example (Krohn, 1963, Schwade & Owen, 1954) are biased for the reason mentioned above, in that epilepsy is often not put on the death certificate with patients with fewer seizures or seizures in the more distant past prone to exclusion. There have been a number of studies of the death rates in populations of epileptics looked after in special epilepsy institutions or clinics. (Birnbach, Wilensky & Dodrill, 1991, Hashimoto, Fukushima, Saito & Wada, 1989, Henriksen, Juul-Jensen & Lund, 1967, Iivanainen & Lehtinen, 1979, Klenerman et al., 1993, White, McLean & Howland, 1979) or in populations of insured patients with epilepsy. (Lewis, 1978) The highly selected nature of these cohorts means that results are not

directly applicable to the wider epilepsy population with other possible mechanisms of death operating.

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. (Hauser et al., 1980, Satishchandra, Chandra & Schoenberg, 1988, Zielinski, 1974) 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 got lost to medical surveillance.

1.1.3.4. The overall mortality rate of patients with epilepsy

Most recent studies have shown that patients with epilepsy have a an increased risk of dying at a younger age, and SMRs for patients with epilepsy of 2-3.5 have been reported. (Hauser et al., 1980, White et al., 1979, Zielinski, 1974) There have been two important population based studies, but both retrospective. Hauser examined the death rate in 516 patients with epilepsy identified from the Mayo linkage system over a 32 year period. Single seizures, provoked seizures and febrile seizures were excluded. The overall SMR was 2.3, and 1.8 for idiopathic epilepsy. (Hauser et al., 1980) Zielinski identified patients with epilepsy as part of a wider study into the epidemiology of epilepsy in Warsaw using patient record review and a selected 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.

Higher rates of death have also been noted in studies of institutionalised patients. There have been two studies that have looked at the death rate of patients resident at the Chalfont Centre, in the UK. (Klenerman et al., 1993, White et al., 1979) The 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, (White et al., 1979) and in the later study 113 deaths were recorded between 1980 and 1990, representing an overall mortality rate almost twice that expected (SMR = 1.9). (Klenerman et al., 1993)

1.1.3.5. The causes of death in patients with epilepsy

1.1.3.5.1. Cancer

There has been concern that there is an increased risk of cancer in patients with epilepsy. Many of the AEDs have a liver enzyme inducing effect, and phenobarbitone 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 that induction of liver enzymes may actually protect against carcinogenesis by diverting any harmful metabolites down safer metabolic pathways. (White et al., 1979) There are anecdotal reports of an association between neuroblastoma and phenytoin therapy, (Pendergrass & Nanson, 1976) and an increased risk of brain tumours in children of mothers on long term AEDs. (Gold, Gordis, Tonascai & Szklo, 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, 1970) Hauser reported an SMR for all neoplasms of 1.8, excluding cerebral neoplasms, but interestingly most of this excess was accounted for by a diagnosis of malignancy before the diagnosis of epilepsy was made. (Hauser et al., 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 (Klenerman et al., 1993, White et al., 1979) One study from Denmark from an analysis of 9136 patients with epilepsy admitted to a specialist centre did not confirm this increased rate, (Clemmensen, 1974) as well as in a much smaller sample of 300 epileptics in a hospital for mental handicap. (Jancar, 1980, 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. (Hauser, 1992, Klenerman et al., 1993, White et al., 1979) However, lung tumours, (Friedman, 1981) and gut malignancies, (Klenerman et al., 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 of cerebral malignancy is not surprising considering the association with the aetiology of many patients with epilepsy. More sophisticated investigation of patients employed before, and after, life will tend to raise the incidence of intracranial malignancy. (Iivanainen & Lehtinen, 1979) A better prognosis for those patients with gliomas who develop epilepsy has been reported, and must reflect earlier diagnosis, rather 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 et al., 1980)

1.1.3.5.2. 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 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 (Linden, 1975) Also, all the AEDs lower serum high density lipoproteins, and may thus reduce the accumulation of atherosclerosis. (Berlit, Krause & Schellenberg, 1982) Most studies have not been able to support this hypothesis, with SMR rates of 1.4 to 0.8 reported (Annegers et al., 1976, 1984, Klenerman et al., 1993) The higher rates are found in patients with symptomatic seizures and probably represents increased rates associated with strokes, which are common causes 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. (Muuronen, Kaste, Nikkila & Tolppanen, 1985) Of the 1399 deaths in patients with epilepsy, 258 were due to IHD compared to 382 in a control group matched for age and sex; 29% less risk for patients with epilepsy.

1.1.3.5.3. Cerebrovascular disease

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

1.1.3.5.4. 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, 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, (Karalus et al, 1991) or prolonged inactivity secondary to the cause of the epilepsy, such as a AED intoxication, strokes, brain tumours, or congenital deficits. In support of this is the high rate of pneumonia deaths in institutionalised patients who are more likely to have frequent seizures, and associated mental handicap, (Iivanainen & Lehtinen, 1979, Krohn, 1963, Penning, Muller & Ciompi, 1969, White et al., 1979, Zielinski, 1974) compared to the lower

rates in population studies. (Hauser et al., 1980) Death rates are also more likely to be higher in institutions because of facilitation of spread of viral and bacterial infections. In spite of having a lower rate in community studies this is still in excess of expected cases, and is still significant in the idiopathic group of patients. (Hauser et al., 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 an susceptibility to infection has not been established.

1.1.3.5.5. 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, 1963, Wolfersdorf & Froscher, 1987, Zielinski, 1974) 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, alcohol, and sedative AEDs will all increase the suicide risk. (Barraclough, 1987) There is a greater risk in patients with temporal lobe epilepsy, with a relation to the degree of severity of the seizures, (Lindsay, Ounsted & Richards, 1979) and those patients who have undergone surgery. (Taylor & Marsh, 1977)

1.1.3.5.6. 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 (SUD)

1.1.3.5.6.1. Accidents

The chance of a patient dying of an accident is higher than in the general population. (Iivanainen & Lehtinen, 1979, Klenerman et al., 1993, Krohn, 1963, Schwade & Owen, 1954, Zielinski, 1974) 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 & Lehtinen, 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 et al., 1993)

1.1.3.5.6.2. 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, Shinnar, Moshe & Alvarez, 1989, Oxbury & Whitty, 1971) This is largely accounted for 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 et al., 1993, Krohn, 1963, Zielinski, 1974)

1.1.3.5.6.3. AED 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 hepatotoxicity (Dreifus, Langer, Moline & Maxwell, 1989, Suchy et al, 1979) These and other idiosyncratic drug reactions, however, are rare and are unlikely to be major causes of death.

1.1.3.5.6.4. 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 SUD 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 et al., 1993)

1.1.3.5.6.5. Sudden Unexpected Death (SUD)

SUD was first described in 1902 in 4% of chronic epileptic patients, (Spratling, 1902), and Munson recognised that 19% of deaths in a centre for epilepsy were sudden and unexplained. (Gowers, 1885) The importance of SUD is its propensity to strike at otherwise apparently fit young adults and its largely unexplained aetiology.

The definition of SUD- There have been many definitions of SUD. SUD has been defined as " non-traumatic death occurring in an individual within minutes or hours of the onset of the final illness or ictus. The individual having been previously relatively healthy, or suffering from a disease which would not ordinarily be expected to produce immediate or sudden death". (Jay & Leestma, 1981) This category thus included cases which were witnessed to have followed a seizure, or where the cause may have been ascertained such as aspiration, pulmonary embolism, or myocarditis, and thus would be more correctly defined as sudden death, alone. Neuspiel in a study of all the SUDs in a childhood and adolescent population similarly included deaths where a cause had been identified, and in the 32 deaths in patients with epilepsy, 6 had been preceded by a seizure. (Neuspiel &

Kuller, 1985) Other studies have used a similar definition of SUD (Norman, Taylor & Clarke, 1990, Sarkioja & Hirvonen, 1984) Most investigators, including Leestma, (Leestma, Walczak, Hughes, Kalelkar & Teas, 1989) would now add that no cause be found at necropsy. (Klenerman et al., 1993) Cases immediately following a seizure are excluded, but patients should probably be included who have suffered brain death, but are maintained on a ventilator following unsuccessful resuscitation. (Leestma et al., 1989)

The incidence of SUD in epilepsy- In Hauser's comprehensive study of the mortality of epilepsy in Rochester there was no mention of SUD as a significant cause of death. (Hauser et al., 1980), although a subsequent report cited an SMR of 2.29 for sudden death, this was made confusing by calling it "sudden cardiac death", no evidence for a cardiac aetiology, apart from the suddenness of the event, being given. (Annegers et al., 1984) In the only other community-based study of SUD, 4.2% of the 218 deaths in the epilepsy population were ascribed to SUD (which was not defined). (Zielinski, 1974)

In more selected populations the incidence of SUD is higher. Krohn described 13% of 107 deaths as "mors subita" where no good post mortem evidence was found. (Zielinski, 1974) In a series of 71 deaths in an epilepsy institution 37% were due to SUD. (Ziegler & Kamecke, 1967) In a review of 58 deaths in Cleveland, Ohio, 4 out 58 sudden deaths remained unexplained. (Hirsch & Martin, 1971) In a more detailed study in a defined population of 1.6 million over 5 years, also using coroners records, there were 37 episodes of SUD giving a rate of 1 in 1,110 per epilepsy patients per year. (Terrence Jr, Wisotzkey & Perper, 1975) A similar study, in which information was obtained prospectively in a population of 5.2 million people over one year, obtained a higher figure of 60 SUDs giving a rate of 1 in 370 per epilepsy patients per year. (Leestma et al., 1989) In Denver, Colorado, a retrospective 5 year study arrived at a near identical figures to those in Cleveland, described above, of 43 deaths in 5 years in a population of 1.5 million. (Earnest, Thomas, Eden & Hossack, 1992) In the UK, the rates of SUD are probably of the same magnitude with a rate of 1 per 480 deaths per year in the epilepsy population. (Klenerman et al., 1993) The main concern with all these figures is that no control population rates for SUD are given. For instance, it is possible that the rate in patients with epilepsy is no different from the general population. Examination of the circumstances surrounding the causes of death in patients with epilepsy will increase the rate of SUD where death certificate information might specify some other cause, as was found in all 11 cases scrutinised by Keeling. (Keeling & Knowles, 1989) In studies of the deaths in mental hospital patients containing

populations of patients not so dissimilar to patients with chronic epilepsy apart from the absence of seizures, there was a rate of SUD up to nearly 20% of all deaths. (Abiodun, 1988, Forssman & Akesson, 1970, McLoughlin, 1988) Thus the incidence of SUD in institution and hospital populations may be more a factor of underlying brain dysfunction or a hazard of institution care, such as phenothiazine consumption, rather than epilepsy per se. In a study of sudden non-traumatic death in the same population as described by Terence, but looking at records between 1972 and 1980 and only at deaths in the under 22 age group, there were 32 deaths in epileptics compared to 29 deaths in non epileptics where no cause could be determined. (Neuspiel & Kuller, 1985) This suggests that there is a higher risk in patients with epilepsy, but the issue will only definitively be resolved by a prospective study comparing patients with epilepsy and patients without epilepsy.

The causes- There is a general consensus that patients with more severe epilepsy found in long term care settings have an increased risk of SUD. (Klenerman et al., 1993) Most studies of institutionalised patients have found a higher rate than the population studies but as iterated above, this could be ascribed to a selection bias in choosing patients for post-mortem and coroner examination because they are epileptics, when otherwise another cause of death might be given.

There is a higher rate in patients aged between the second and fifth decades. (Neuspiel & Kuller, 1985, Terrence Jr et al., 1975) There is a higher rate in blacks in the USA, (Leestma et al., 1989, Terrence Jr et al., 1975, Wise, Kotelchuck, Wilson & Mills, 1985), patients who abuse alcohol, (Leestma et al., 1989) and in patients with an anatomic aetiology for their epilepsy such as trauma. (Terrence Jr et al., 1975) AED non-compliance may also be a factor (Bowerman, Levisky, Urich & Wittenberg, 1978, Earnest et al., 1992, Lund & Gormsen, 1985, Terrence Jr et al., 1975), but the low AED levels often found in such patients may be no different from the normal epilepsy population and is not always a consistent finding. (Schwender & Troncoso, 1986) Nearly all patients with SUD have generalised tonic clonic convulsions. (Hirsch & Martin, 1971, Leestma et al., 1989, Terrence Jr et al., 1975) but the patient's prior seizure severity varies, and in up to 50% of patients seizures are infrequent, (Hirsch & Martin, 1971) 32% have less than 3 per year, (Leestma et al., 1989) with a mean of 12 per year (Earnest et al., 1992) Earnest reported a high incidence of psychiatric disorders in his patients but this has not been confirmed elsewhere. (Earnest et al., 1992)

Various mechanisms have been proposed to explain the pathophysiology of SUD. There are a number of descriptions of patients dying as a result of a single seizure,

(Hirsch & Martin, 1971) and this may thus have occurred unwitnessed in patients with SUD. A seizure itself can produce arhythmias, and this may cause death by precipitating ventricular fibrillation or asystole. (Dasheiff, 1991, Jay & Leestma, 1981, Schraeder & Lathers, 1989) Other speculations include centrally mediated pulmonary oedema, (Fredberg, Botker & Romer, 1988) the effect of AEDs on the cardiovascular system, (Stone & Lange, 1986) and the release of endogenous opiods causing respiratory arrest. (Jay & Leestma, 1981)

1.1.3.6. Other factors affecting the mortality rate in patients with epilepsy

1.1.3.6.1. 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, (Kurokawa, Fung, Hanai & Goya, 1982, Miyake et al, 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 et al., 1980, Zielinski, 1974) Epilepsy in the first year of life has a high mortality because of associated neurological dysfunction in many of these patients, (Brorson & Wranne, 1987, Chevrie & Aicardi, 1978) so that in older patients the high-risk patients have already been selected out. As discussed above, the middle years between 15-50, is where patients are most likely to suffer SUD, and other ERD. Later the mortality due to strokes and tumours increases. (Hauser et al., 1980, Luhdorf, Jensen & Plesner, 1987)

1.1.3.6.2. 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, 1974) Hauser found that the SMR of idiopathic epilepsy for men was 2.1 and women 1.6. (Hauser et al., 1980)

1.1.3.6.3. Time from diagnosis

This has only been examined in two studies. (Hauser et al., 1980, Luhdorf et al., 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 et al., 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 et al., 1987)

1.1.3.6.4. Type of epilepsy and type of seizures

Because of variation in classification of epilepsy and seizures in mortality studies there is no hard 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 against the standard population. (Hauser et al., 1980)

1.1.3.6.5. 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 et al., 1980) suggesting an independent risk of having epilepsy apart from frequent seizures.

1.2. SECULAR TRENDS IN THE EPIDEMIOLOGY OF EPILEPSY

The epidemiology of epilepsy in the developed world has been subject to a number of influences over the last fifty years. Firstly, there have been demographic alterations in the population structure with a declining birth rate, a rising life expectancy, and a corresponding increase in the numbers of elderly people. Epilepsy is more common in the early and later decades of life and, therefore, changes to the population structure will also affect the age specific prevalence rates. Secondly, there may have been changes in the different aetiologies that cause epilepsy. For instance, there has been a fall in the perinatal mortality rate in the developed world, (Office of Population Census and Surveys, 1991) with a general improvement in perinatal health, so epilepsy which arises as a consequence of perinatal infection and trauma might also be expected to decline. Suggestions that the incidence of epilepsy has fallen in the last decades in both the UK, and USA, have been made. (Annegers, Hauser & Elveback, 1979, Sander, Cockerell, Hart & Shorvon, 1993) Lastly, the treatment of epilepsy has improved over the last three decades with the introduction of new AEDs, better use of existing AEDs, and advances in the early recognition and treatment of status epilepticus, and other complications of epilepsy. This has lead to speculation that there has also been an improvement in the prognosis of epilepsy in recent years. (Annegers et al., 1979, Okuma & Kamashiro, 1981) Discerning such patterns would have important implications for determining epilepsy aetiology, assessing the success of different interventions, as well as aiding public health strategies for prevention and treatment.

1.2.1. Incidence and prevalence of epilepsy

Incidence and prevalence studies throughout the globe have produced a wide variation in results, between 11/100,000 and 134/100,000 for incidence rates, (Blom, Heijbel & Bergfors, 1978, Krohn, 1961) and 1.5/1000 to 31/1000 for prevalence rates. (Chiofalo, Kirschbaum, Fuentes, Cordero & Madsen, 1979, Sato, 1964) Although there are some geographical differences, the key determinate of these results is the particular study methodology used (Sander & Shorvon, 1987). The classification systems are often different and case ascertainment methods often flawed. In this context it is even more difficult to determine if there has been any change in incidence and prevalence, as not only will these faults be operating, but also the base population must be stable and correspond over time. A summary of selected studies of incidence and prevalence are shown in tables 3 and 4.

1.2.1.1. The incidence and prevalence of epilepsy in the UK

In the UK there have been relatively few incidence studies, all carried out in the 1960s. (Brewis et al., 1966a, Crombie, Cross, Fry, Pinsent & Watts, 1960, Pond et al., 1960a) Two of the earlier studies were carried out in general practice populations. Pond looked at the incidence of epilepsy in a base population of 39,500 persons covered by 14 practices, and reported an incidence of 70/100,000. (Pond et al., 1960a) Crombie, in a similar study in 1960 that covered 288,830 people, found an incidence of 63/100,000. (Crombie et al., 1960) Crombie included febrile seizures and symptomatic seizures which were excluded by Pond. A later study in 1966, that should have produced higher rates because of more optimum ascertainment methods (a household survey and survey of hospital records supplemented the GP record search), only reported an incidence 30 per 100,000, (Brewis et al., 1966b) although symptomatic seizures and febrile seizures were analysed separately. There is thus no evidence for any secular change in the incidence of epilepsy in the UK, and the twofold difference in incidence rates over the 6 year period is almost certainly due to the efficiency of the case ascertainment systems rather than any temporal or geographical variation.

The same difficulty in found when attempting to interpret prevalence figures in populations at different periods of time, as studies have usually used different methodologies. The more thorough the case ascertainment methodology the higher the figures. Thus the last prevalence study in 1983 in the UK also carried out in GP population found a prevalence of 20/1000 for all seizures. (Goodridge & Shorvon, 1983) This compares to 4-6.2 per 1000 in other UK studies, discussed above, carried out in the 60s. (Crombie et al., 1960, Pond et al., 1960b) The Tonbridge study employed a more thorough system to ascertain cases by searching through notes rather than relying on GP reporting, and also included single and symptomatic seizures.

Table 3 *Selected studies of prevalence*

Study	*Country*	*Type of measure*	*Prevalence (per 1000)*	*Peak age specific prevalence*
Logan and Cushion, 1958	UK	-	3.3	-
Crombie, 1960	UK	Active epilepsy	4.2	5.86, 15-24 years
Pond, 1960	UK	Active epilepsy	6.2	16.8†, 60+
Krohn, 1961	Norway	Lifetime prevalence	2.3	-
Lessel, 1962	Mariana Islands	Lifetime prevalence	3.7	-
Bird, 1963	South Africa	-	3.7	-
Sato, 1964	Japan	Active epilepsy	1.5	-
Brewis et al, 1966	UK	-	6.0	8.2, 30-39
Gudmundsson, 1966	Iceland	Lifetime prevalence	5.2	-
Wajsbort, et al 1967	Israel	-	2.3	4.1, males >50 years
Liebowitz & Alter, 1968	Israel	Lifetime prevalence	4.1	5.0, 10-19 years
Stanhope, 1972	Guam	Active epilepsy	5.3	13.5, 20-29 years
Rose, 1973	USA	Lifetime prevalence	18.6*	-
De Graaf, 1974	Norway	Lifetime prevalence	3.5	5.0, 15-19 years
Zielinski, 1974	Poland	Active epilepsy Lifetime prevalence	7.8 9.2	19.2, 50-59 years 18,.3, 60-90 years
Gomez, 1978	Colombia	Lifetime prevalence	19.5	-
Chiofale, 1979	Chile	Active epilepsy	27.7*	-
Ross, et al 1980	UK	Lifetime prevalence	4.1	-
Cavazutti, 1980	Italy	Active epilepsy	4.4	-
Goodridge & Shorvon, 1983	UK	Active epilepsy Lifetime prevalence	5.3 16.7	- -
Granieri et al, 1983	Italy	Active	6.2	13.9, 10-19 years
Juul-Jensen & Foldspang, 1983	Denmark	Lifetime prevalence	12.7	-
Haerer et al, 1986	USA	Active epilepsy Lifetime prevalence	6.7 10.4	8.8, 40-59 years 11.5, 20-39 years
Joensen, 1986	Faroes	Lifetime prevalence	7.6	8.8, 10-19 years
Bharucha et al, 1988	India	Active epilepsy Lifetime prevalence	3.6 4.7	4.6, 0-4 years 6.4, 20-39 years
Osuntokun et al, 1987	Nigeria	Active epilepsy	5.3	6.2, 10-19 years
Tsuboi, 1988	Japan	Active epilepsy Lifetime prevalence	2.8 5.4	2.76, age 1 year -
Hauser et al, 1991‡	USA	Active epilepsy Lifetime prevalence	6.8 8.2	14.8, > 75 years 16.8, > 75 years
Placencia et al, 1992	Ecuador	Active epilepsy Lifetime prevalence	8.0 14.3	13.1, 40-49 years 23, 40-49 years

* Children only † Rate for < 1 year 19.9/1000 ‡ Only latest Rochester study shown

Table 4 *Selected studies of incidence*

Study	*Country*	*Inclusion criteria*	*Incidence (per 100,000)*	*Peak age specific incidence (per 100,000)*
Crombie, 1960	UK	All seizures	63	355, 0-4 years
Pond, 1960	UK	All seizures	70	510, 0-4 years
Krohn, 1961	Norway	All seizures	11	-
Sato, 1964	Japan	All seizures	17	-
Brewis et al, 1966	UK	Not single, or febrile seizures	30	-
Gudmundsson, 1966	Iceland	Not single, or febrile seizures	26	-
Mathai at al 1968	Mariana Islands	Not febriles	30	150, 0-4 years
Stanhope, 1972	Guam	Not single, provoked or febrile seizures	46	-
De Graaf, 1974	Norway	-	33	84.3, 0-6
Zielinski, 1974	Poland	Not single, provoked or febrile seizures	26	-
Heijbel, et al, 1975	Sweden	Children only, not single, provoked or febrile seizures	134	-
Cavazutti, 1980	Italy	Children only: not single, provoked or febrile seizures	82	-
Juul-Jensen & Foldspang, 1983	Denmark	Not febriles	39 male 28 female	149, 0-9 years
Granieri et al, 1983	Italy	Not single, provoked or febrile seizures	31	100.4, 1-4*
Li et al, 1985	China	Not single, provoked or febrile seizures	35	-
Joensen, 1986	Faroes	Not single, provoked or febrile seizures	43	73.2, 1-9 years†
Verity et al, 1992	UK	All afebrile seizures under 10 years	570	-
Placencia et al, 1992	Ecuador	Not febriles	190	268.3, 10-19
Hauser et al, 1993‡	USA	Not single, provoked or febrile seizures	44	139, >75 years
Siddenval, 1993	Sweden	Children only, not single, provoked or febrile seizures	89	-

* 212/100,000 given for <1 year
† 202.9/100,000 given for < 1 year
‡ Only latest Rochester study shown

1.2.1.2. Evidence for secular changes in the prevalence and incidence of epilepsy

There are only a few studies that have applied the same methodologies to the same population. In Norway, cases were ascertained in a population of 215,000 that was served by the Tromsø medical centre. (De Graaf, 1974) No attempt was made to establish the percentage of patients with seizures who attended the clinic although the suggestion was that distances could be large and that this might limit attendance. However, annual rates over a five year period from 1968 to 1972 were given. Although the overall rates per year were between 31 and 32 per 100,000 the age rates varied greatly. In 1968 the incidence in the 0-6 age group was 101/100,000 but this fell to 45/100,000 in 1972. This compares to a rise in the older age groups, for instance in the 70 plus ages the incidence rose from 7 to 22/100,000. These annual differences and the causes underlying them were not commented on in the text. The population figures were only given for 1971 and it was not stated whether the rates in each age group were age specific or per the whole population. Obviously demographic changes with increased numbers of elderly people and a lower birth rate could be highly significant if the rates were calculated for the population as a whole.

A similar study was carried out in Italy to determine the epidemiology in a specific region caller Copparo. (Granieri et al, 1983) Unlike Tromsø there was a less well established system of medical care and the study ascertained cases retrospectively from hospital, private doctor, and institution records. Also only active cases were included. However, the average incidence rates were identical (33/100,000), although the overall prevalence of epilepsy in this study was slightly low (6.2/1000), suggesting poor case ascertainment. Annual incidence rates from 1964-1978 did not differ significantly and were between 30.5-36.6/100,000. Interestingly the incidence was higher in the earlier period which is the opposite one would expect assuming older cases are more likely to escape ascertainment. The aetiology in the earlier years included a higher proportion of symptomatic cases resulting from peri-natal injuries. Both the Norwegian and Italian studies suffered from major errors when attempting to estimate incidence rates from retrospective data. Neither study obtained information on the patients with epilepsy who died in this period, and as the death rates of epilepsy are highest in the immediate period after diagnosis, (Hauser, Annegers & Elveback, 1980) this will significantly affect any calculations unless an adjustment is made according to an estimated annual death rate. (Juul-Jensen & Foldspang, 1983) Also, retrospective analysis is prone to miss cases,

which have either moved out from the surveyed population, or who are simply not ascertained (see above for the difficulties in conducting retrospective studies).

A study recently carried out in Northern Sweden found that the incidence of childhood epilepsy (0-15 years) was 89/100,000 in the period 1985-87, (Sidenvall, Forsgren, Blomquist & Heijbel, 1993) which compared to 134/100,000 between 1973-74 which was found in an earlier study of the same population which used similar ascertainment methods. (Heijbel, Blom & Bergfors, 1975) In the earlier study 13 cases were not included because of difficulty with classification, whereas this had fallen to 2 in the later study, suggesting a less good system of ascertainment. Also, as only two incidence periods were examined, the differences could have been due to sampling error and no confidence limits were calculated.

The two main components needed to carry out an analysis of temporal trends are a stable population that has been subject to study over a reasonable time period, and the application of the same method to different time periods. Both these factors were present in the Rochester population which was the subject of a number of reports. (Annegers et al., 1979, Hauser & Kurland, 1975) Between 1935 to 1967 the incidence of epilepsy was 34.7/100,00 in the interval 1935 to 1944, and about 54/100,000 in the other decades. The authors regarded this difference as due to less stringent ascertainment in the early years. There was also a considerably higher incidence rate for children and young adults between 1935 and 1944. Because patients were not included who had migrated, the lower rates after 1944 might be due to selective emigration of the 20 to 59 ages either to fight in W.W.II, or to find work in the industrial North.

Prevalence rates in the Rochester study mirrored the incidence rates. (Hauser & Kurland, 1975) The prevalence was lowest in 1940 at 3.7, compared to 5.3 in 1950, 6.2 in 1960, and 5.7 in 1965. The study also found much higher age specific rates in the 0-9 age band in 1940, which was 6.2, compared to 3.3 in 1965. Out-migration was cited as a factor, and other possible causes, such as better ascertainment or increased peri-natal problems in this period, were discounted.

Changes in the diagnostic labelling of seizure types from "petit mal" and "grand mal", to variations of the ILEA system probably underlie the difference in incidence and prevalence of partial seizures before 1944 and after. After 1944 the rate of partial seizures recorded almost doubles. Changes in aetiology over time did not alter, nor did sex incidence or prevalence rates.

In the later report which was up to 1974, the incidence averaged out over the five 10 year intervals did not alter greatly, but there was however a significant trend for decreasing incidence in children with time and an increase in the elderly. Whether this affect was explained by the migration effect first commented on in the 1975 paper was not elaborated upon.

1.2.2. Prognosis

Any analysis of the secular trends in the prognosis of epilepsy is hampered by the same handicaps as were found when looking at incidence and prevalence: different populations studied with different methodologies. The prognosis of epilepsy prior to the 1970s was held to be poor with less than 20% entering remission, with more recent evidence showing that over 80% probably enter long term remission. This difference is of course nothing to do with the changing fortunes of people with epilepsy, but rather the differing results evinced from hospital, as opposed to, population-based studies. However, there is some evidence that there has been some improvement in the remission rate for patients with epilepsy over the century, and this has been suggested by Okuma. (Okuma & Kumashiro, 1978) Okuma drew attention to the very early studies prior to the introduction of phenobarbitone (1912) and phenytoin (1938) which indicated that remission rates were as low as 2-30%, (Habermas, 1901, Turner, 1907) whereas studies between 1940 and 1970 reported rates between 20 and 40%. (Rodin, 1972) Also, studies in Japan in 1940 and 1952 gave rates of 27% and 22%, (Okuma & Kamashiro, 1981) and by 1963-1969 the rates had increased to 41% and 45%. (Fukishima, 1969, Wada, 1963)

The only data on secular trends of prognosis in a single population comes from the Rochester series. Between 1935 and 1974 no difference in remission rates was observed for patients diagnosed in the first decade, as compared to the last. (Annegers et al., 1979) The authors however highlighted the effect of possible confounding factors. For instance, in the first 25 years and in the last 15 years there may have been different mechanisms which were underlying the group classified as "idiopathic" and more successful treatment in the latter years may have been masked by the appearance of a more aggressive "idiopathic" form of epilepsy. The other important point is that the incidence of epilepsy in children appears to have fallen, and as this group has the highest remission rates this would lead to a more pessimistic overall view. Despite commenting on this the authors did not then give the age specific remission rates for the earlier as compared to the later decades.

One more definite indication of improved prognosis in the Rochester series is shown in the relative decline in the total epilepsy population against the increase in the

number of patients with single seizures. (Annegers et al., 1979) In Rochester single seizures are always analysed separately from patients with more than one seizure. This may thus be due to earlier and more effective treatment of patients after their first seizure preventing patients from going on to have further seizures. This would also have the effect of decreasing the number of milder cases of epilepsy in the overall epilepsy series and so lower the later overall remission rates.

1.3. THE ECONOMIC COST OF EPILEPSY

Epilepsy is a common condition, and in the UK it is estimated that there are over 300,000 persons with active epilepsy and over 1 million persons with a history of seizures. (Duncan & Hart, 1993) Despite the problems that epilepsy is thus likely to pose in any society, there have only been a handful of estimates of the financial costs of epilepsy, in the UK, (Davidson, Swingler & Moulding, 1992, Griffin & Wiles, 1991) or indeed elsewhere in the world, (Anonymous., 1993, Begley, Annegers, Lairson, Reynolds & Hauser, 1993, Beran & Regan, 1993, Gessner, Sagmeister & Horisberger, 1993, Lindholm & Silfvenius, 1993, US Commission for the control of Epilepsy, and its consequences., 1978) It is important to establish these costs if health care and other provisions for people with epilepsy are to be rationally planned.

1.3.1. Approaches to cost of illness studies

There are two principal ways of approaching the analysis of the costs of epilepsy. The first is to examine the costs incurred by individuals with epilepsy, either on a cross sectional basis in a population of patients, which is called a prevalence-based analysis, or as a longitudinal analysis of individuals, which is called an incidence-based analysis. A longitudinal analysis is advantageous because it takes into account the temporal aspects of epilepsy and can measure directly the way the cost profile changes over the course of the disease, but is more difficult to perform because of the logistics of prolonged follow up. It is easier to calculate the costs for a sample of patients fixed in time, and the only individual centred study to date in the UK used a prevalence-based analysis. (Davidson et al., 1992)

The second method is a service based analysis which calculates the costs from the service provider. Most national government institutions provide data on health and social provisions which are readily available, and the UK is no exception. The main providers in the UK are the Departments of Health and Social Security, and ultimately the government, with private contributions being much less significant in meeting the costs of chronic disorders. A number of studies have used these gross national costs to estimate the cost of epilepsy by calculating the percentage of the overall

services consumed by patients with epilepsy. (Begley et al., 1993, US Commission for the control of Epilepsy, and its consequences., 1978)

1.3.2. Problems with cost study methodology

In principle, the correct application of individual based and service based analysis should yield similar results, both in terms of cost per patient and cost to the nation. However, service based cost studies of patients with epilepsy have produced estimates of between £400-£4000 per patient per year, (Griffin & Wiles, 1991, US Commission for the control of Epilepsy, and its consequences., 1978) whereas individual based study estimates have been between £2000 -£3000 per patient per year. (Begley et al., 1993, Davidson et al., 1992) This variation is due to the differences between study methodology and other problems, of which a number of examples can be cited. There has, for instance, been a lack of consensus about what indices of disease burden should be included and how they should be measured and costed. The indices of disease burden that are typically considered are shown in table 5.

Table 5 *Indices of disease burden in epilepsy*

Direct burden	Indirect burden
Medical-	
General practice	(Transfer payment)
Hospital in-patient	Unemployment
Hospital out-patient	Mortality
Hospital surgical	Under employment*
Hospital A&E	Dependency*
Investigations	Social effects*
Drugs	Psychological effects*
Ancillary*	
Non-medical-	
Residential care	
Community care	
Training and rehabilitation*	
Travel costs to hospital	

* No reliable data available

The indirect indices (unemployment and mortality) have proved particularly difficult to assess, both in terms of what to measure and how to calculate costs. For example, in an influential American study it was argued that the increased mortality rate of epilepsy will result in costs incurred by society equivalent to the lifetime loss of the wages that the deceased would have

earned (the human capital method). (US Commission for the control of Epilepsy, and its consequences., 1978) This amounted to 23% of the total estimated national cost of epilepsy to the USA of $8,002 million (1974 figures updated). In times of unemployment it could be argued that this assumption is incorrect, as each dead person's job is then filled by one of the unemployed, thus still generating the same income to society. The same argument can be applied against calculating the costs of unemployment. Furthermore, this cost was calculated without adequate regard to "discounting" over the years of follow up, which will lead to considerable error (see Robinson, 1993a for a full discussion of this issue). In the same study the estimated cost of under-employment was $1,143 million (1974 figures updated). (US Commission for the control of Epilepsy, and its consequences., 1978) This figure was derived from a selected sample of patients attending an epilepsy clinic in which the proportion of patients doing a less well paid job than their qualifications would otherwise have allowed was estimated. This ignores the selected nature of the sample, and also in the UK at least, one community based study showed that people with epilepsy who are employed have an equal chance of working in a skilled and well paid job as any one else in the population. (Scambler & Hopkins, 1980) Another of the problems in calculating the costs of indices, both indirect and direct, is the difficulty of deciding whether a cost is incurred because the patient has epilepsy or whether the cost is due to other factors. This is a particular problem when calculating social costs (e.g. unemployment, under-employment). For instance, is a patient unemployed because of inability to find work because of the epilepsy or associated personality, psychiatric, or physical handicaps, or because of the overall economic situation? Such questions are difficult to answer. Epilepsy is often considered a major component, and in the Dundee study, for instance, over 60% of unemployed patients blamed their inability to find a job on their epilepsy, (Davidson et al., 1992) but this is difficult to measure with certainty. Unravelling the relative contributions to costs of patients with epilepsy and mental handicap is even more problematic, for example, when considering the costs of institutionalisation. This is an important issue, for although the numbers are relatively small, the high cost of institution care results in a total which is a high percentage of the overall burden. In the US study the cost of institutionalisation of patients with mental handicap and epilepsy was wholly attributed to epilepsy and contributed 35% of the overall cost of epilepsy. (US Commission for the control of Epilepsy, and its consequences., 1978)

Transfer payments (e.g. social security benefits) constitute another problem. Studies carried out by economists do not usually include transfer payments as a true cost, (Gray & Fenn, 1993, Pachlatko, 1993) a convention which can be reasonably justified on economic grounds. In spite of this, the majority of cost studies carried out by clinicians have often included such payments in the assessment of indirect cost. (Beran & Regan, 1993, Davidson et al., 1992)

1.3.3. The desirability of cost stratification

Not all patients incur the same costs, and a failure to recognise this will lead to a poor understanding about where possible savings can be made. For instance the cost of a patient with intractable seizures and associated mental handicap is not the same as a patient with seizures in remission who is not on treatment. In a service based study a gross cost of epilepsy is usually calculated, but it is then not easy to deduce the relative costs incurred by different patient groups. A stratification of costs is desirable and this may be done for a number of aspects of epilepsy (table 6).

Table 6 *Cost categories for patients with epilepsy*

Cost category			Number per year (UK)
Chronicity	Newly diagnosed patients		30,000
	Established epilepsy	- active with medication	275,000
		without medication	50,000
		- inactive (in remission)	
		with medication	100,000
		without medication	1 million
	Undiagnosed patients		100,000
Severity			
	Remission		750,000
	Mild		100,000
	Severe		100,000
Aetiology			
	Specific aetiologies		-
	Acute / remote /symptomatic / idiopathic		-
Care status			
	Hospital care		50,000
	Community care		250,000
	Residential care		25,000
Epilepsy components of other handicaps			100,000

Selection bias is a related problem, and for example, in the Dundee study the only patients attending a special epilepsy clinic were included. (Davidson et

al., 1992) Such cases only represent about 10-20% of patients with epilepsy and are largely composed of those with more severe disease or who have other associated problems, making their costs proportionally higher than the general epilepsy population. Extrapolation from one strata to the other is fraught with difficulty, and data from an epilepsy clinic should not be used to estimate costs for patients in the community or in institutions.

1.3.4. Cost of illness studies

A cost of illness study is a form of economic evaluation which computes the current economic impact of a disease to the whole of society, including the costs and consequences of treating the disease. (Luce & Elixhauser, 1990, Robinson, 1993) The cost of epilepsy has been estimated in a number of studies. (Anonymous., 1993, Begley et al., 1993, Beran & Regan, 1993, Blom, 1990, Gessner et al., 1993, Griffin & Wiles, 1991, Gumnit, 1991, Lindholm & Silfvenius, 1993, US Commission for the control of Epilepsy, and its consequences., 1978) These have varied from £400-£4000 ($600-$6000) per patient per year. The different methods used and the problems with assessing costs discussed above largely accounting for these wide variations. These studies are summarised in table 7.

Table 7 *The cost of epilepsy in different countries*

Study origin	*Country*	*Total national annual cost (£) Millions*	*Annual cost per patient (£)*
OHE estimate of direct medical costs only (Griffin and Wiles 91)	UK	109	397
NIH estimate. Figures updated (US Commission 1978)	USA	6,900	3,600
New South Wales (Banks et al 1993)	Australia	170	1,300
Swiss estimate (Gessner et al 1993)	Switzerland	106	2,300
Sweden (Lindholm & Silfvenius, 1993)	Sweden	80	1,300

A number of studies have stratified patients according to seizure severity. (Begley et al., 1993, Gessner et al., 1993) In a recent Swiss study the number of patients with intractable epilepsy was only 15-20% of all patients with epilepsy and yet used up over 46% of the total cost of epilepsy which was $22.5 million. (Gessner et al., 1993) The definition of intractable, and the cost breakdown, was not specified.

In a recent study from the USA this analysis was taken further, but instead of costs based on actual data, the study looked at a hypothetical cohort of patients with epilepsy which started in 1990. The course of the epilepsy was based on known epidemiological data and a panel of experts estimated the interventions and outcomes for the differing types of patient, and the costs were then extrapolated nationally. Patients with continuing seizures were split into three groups: persistent but rare seizures, non-institutionalised with frequent seizures, and institutionalised patients. The total lifetime cost to the US economy of patients with non-institutionalised but frequent seizures since 1990 was estimated to be over £1147 million, which equated to £90,000 per individual patient. This compared to over £280 million for patients entering earlier remission, equivalent to £2600 per patient. The lifetime cost to the USA of institutionalised patients was a much lower overall cost of £2.4 million, partly because the assumption was used that this group did not incur the significant indirect costs of lost employment. The disparity between the overall costs are ascribed to the epidemiology: nearly 80% of patients enter early and complete remission. Drug costs were the most costly intervention in the intractable groups, making up to 60% of total indirect cost. In-patient and out-patient services incurred a significant burden especially in patients with frequent seizures in the community where out-patient costs were 8% and in-patient costs 17% of the totals.

SECTION 2

AIMS

2.1. THE PROGNOSIS OF EPILEPSY

2.1.1 Remission Of Epilepsy

1. To calculate the proportion of patients who enter a sustained remission, at any time in their course and at the latest follow up, and to examine factors that influence the chance of achieving remission.

2. To analyse the patterns of seizure occurrence and identify factors that influence these patterns

2.1.2 Mortality of epilepsy

1. To determine the cause of death of all patients in the NGPSE using the ICD 9 classification from death certificates, GP records, hospital records, and post mortem data.

2. To calculate the standardised mortality rate for the whole NGPSE, and for specific causes of death in the different sub-groups of patients and identify the time changes in the mortality rate and the effects of age and aetiology.

2.2. THE RISK FACTORS FOR ISCHAEMIC HEART DISEASE, STROKES, AND LUNG CANCER IN PATIENTS WITH EPILEPSY

1. To determine the risk factors for ischaemic heart disease, strokes, and lung cancer in these patients and matched controls. The risk factors are smoking, blood pressure, body mass index, and alcohol intake.

2. To carry out a case control study with patients and their age and sex matched controls to determine differences in the prevalence of these risk factors.

2.3. SECULAR TRENDS IN THE EPIDEMIOLOGY OF EPILEPSY

1. To calculate the prevalence of epilepsy in the population and compare the prevalence with the original 6000.

2. To calculate annual first attendance rates for the years 1948-1993 as an estimate of the incidence of epilepsy in this period.

3. To calculate the prognosis in terms of the chance of achieving a remission of 2 and 4 years and compare these rates for patients with an onset of seizures before and after 1974.

2.4. THE ECONOMIC COST OF EPILEPSY

1. To calculate the economic cost of epilepsy in a longitudinal cohort of patients: the NGPSE.

2. To compare this with the economic cost of epilepsy calculated from a cross-sectional survey of patients with established epilepsy: the National Epilepsy Survey.

3. To derive total annual costs to the whole UK.

SECTION 3

METHODS

3.1. THE PROGNOSIS OF EPILEPSY

Background

The most important aspects of the prognosis of a patient with epilepsy are the chances for the remission of seizures and the chances of a premature death. In order to establish the three and five year remission and the standardised mortality rates of patients with epilepsy, a cohort of newly diagnosed patients with seizure disorders was identified between 1984 and 1987 as part of the NGPSE. The design of the NGPSE enabled an incident cohort to be identified and so this minimised the loss of patients with milder seizures or who died early in the course of the illness who might not be ascertained by more traditional retrospective studies. Also, the definition of what constitutes epilepsy is not always certain and often the diagnosis does not become established until some years has elapsed. To avoid missing these patients all patients ,even if they only had a possible seizure, were included, so that patients who were first thought to have a possible seizure disorder, but subsequently turned out to have epilepsy, could also be followed. This section sets out the methodology utilised to determine the prognosis of epilepsy in the NGPSE cohort, and is split into two main sections: the remission and the mortality of epilepsy.

3.1.1 The National General Practice Study of Epilepsy

3.1.1.1 The identification of the incident cohort of patients with newly diagnosed seizures

3.1.1.1.1 Basic design

The design aim was to identify all patients with a possible undiagnosed seizure disorder in a population and establish a system of follow up so that the prognosis could be assessed. The population based identification was carried out by ascertaining patients who were looked after by a general practitioner, who was responsible for the medical care of a defined and specific population. Once identified the patient was classified, and then a system of continued active surveillance was adopted in order to minimise cases lost to follow up. Analysis used standard life table techniques.

3.1.1.1.2 Inclusion criteria

Any patient who had experienced a possible seizure of any type and at any age regardless of aetiology was included in the study.

3.1.1.1.3 Exclusion criteria

Patients with neonatal seizures or patients with a previous diagnosis of epilepsy were excluded from the study.

3.1.1.1.4 Case ascertainment

In 1984 a programme of GP recruitment was begun. This was conducted by a national advertising campaign in the GP and general medical press, as well as by writing to every Family Health Authority (FHA) in the country asking them to forward an invitation to join the NGPSE study. GPs were also recruited via word of mouth and by self-selection after hearing about the study. Once identified, a letter outlining the study in detail was sent, and if the GP was happy to proceed the GP was formally entered.

Once a GP was entered into the study he or she was asked to report all patients with a possible seizure disorder to the study office using a notification form. Postage was free.

3.1.1.1.5 The prevention of bias

3.1.1.1.5.1 Random selection

GPs were recruited via a number of different methods to reduce selection bias emanating from different GP practice. The wide inclusion criteria helped to reduce bias from under-reporting of patients with more difficult to diagnose or milder seizure disorders.

3.1.1.1.5.2 Demographic heterogeneity

To ensure that the patient population was heterogeneous and referable to the UK population as a whole, the GPs were recruited throughout the UK in both rural and urban settings.

3.1.1.1.5.3 Completeness of ascertainment

In the instructions the completeness of reporting was stressed and the GP was asked still to report patients in whom the cause of the seizure was obscure or in whom the GP was uncertain of the nature of the attacks. This policy raised the sensitivity of the ascertainment, although at the expense of specificity.

3.1.1.2 Initial data collection

3.1.1.2.1 The initial notification form

This form was sent in when the GP had identified a patient with a possible seizure disorder. The patient was identified by name, date of birth, and NHS number. Information was obtained on: age, sex, seizure description, time of onset of seizures, clinical features of seizures, number and timing of seizures that were experienced, drug treatment, neurological and medical history and signs, investigations, and hospital follow up.

3.1.1.2.2 The six month follow up form

This form was sent to the GP 6 months after the initial notification form. The GP was asked about any further developments in terms of diagnosis, seizure type, or aetiology. Seizure recurrences were noted and any changes in treatment. Other medical problems or psycho social aspects were also questioned.

3.1.1.2.3 Hospital follow up

In order to improve the quality of information on each patient, a follow up form was also sent at 6 months to the hospital specialist who had seen the patient (over 80% of patients were referred). Similar information was requested as on the initial GP notification form.

3.1.1.3 Patient classification

3.1.1.3.1 The six month classification

After 6 months from notification and on receipt of the hospital follow up form and 6 month GP follow up form, the patient data was analysed by a panel comprising a neurologist, a neuro-paediatrician, and a GP. The patient was then assigned to one of the classification categories: definite epilepsy, probable or possible epilepsy, febrile seizures, not epilepsy, or excluded due to unearthing of one of the exclusion criteria. The seizure types reported were checked against the seizure descriptions, and an aetiology was assigned from the information available.

3.1.1.3.2 Classification of seizures

This was performed on data collated at the 6 month period. Seizure types were classified according to the recommendations of the ILEA 1981 criteria. Although only 65% of patients in the definite group had an EEG performed within the first 6

months, a further 15% had an EEG subsequently and this was taken into account when classifying seizures.

3.1.1.3.3 Aetiological classification

Patients with definite epilepsy were classified according to the broad aetiological groups,(Annegers, Hauser & Elveback, 1979) and the following definitions were used:

- Idiopathic seizures where no identifiable cause could be isolated. This included patients with primary generalised epilepsy, as well as patients who had cryptogenic partial epilepsies, but where investigations has failed to find a cause.
- Remote symptomatic seizures where seizures were caused by an identified cerebral lesion or aetiology such as a tumour or vascular disease. Patients were not included where the cause had arisen within 6 months of the first seizure.
- Acute symptomatic included all patients where the cause had arisen within 6 months of the first seizure, such as a stroke or metabolic cause.
- The final group were those patients whose epilepsy had arisen in association with a neurological abnormality present at birth, such as cerebral palsy.

Further classification was performed on patients into more defined causes such as post-traumatic, vascular, associated with tumours, alcohol, or other identifiable causes. The following definitions were used:

- Tumour- confirmed by radiological or good clinical evidence of an intracranial expanding lesion.
- Trauma- associated head injury with loss of consciousness longer than 1 hour within the preceding year.
- Vascular- good clinical history of a vascular event, radiological evidence of cerebrovascular disease.
- Alcohol- history of withdrawal seizures secondary to alcohol abuse or actually during a period of excess alcohol intake.
- Post infective- secondary to intracranial infection; abscess, meningitis, or encephalitis.

- Idiopathic- no cause identified. Includes seizures associated with neurological deficit present at birth and so this category is different to the Annegers classification.

3.1.1.4 Patient follow up

The author was responsible for this aspect of the NGPSE from 1992-94

3.1.1.4.1 The annual follow up form

One of the major hurdles of any longitudinal prospective study is the continuation of data collection, often over many years. After more than a few years have elapsed often even the most enthusiastic doctors can loose interest in the study. Therefore to avoid data loss due to poor compliance a system of active surveillance was adopted. This took the burden of having to remember when further information had to be collected away from the GP. Every year each GP was asked to fill in a brief from asking about further seizures, changes of treatment, or changes to the putative diagnosis or aetiology, as well as any recent hospital treatment or other medical problems. The advantages of active surveillance is that this gave a much better record of the ongoing seizure activity than is possible from a retrospective analysis or a prospective analysis that relies on passive reporting, and is one of the strengths of the NGPSE system.

3.1.1.4.2 Five year hospital follow up

To check on the data received from the GP a further from was sent in 1993 to the hospital specialist on all patients who were on continued hospital follow up.

3.1.1.4.3 Data recording

The data was stored on a stand alone PC using a software database called Dataease. Dataease is a versatile system allowing easy storage and retrieval, with compatibility with all the common word-processing and statistical packages.

3.1.1.4.4 The minimisation of patients lost to follow up

As the study has progressed the paramount problem facing the study has been the continued acquisition of data on each patient. Between 5-30% of a GPs population moves to a new GP each year, and so after 5 years over 50% of patients had registered with a new GP, and some patients have moved more often. To keep up the active surveillance the NGPSE has had formal links established with the central office of the Office of Population and Census NHS central register (NHSCR).

When a patient moves practices, the GP sends the notes to the local Family Health Authority (FHA) who then forwards it to the patients new FHA, or if this is not known, then the NHSCR. All these movements are tracked by the NHSCR, who then inform the NGPSE office of the new FHA. The NHSCR were also able to tell us if the patients had left the country, died, gone to prison, or joined the armed services. The new FHA was written to who then passed on the NGPSE form to the new GP. The new GP was sent a letter explaining the aims and methods of the study, and invited to join the study, and then asked to complete the annual follow up form. Non-responders were contacted by telephone and asked about participation.

3.1.1.4.5 The five year classification

At 5 years after notification the panel reviewed all the data present, from hospital and GP, on the patients and made any changes to the classification, aetiology, or seizure types, that were warranted. Often MRI or CT scan evidence was an important new piece of information that assisted classification.

3.1.2 Remission of epilepsy

3.1.2.1 Definition of remission

Remission was defined as a seizure free interval occurring at any time after the first seizure. Patients, whether on or off AEDs were included. Terminal remission was also examined, which was defined as the seizure freedom at the time of last follow up. Remission was calculated for one, two, three and five years.

3.1.2.2 Analysis of remission

Remission was examined for patients with definite epilepsy and for patients with possible epilepsy, separately, and combined. Periods of remission examined were: one, two, three and five years, and this was up to 9 years of follow up. Remission was examined both from first seizure and from the index seizure (seizure which led to identification), when the index seizure was the first seizure and when the first seizure occurred within 6 months of the index seizure. Analysis also included, and excluded, single seizures and acute symptomatic seizures. 3 and 5 year remission was stratified by the following variables:

- Aetiology according to idiopathic, acute symptomatic, remote symptomatic, and congenital deficits acquired from birth.

- Aetiology: alcohol induced seizures, tumours, and vascular causes.
- Age of onset: < 16 years, 16-39 years, 40-60 years, > 60 years.
- Seizure type: generalised onset, partial onset.
- Number of seizures between index and first seizure.
- Time between index and first seizure.

3.1.2.3 Statistical method

All data was encoded and entered into the Dataease PC database. The data was then transferred to SPSS/PC and SPSS-X. Analysis used actuarial techniques. This was performed in collaboration with the Medical Research Council Biostatistics Unit in Cambridge.

3.1.2.4 The patterns of remission

Patients were divided into one of four patterns based on the temporal seizure activity.

- Single seizures: only one seizure experienced
- Burst pattern: a period of seizure activity followed by a remission of at least two years which was continued to the last follow up
- Intermittent pattern: a period of seizure activity followed by a remission period of two years, with a subsequent relapse
- Continuous pattern: continuous seizures with no remission

3.1.3 The mortality of epilepsy

3.1.3.1 The identification of patients who died

All patients who were identified by the NGPSE were tagged by the NHSCR as stated. If any patient died the NGPSE office was informed by the GP on one of the annual follow up forms, by letter, or even by telephone. All patients who died were also picked up by the NHSCR, and the NGPSE office was notified some months (maximum delay of 3 months) after the event. Only patients who died out of the country could have been missed, and to date there have only been 3 emigrations from the whole NGPSE cohort, and one death outside the UK.

3.1.3.2 Determination of the cause of death

A copy of the death certificate was sent to us by the NHSCR on every patient who died in the UK. This was supplemented in every case by enquiry to the GP and hospital records, when the death had occurred in hospital. This enquiry was often by telephone and was facilitated by the personal knowledge many GPs had of their practice population. Some patients also had a post-mortem or a coroner's enquiry, and details of the outcome of these investigations was also obtained by writing to the relevant authority. Each patient who died was assigned a single cause of death according to the ICD-9 classification system.

3.1.3.3 Statistical analysis

Statistical analysis was carried out using the person-years method, (Coleman, Herman & Douglar, 1989) and summarised by standardised mortality ratios (SMR) with 95% confidence limits, and two-tailed significance tests. Expected numbers of deaths were calculated for all causes, and for specific causes of death (based on ICD-9), using sex and age groups (0, 1, 2, 3, 4, 5-9, 10-14, ..., 85-89, 90-100), and by calendar year specific death rates for the population of England and Wales (1984 to 1992). Rates were calculated for the whole cohort and also for the sub-classifications of patients with definite epilepsy, possible epilepsy, and febrile seizures. Also calculated were rates for patients from the time of first seizure and from the time of registration (index seizure: which was the first seizure in 45% of cases). SMRs were also calculated for patients with definite epilepsy who were classified by the broad aetiology of their epilepsy into remote symptomatic (e.g. brain tumours and vascular disease), acute symptomatic (e.g. alcohol and metabolic), idiopathic, and causes due to a neurological deficit acquired at birth. Patients were identified between 1984-1987 and followed until the date of death, or if still alive to 31 December 1992. This was performed in collaboration with the Medical Research Council Biostatistics Unit in Cambridge.

3.2. THE RISK FACTORS FOR ISCHAEMIC HEART DISEASE, STROKES, AND LUNG CANCER IN PATIENTS WITH EPILEPSY

Background

The mortality of epilepsy was calculated from the NGPSE. This data and other work has shown that the standardised mortality ratio is two to three times higher than expected. The most frequent causes of death are cancer, ischaemic heart

disease, pneumonia, and strokes. It is not known whether these causes of death are due to the underlying aetiology of epilepsy, an effect of AEDs, or due to the increased presence of risk factors for these diseases such as smoking and hypertension. The determination of such risk factor profiles has important aetiological importance as well as providing possible avenues of prevention.

3.2.1 Community cases

3.2.1.1 Population

All patients with epilepsy in a population of 12,000 persons who were registered with the "Warders" health centre in Kent.

3.2.1.2 Case definition

Any patient over the age of 16 years who has suffered more than one afebrile seizure was included. Patients were subdivided into the following groups:

- active epilepsy: definite seizures in last 2 years, on or off AEDs.
- inactive epilepsy on treatment: no seizures in last 2 years but on AEDs.
- inactive epilepsy and not on AEDs: no seizures in last 2 years, and not on AEDs.

3.2.1.3 Case ascertainment

Three different systems were used to identify all patients with epilepsy in the Warders surgery. Examination of the computer records, passive reporting by the GPs of all patients who have attended the practice during the year 1993, and any patient who was identified during the prognosis study (see below).

Every patient identified had their notes scrutinised to confirm diagnosis and to determine the activity of epilepsy, and AED treatment.

3.2.1.4 Risk factor identification

The computer records system and/ or notes were used to obtain the smoking history, body mass index, blood pressure, and alcohol intake of all patients ascertained with epilepsy. Smoking history was divided into two variables, smoking or non smoking , and if smoking approximate number of cigarettes smoked per week. Any patient on whom this data was absent was sent one of the Warders

health questionnaires together with the prognosis questionnaire which was sent out as part of the secular trends study (see below).

3.2.1.5 Controls

The risk factor status was compared to the general population of the GP practice. Each patient was compared to an age and sex-matched control. Controls were randomly identified by selecting the next patient occurring alphabetically on the GP list of the same age and sex.

3.2.2 Long term residential patients

3.2.2.1 Population

One hundred and thirty eight patients at the Chalfont Centre for Epilepsy.

3.2.2.2 Case definition

Any patient resident at the centre with a diagnosis of epilepsy.

3.2.2.3 Case ascertainment

Patients were randomly identified who attended one of the general clinics or who were admitted for long term care assessment.

3.2.2.4 Risk factor identification

Details of name, age, sex, blood pressure (BP), body mass index (BMI) (weight^2 ÷ height), alcohol intake and smoking history were ascertained from each patient by means of a simple questionnaire.

3.2.2.5 Controls

The risk factor status was compared to the general population of the Warders GP practice. Each patient was matched to an age and sex-matched control. Controls were also randomly identified by selecting the next patient occurring alphabetically on the GP list of the same age and sex.

3.2.3 Data collection and Analysis

Data from both populations and controls was collected on a proforma and then entered onto a computer data base.

Data was transferred to SPSS and differences between the variables in each sample (active, inactive on AEDs, inactive off AEDs, and Chalfont Centre patients) and their control samples were analysed.

3.3. SECULAR TRENDS IN THE EPIDEMIOLOGY OF EPILEPSY

Background

The treatment of epilepsy has changed dramatically over the century. Newer and more effective anti epileptic drugs with more favourable side effect profiles are now available, other treatments such as neurosurgery are more effective, and the increased body of knowledge has lead to improvements in the treatment of status epilepticus and refractory epilepsy. However, although the treatment of epilepsy has improved there is scant evidence of its effect on the prognosis of patients with epilepsy. This study examined the time trends of the prevalence, first attendance rates, and the prognosis of patients with epilepsy in a population of 6000. This was facilitated by an earlier study carried out in 1982 which ascertained all patients with epilepsy in this population, and records of these patients are still available. Patients from 1982 to 1993 were ascertained by the same method (examining all the notes of the same population), and supplemented by other methods.

3.3.1 Population

A population of 6000 defined as the first 6000 alphabetical names on the practice list (all 1,200 patients on Dr Goodridge's list, and then the next 3,800 in the rest of the surgery), in the Warders surgery in Kent. This was the same population that was examined in 1982.

3.3.2 Case ascertainment

Ascertainment of patients was carried out by examination of all GP notes in the population of 6000 looking at the GP hand-written notes, hospital letters, and discharge summaries as well as old prescriptions.

This was supplemented by:

- Patients originally ascertained in the 1983 study
- Patients registered on the practice computer as having epilepsy

- Patients identified as part of the National Hospital linkage scheme which is a system currently surveying all neurological disease in a GP population covering 100,000 persons, which included the Warders surgery.

- Any patient who has had an AED prescription listed on the practice computer

3.3.3 Case definition and classification

The same case definition for epilepsy as in 1983 was used; a history of at least one non-febrile convulsion. (Goodridge & Shorvon, 1983) All patients with definite seizures were included, as well as acute symptomatic seizures (seizures secondary to an acute cerebral insult, such as alcohol). All patients notes were reviewed. Seizures were classified according to the 1981 ILEA revised classification of epileptic seizures.(Commission on Classification and Terminology of the International League Against Epilepsy, 1981) When classification was not possible on the information available, instead of assigning them to a category of probable generalised tonic clonic seizures, as had been done previously, (Goodridge & Shorvon, 1983) the patients were left as unclassified. Aetiology was based on ILEA guidelines (except that brain tumours were considered to be a remote symptomatic cause in the absence of progressive neurological decline).(ILEA Commission on Epidemiology and Prognosis, 1993) Active epilepsy was defined as any patient experiencing one or more seizures in the two years prior to survey date. Other data collected was: age, sex, and initial treatment (AEDs started within the first 6 months), current treatment and the time of first and last seizure, and details of remission. Remission was defined as seizure freedom, which could occur at any time, for two and four years. First attendance rates were first used by Zielinski in 1974, and are measured as per 100,000 persons. (Zielinski, 1974) The first attendance was the time of the first medical consultation which lead to a diagnosis of epilepsy being made.

3.3.4 Data collection and analysis

3.3.4.1 Prevalence

The demographic data of the 1983 practice population was obtained and compared to the 1993 population and this enabled calculation of the prevalence rates for the 1983 and 1993 practice populations. The characteristics of the patients with epilepsy in terms of age, sex, seizure type, aetiology was analysed and compared to the 1983 prevalence population.

3.3.4.2 First attendance rates

The urban population of Tonbridge was obtained from OPCS data sources and was used to estimate the age structure back to 1951, and this was used to calculate average annual age specific first attendance rates for the periods 1948-63, 1964-73, 1974-83, and 1984-93. Confidence limits to 95% (95% CI) were calculated. (Schoenberg, B.S. 1983)

3.3.4.3 Prognosis

The prognosis was first assessed from the notes, according to the continuation of seizures, and was defined in terms of attainment of 2 and 4 year remissions regardless of treatment.

It was not feasible to attempt to interview the patients identified as in 1983, but as there was less interest in detailed treatment patterns or exact numbers of seizures, this was felt to be unnecessary. The notes were examined to determine whether seizures were continuing or when they stopped. There were often clear indicators in the notes, such as DVLC documentation allowing the patient to drive. However, the accuracy of this data could be questioned and all the patients ascertained were contacted and sent a questionnaire to ask about current and past seizure activity.

The results of the postal survey were compared to the notes and any discrepancies were discussed by the patient's GP the next time they attend the surgery.

Analysis of the prognosis utilised life table methods using the SPSS/PC statistical programme.

3.4. THE ECONOMIC COST OF EPILEPSY

Background

Epilepsy has important socio-economic costs to a population. It is important to assess these costs so that health care priorities can be set. A methodology was used to assess the burden of illness of epilepsy at the community level, and from this, costs for an individual, and the cost to the United Kingdom (UK) as a whole, were estimated. Cost analysis was based on two different populations of patients with epilepsy, a prevalent and an incident population. Patients with newly diagnosed epilepsy (n=602), from the NGPSE were compared with patients with established epilepsy (n=1628), who were identified from general practices throughout the UK as part of the National Epilepsy Survey (NES. Indirect and direct costs were assessed in the NES, and direct costs in the NGPSE.

3.4.1 Subjects

3.4.1.1 Established active epilepsy, the National Epilepsy Survey (NES)

One thousand eight hundred and fifty patients with definite epilepsy participated in the study having been identified anonymously from 104 general practices as part of a wider survey into the care of epilepsy in the community, called the National Epilepsy Survey (NES), carried out previously.(Hart, 1992) The general practices were randomly selected from all over the UK, by sending details of the study and invitations to participate to every the Family Health Service Authority in the country. Participating GPs included all patients with definite epilepsy of any aetiology who were receiving anti epileptic medication in their catchment population. 222 patients were excluded who had febrile seizures or only one seizure. 1628 patients with a definite seizure disorder who were on treatment were included in the analysis, of whom 14% were under 20, and 23% aged 60 or more years, 50% were male, 70% had epilepsy for 5 years or more, and 8% were diagnosed in the previous 12 months. 64% had at least one seizure in the previous 2 years. 20% had seizures at a frequency of one month or more. Each patient was sent an anonymous questionnaire asking about seizure severity, treatment, medical care, and state benefits received. Medical information was then cross-checked with the GP records and further details of this study can be found elsewhere (Hart, 1992). The average cost for each patient was calculated per annum for those with active epilepsy (defined as the occurrence of at least one seizure in the previous 24 months) and those with inactive epilepsy (no seizures in last 2 years), and then projected for the whole UK, based on the number of patients with active and inactive epilepsy in the NES, and the total number of patients in the UK with epilepsy on AEDs = 7.8/1000. (Goodridge and Shorvon , 1983)

3.4.1.2 Newly diagnosed epilepsy, the National General Practice Study Of Epilepsy (NGPSE)

The classification at five years after entry was used. 602 patients were classified as having definite epilepsy. The costs were calculated for each year after the patient was entered into the study up to 8 years of follow up, and a projected total cost to the UK was calculated assuming the incidence of epilepsy to be 30, 000 new cases per year in the UK. Costs were based on data obtained by the annual questionnaire: investigations, drug therapy, GP, and hospital attendances. No data was collected on the social or transfer costs.

3.4.2 Cost derivations

In this study the following costs were calculated.

Direct costs: the drug costs were calculated from the British National Formulary for the stated minimum recommended dosage (costs per annum: carbamazepine £93, phenytoin £22, valproate £120, clonazepam £128, clobazam £63, phenobarbitone £4, primidone £13, ethosuximide £126, lamotrogine £840, vigabatrin £670) (British Medical Association and Royal Pharmaceutical Society of Great Britain, 1993). The cost of GP services were taken from the Compendium of Health Statistics, (Office of Health Economics, 1989) and the hospital services were from one Health Authority (annual cost of out patient care per patient £200; based on average of 1 new consultation & 1 follow up for new patients, and 4 consultations for old patients; annual cost of in-patient care per patient £2000: based on average stay of 4.5 days).

Indirect costs: the cost of benefits received was calculated from data supplied by the National Hospitals for Neurology and Neurosurgery social work department (mean values). The cost of unemployment was based on the Department of Employment's average weekly wage figures for 1992 of £304. The cost of residential care and special schooling used data supplied by the Chalfont Centre for Epilepsy (mean £21,000 per annum per patient), and the St Piers Lingfield school (mean £27,000 per annum per patient). Mortality costs of epilepsy were calculated from data obtained on patients with severe chronic epilepsy from our own practice, with 1 in 260 patients with epilepsy dying directly due to epilepsy per annum, at a mean age of 38 years, (Klenerman et al., 1993) which is similar to other estimates. (Leestma et al., 1989) The cost of excess mortality for the NES population was estimated for each death, assuming a mean number of years lost productivity of 65 years minus 38 years, and then using the discounting method, based on the Treasury's current recommended rate of 6%. (Robinson, 1993a) Total costs were to the nearest significant digit.

SECTION 4

RESULTS

4.1. THE PROGNOSIS OF EPILEPSY

4.1.1. The NGPSE cohort at 6 months and 5 years

The NGPSE cohort was classified at 6 months by a diagnostic review panel and this exercise was repeated for all patients after 5 years from entry. To avoid bias this thesis will use the 6 month classification, but the 5 year classification is still of interest in terms of what happens to patients when the diagnosis was not at first clear. This section summarises the demographic and clinical features of the cohort, and examines why patients were diagnosed as having possible or probable epilepsy and what has happened to the classification of these patients at the present time.

Table 8 shows the classification of patients at 6 months and 5 years after registration. Of the 1091 patients who presented with a possible seizure disorder, only half had definite epilepsy, and 228 patients had possible epilepsy, the remainder having febrile seizures or some other disorder. After 5 years this has not changed significantly. 52 patients with possible epilepsy were able to be classified as definite epilepsy, leaving 176 patients whose diagnosis remained uncertain. This is principally because most patients with definite or possible seizures entered remission and the information on each patient did not substantially change if further seizures were not witnessed or investigated further.

Table 8 *The 6 month and 5 year classification of the NGPSE cohort*

Classification	*6 months*	*5 year*
Definite epilepsy	564	602
Possible / probable epilepsy	228	176
Not epilepsy	79	97
Febrile convulsions	220	216
Excluded	104	104

Table 9 shows the classification of patients with definite epilepsy according to the 1981 ILEA classification of seizures.

Table 9 *The 6 month classification of seizures*

Seizure type	*No.*	*%*
Generalised		
Tonic clonic	198	35
Absence	6	1
Mixed	14	2
Others	3	<1
Partial		
Simple	15	3
Complex	61	11
2^0generalised	151	27
Mixed	65	12
Unclassifiable	51	9

Table 10 shows the age distribution at registration of patients with possible and definite epilepsy. 37% were under 20 years of age, and 25% were over 60 years. The sex distribution was approximately equal in patients with definite epilepsy at all ages, 51% male, and 49% female. However, in patients with possible epilepsy 41% were male and 59% female.

Table 10 *Age distribution of patients with definite and possible seizures in NGPSE*

	Definite epilepsy		*Possible epilepsy*		*Definite & possible*	
Age	No.	%	No.	%	No.	%
0-4	39	7	35	15	74	9
5-9	51	9	12	5	63	8
10-14	49	9	23	10	72	9
15-19	66	12	20	9	86	11
20-29	74	13	28	13	102	13
30-39	62	11	21	9	83	10
40-49	35	6	12	5	47	6
50-59	52	9	17	8	69	9
60-69	63	11	16	7	79	10
70-79	43	8	20	9	63	8
80-89	23	4	19	8	42	5
>90	7	1	5	2	12	2

Table 11 shows the aetiology of patients with definite epilepsy when classified according to broad groupings. The majority of patients (61%) had idiopathic epilepsy, with remote symptomatic causes contributing 21% of patients.

Table 11 *NGPSE broad aetiology*

Aetiology	*No.*	*%*	*95% CI*
Idiopathic / Cryptogenic	346	61	57, 65
Remote symptomatic	119	21	18, 25
Acute symptomatic	83	15	12, 18
Neurological deficit at birth	16	3	2, 4

A more defined aetiology could be identified in 41% of patients, the commonest cause of which was vascular disease in 90 (16%) of patients, and tumours in 38 (7%). This is shown in table 12.

Table 12 *Aetiology in patients with definite epilepsy*

Aetiology	*No.*	*%*	*95% CI*
Idiopathic / Cryptogenic	335*	59	55, 63
Vascular	90	16	13, 19
Tumour	38	7	5, 9
Alcohol	35	6	4, 8
Trauma	15	3	1, 4
Infection	9	2	1, 3
Other†			

* Different from the "idiopathic" group in table 11.

† Includes metabolic, eclampsia, drugs.

4.1.2. The remission of epilepsy

Summary

564 patients with definite epilepsy and 228 patients with possible epilepsy were followed up to death or 9 years. From the index seizure 95.5% (95% CI 93.2, 97.8) achieved a 1 year remission, 92.9% (95% CI 89.7, 96.1) achieved a 2 year remission, 85.7% (95% CI 81.5, 89.9) achieved a 3 year remission, and 68.1% (95% CI 61.2, 75.0) achieved a remission of 5 years after 9 years of follow up. With possible epilepsy included the rates increases to 87.2% (95% CI 83.7, 90.7) for 3 years, and 71.3% (95% CI 65.8, 76.9) for 5 year remission. The proportion of patients with definite epilepsy in terminal remission at 9 years follow up from the index seizure was 84.2% (95% CI 77.9, 90.5) for 1 year, 75.9% (95% CI 70.0, 81.8) for 2 year, 67.8% (95% CI 62.3, 73.3) for 3 year, and 54.4% (95% CI 48.9, 59.9) for 5 year remission. 86.3% (95% CI 81.1, 91.5) of idiopathic seizures achieved a 3 year remission by 9 years, and 62.0% (95% CI 56.2, 67.9) achieved a 5 year remission by 9 years, compared to 93.0% (95% CI 86.3, 99.7) of patients with remote symptomatic who achieved a 3 year remission, and 60.5% (95% CI 46.3, 74.8) who achieved 5 year remission by 9 years. The 3 year remission rates stratified by the ages at onset for < 16 years, 16-39 years, 40-60 years, and > 60 years by 9 years were 96.3% (95% CI 88.9, 103.6), 82.0%(95% CI 75.7, 88.4), 90.0% (95% CI 81.5, 98.6), and 84.9% (95% CI 73.4, 96.4) respectively, and for the 5 year remission rates by 9 years were 57.2% (95% CI 48.4, 65.9), 72.6% (95% CI 61.5, 83.8), 83.5% (95% CI 67.8, 99.2), and 60.7% (95% CI 45.0, 76.4) respectively. Seizure types, early patterns of seizures had a relatively weak affect on outcome.

4.1.2.1. Cumulative remission

Cumulative remission measures the proportion of patients who have ever achieved a particular remission period. These results were calculated using the Product-Limit method of actuarial analysis. All the results show the % achieving remission from the index, or first seizure, in 52 week periods. When the remission towards the end of the follow up periods does not alter (because every patient has already entered remission or no further patients reached the follow up time) a blank is inserted in the tables. The results will concentrate on 3 and 5 year remission, which are the preferred remission periods.

4.1.2.1.1. Remission from index and first seizure, for definite epilepsy and possible epilepsy

This section shows the remission for all the patients with definite or possible epilepsy. From the index seizure 95.5% (95% CI 93.2, 97.8) achieved a 1 year remission, 92.9% (95% CI 89.7, 96.1) achieved a 2 year remission, 85.7% (95% CI 81.5, 89.9) achieved a 3 year remission, and 68.1% (95% CI 61.2, 75.0) achieved a remission of 5 years by 9 years of follow up. From the first seizure the rates were 94.5% (95% CI 92.3, 96.7) for 1 year, 89.9% (95% CI 86.8, 93.0) for 2 year, 82.7% (95% CI 78.8, 86.6) for 3 year, and 64.3% (95% CI 59.1, 69.5) for 5 year remission. These rates are all higher for patients with possible epilepsy.

Tables 13-20 show the remission from the index seizure and tables 21-28 from the first seizure. The results are summarised in figures 1 and 2.

Table 13 *Definite epilepsy: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	53.5	79.9	86.3	90.1	92.6	93.5	94.4	94.7	95.5
95% CI	49.2, 58.8	76.38 3.5	83.2, 89.4	87.4, 92.8	90.2, 95.0	91.3, 95.8	92.2, 96.6	95.6, 96.8	93.2, 97.8
Number at risk	564	238	101	62	44	33	27	18	16
Withdrawals	52	12	5	1	0	1	6	0	9

Table 14 *Possible epilepsy: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	69.5	89.0	93.1	94.7	94.7	94.7	96.3	-	-
95% CI	63.3, 75.7	84.7, 93.3	89.6, 96.6	91.6, 97.8	91.6, 97.8	91.6, 97.8	93.4, 99.2	-	-
Number at risk	228	64	22	14	10	10	10	-	-
Withdrawals	18	2	1	0	0	0	4	-	-

Table 15 *Definite epilepsy: 2 year remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	47.5	68.0	77.5	82.2	86.1	88.5	90.6	92.9
95% CI	43.1, 51.9	63.8, 72.2	73.7, 81.3	78.7, 85.7	82.9, 89.3	85.5, 91.5	87.7, 93.5	89.7, 96.1
Number at risk	564	259	150	102	79	58	39	26
Withdrawals	71	10	5	2	4	11	6	15

Table 16 *Possible epilepsy: 2 year remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	65.5	78.8	85.4	87.6	90.0	90.7	92.0	-
95% CI	58.9, 72.1	73.0, 84.6	80.4, 90.4	82.9, 93.3	85.7, 94.3	86.5, 95.0	87.6, 96.4	-
Number at risk	228	69	39	26	22	17	13	-
Withdrawals	28	5	1	0	1	3	6	-

Table 17 *Definite epilepsy: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	44.2	61.4	68.5	73.9	78.4	82.9	85.7
95% CI	39.7, 48.7	57.0, 65.5	64.3, 72.7	69.9, 77.9	74.5, 82.3	79.1, 86.7	81.5, 89.9
Number at risk	564	265	177	141	111	73	41
Withdrawals	89	8	4	6	22	20	24

Table 18 *Possible epilepsy: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	61.5	73.5	79.8	84.6	88.0	90.1	-
95% CI	54.4, 68.6	67.0, 80.0	73.9, 85.7	79.2, 79.2	82.9, 93.1	85.1, 95.1	-
Number at risk	228	69	46	35	26	14	-
Withdrawals	44	2	0	1	8	4	-

Table 19 *Definite epilepsy: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	39.8	54.3	59.8	63.3	68.1
95% CI	35.3, 44.3	49.7, 58.9	55.1, 64.5	58.4, 68.2	61.2, 75.0
Number at risk	564	271	195	125	69
Withdrawals	114	12	50	48	43

Table 20 *Possible epilepsy: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	55.0	64.9	69.7	71.5	81.0
95% CI	47.6, 62.5	57.7, 72.1	62.5, 76.9	63.9, 79.1	69.1, 92.9
Number at risk	228	77	55	32	16
Withdrawals	57	6	17	15	10

Table 21 *Definite epilepsy: 1 year remission from first seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	41.3	74.3	82.4	87.1	90.2	91.7	92.4	94.2	94.5
95% CI	37.1, 45.6	70.5, 78.1	79.0. 85.8	84.2, 90.1	87.5, 92.9	89.2, 94.2	90.0, 94.8	92.0, 96.4	92.3, 96.7
Number at risk	564	303	125	83	60	45	37	29	18
Withdrawals	48	13	3	1	1	1	5	5	3

Table 22 *Possible epilepsy: 1 year remission from first seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	50.9	78.9	88.4	93.1	93.6	94.7	95.8	-	-
95% CI	44.2, 57.6	73.4, 84.4	84.0, 92.8	89.6, 96.6	90.2, 97.0	91.5, 97.9	93.0, 98.6	-	-
Number at risk	228	105	43	22	13	12	11	-	-
Withdrawals	14	3	1	1	0	0	1	-	-

Table 23 *Definite epilepsy: 2 year remission from first seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	33.9	60.6	72.7	78.5	83.2	85.5	87.1	89.9
95% CI	29.7, 38.1	6.3, 64.9	68.7, 76.7	74.8, 82.3	79.8, 86.6	82.3, 88.7	84.0, 90.2	86.8, 93.0
Number at risk	564	328	192	129	97	75	54	40
Withdrawals	68	5	5	5	1	12	8	12

Table 24 *Possible epilepsy: 2 year remission from first seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	44.7	68.5	82.2	85.0	87.2	89.5	90.7	-
95% CI	37.9, 51.5	62.1, 74.9	76.8, 87.7	79.9, 90.1	82.4, 92.0	85.1, 93.9	86.2, 95.2	-
Number at risk	228	115	61	32	27	23	17	-
Withdrawals	20	8	3	0	0	2	8	-

Table 25 *Definite epilepsy: 3 year remission from first seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	30.3	52.9	62.6	70.4	75.8	80.5	82.7
95% CI	26.8, 33.8	48.4, 57.4	58.3, 67.0	66.1, 74.7	71.8, 79.8	76.7, 884.3	78.8, 86.6
Number at risk	564	338	222	169	132	88	54
Withdrawals	79	8	8	2	22	19	20

Table 26 *Possible epilepsy: 3 year remission from first seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	40.6	60.4	72.6	77.4	82.1	84.9	84.9
95% CI	33.7, 47.5	53.4, 67.4	66.1, 79.1	71.2, 83.6	76.3, 87.9	79.2, 90.6	79.2, 90.6
Number at risk	228	114	71	47	37	23	15
Withdrawals	36	7	3	2	7	5	0

Table 27 *Definite epilepsy: 5 year remission from first seizure*

Weeks	260	312	364	416	468
Remission (%)	26.1	44.1	52.9	59.2	64.3
95% CI	22.1, 30.1	39.6, 48.7	48.3, 57.6	54.4, 64.0	59.1, 69.5
Number at risk	564	339	252	173	112
Withdrawals	105	5	42	41	48

Table 28 *Possible epilepsy: 5 year remission from first seizure*

Weeks	260	312	364	416	468
Remission (%)	36.5	53.8	64.0	65.8	75.2
95% CI	29.4, 43.6	46.4, 61.2	56.6, 71.4	58.4, 73.2	67.2, 83.2
Number at risk	228	113	78	47	38
Withdrawals	50	5	16	7	14

Figure 1 *Definite epilepsy remission from index seizure: 1, 2, 3, 5 year remission*

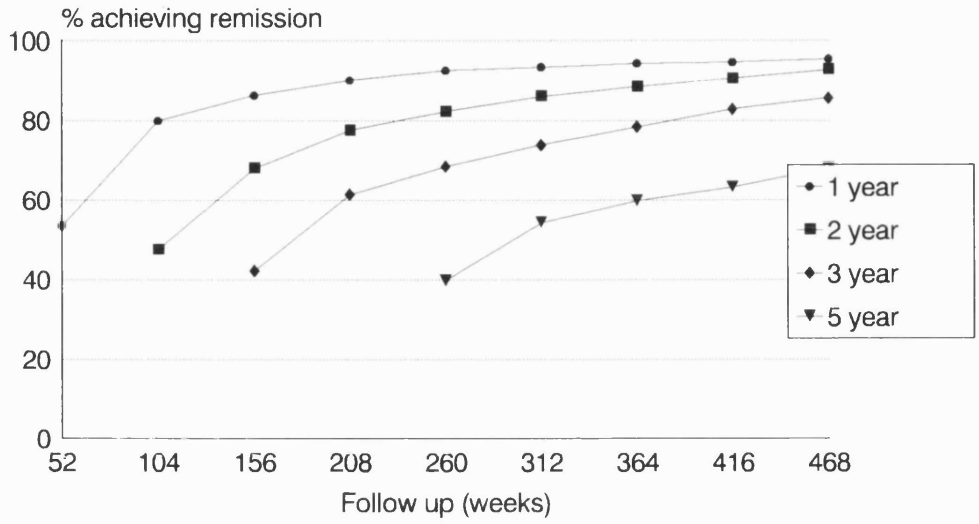
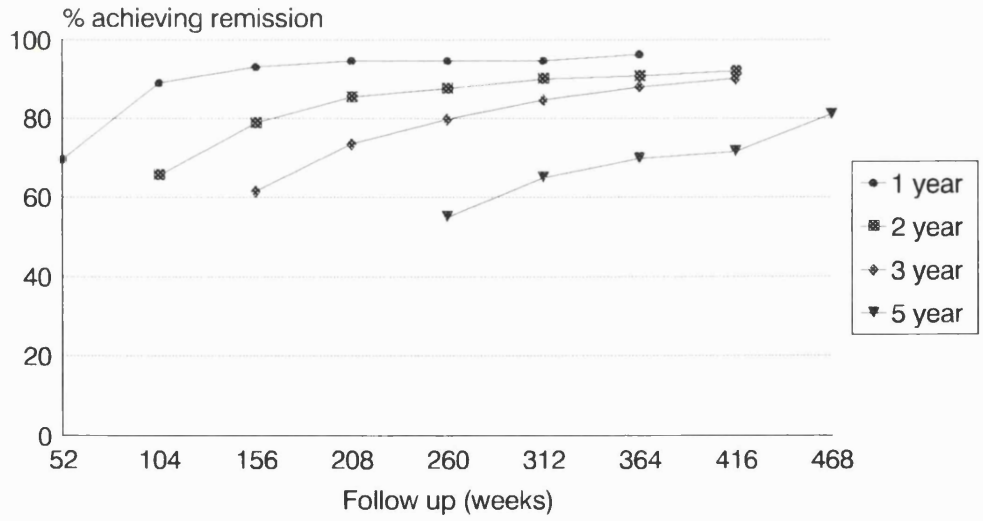


Figure 2 *Possible epilepsy remission from index seizure: 1, 2, 3, 5 year remission*



4.1.2.1.2. Possible and definite epilepsy combined: 1, 2, 3, and 5 year remission rates from index seizure

When patients with definite epilepsy and possible epilepsy were combined, the rates of remission by 9 years were 95.7% (95% CI 93.9, 98.5) for 1 year, 93.0% (95% CI 90.2, 95.8) for 2 year, 87.2% (95% CI 83.7, 90.7) for 3 year, and 71.3% (95% CI 65.8, 76.9) for 5 year remission.

The results are shown in tables 29-32, and summarised in figure 3.

Table 29 *Definite & possible epilepsy: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	58.2	81.9	88.3	91.4	93.0	93.8	94.9	95.2	95.7
95% CI	61.8, 51.6	84.7, 79.1	85.9, 90.7	93.5, 91.0	91.1, 94.9	92.0, 95.7	93.2, 96.6	93.5, 96.9	93.9, 98.5
Number at risk	792	302	123	75	54	44	37	22	20
Withdrawals	70	14	6	1	0	2	10	1	8

Table 30 *Definite & possible epilepsy: 2 year remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	52.7	71.4	79.8	83.8	87.2	89.1	91.0	93.0
95% CI	49.0, 56.4	68.0, 74.8	76.7, 82.8	81.0, 86.6	84.7, 89.8	86.7, 91.6	88.6, 93.4	90.2, 95.8
Number at risk	792	328	188	128	101	75	50	32
Withdrawals	99	5	6	2	5	16	11	21

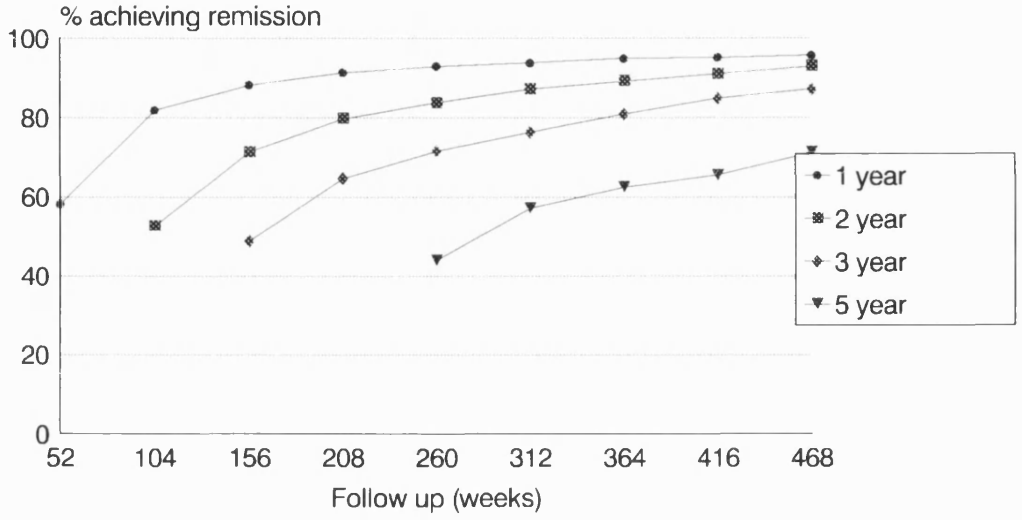
Table 31 *Definite & possible epilepsy: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	48.9	64.7	71.6	76.4	81.0	84.9	87.2
95% CI	45.1, 52.8	61.0, 68.4	68.1, 75.1	73.1, 79.7	77.8, 84.2	81.8, 88.0	83.7, 90.7
Number at risk	792	334	223	176	137	87	48
Withdrawals	138	10	4	7	30	25	31

Table 32 *Definite & possible epilepsy: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	44.0	57.2	62.5	65.5	71.3
95% CI	40.1, 47.9	53.3, 61.2	58.6, 66.4	61.4, 69.6	65.8, 76.9
Number at risk	792	348	250	157	82
Withdrawals	171	18	67	66	53

Figure 3 *Definite and possible epilepsy combined, remission from index seizure: 1, 2, 3, 5 year remission*



4.1.2.1.3. Possible and definite epilepsy: 3, and 5 year remission rates from first seizure if seizure within 6 months of index seizure

The NGPSE identified patients with new onset epilepsy, not necessarily from the first seizure. These results show the remission rates from the first seizure where this occurred within six months of the index seizure, thus excluding those patients where there was a significant delay before coming to medical attention. 86.1% (95% CI 81.6, 90.6) of patients with definite epilepsy whose first seizure occurred within 6 months of the index seizure achieved a remission of 3 years, and 66.3% (95% CI 60.5, 72.1) a remission of 5 years. The rates for possible epilepsy were higher, at 89.8% (95% CI 84.3, 95.4) for 3 year, and 84.9% (95% CI 72.6, 97.2) for 5 year remission.

This is shown in tables 33-36.

Table 33 *Definite epilepsy: 3 year remission from first seizure if seizure within 6 months of index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	35.1	62.1	70.7	75.8	80.3	84.3	86.1
95% CI	30.0, 40.2	56.9, 67.3	65.8, 75.6	71.1, 80.5	75.8, 84.8	80.0, 88.7	81.6, 90.6
Number at risk	412	218	121	92	75	46	26
Withdrawals	76	8	2	1	17	12	9

Table 34 *Definite epilepsy: 5 year remission from first seizure if seizure within 6 months of index seizure*

Weeks	260	312	364	416	468
Remission (%)	32.5	54.4	61.5	64.5	66.3
95% CI	27.3, 37.7	48.9, 59.9	56.0, 67.0	59.0, 70.0	60.5, 72.1
Number at risk	412	214	141	89	55
Withdrawals	95	4	32	28	17

Table 35 *Possible epilepsy: 3 year remission from first seizure if seizure within 6 months of index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	51.2	74.2	80.9	85.9	89.8	-	-
95% CI	42.4, 60.0	66.5, 81.9	74.0, 87.9	79.7, 92.1	84.3, 95.4	-	-
Number at risk	155	61	31	23	17	-	-
Withdrawals	30	2	3	0	0	-	-

Table 36 *Possible epilepsy: 5 year remission from first seizure if seizure within 6 months of index seizure*

Weeks	260	312	364	416	468
Remission (%)	47.9	65.1	71.3	84.9	-
95% CI	38.9, 56.0	56.6, 73.6	62.8, 79.8	72.6, 97.2	
Number at risk	155	62	37	22	-
Withdrawals	36	3	11	16	-

4.1.2.1.4. Remission in Definite epilepsy where index was the first seizure; 1, 2, 3, and 5 year remission

In about half of the patients with definite epilepsy, the index seizure was actually the first seizure, and these results show the remission rates for these patients. The remission rates are higher than for the group as a whole. By 9 years 98.1% (95% CI 95.1, 101.2) achieved a 1 year remission, 96.4% (95% CI 93.2, 99.6) a 2 year remission, 92.2% (95% CI 87.7, 96.7) a 3 year remission, and 72.1% (95% CI 65.4, 78.9) a 5 year remission.

These results are shown in tables 37-40.

Table 37 *Index = first seizure: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	63.5	87.1	92.1	94.9	96.2	98.1	-	-	-
95% CI	57.1, 69.8	82.5, 91.7	88.3, 95.9	91.8, 98.1	93.4, 99.2	95.1, 101.2	-	-	-
Number at risk	252	80	25	14	8	6	-	-	-
Withdrawals	33	7	2	1	0	2	-	-	-

Table 38 *Index = first seizure: 2 year remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	58.5	77.1	86.8	91.9	93.1	95.2	95.2	96.4
95% CI	51.7, 65.2	71.3, 82.9	82.0, 91.5	88.0, 95.9	89.9, 96.8	91.9, 96.3	91.9, 96.3	93.2, 99.6
Number at risk	252	86	45	23	14	12	7	5
Withdrawals	45	4	4	0	0	2	2	1

Table 39 *Index = first seizure: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	55.3	69.8	77.5	83.5	85.5	92.2	-
95% CI	48.4, 62.2	63.4, 76.2	71.5, 83.4	78.2, 88.8	80.4, 90.64	87.7, 96.7	-
Number at risk	252	89	55	41	29	21	-
Withdrawals	53	5	1	1	5	5	-

Table 40 *Index = first seizure: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	52.2	64.1	69.8	72.1	-
95% CI	45.0, 59.3	57.2, 71.0	63.1, 76.5	65.4, 78.9	-
Number at risk	252	89	65	41	-
Withdrawals	66	2	15	5	-

4.1.2.1.5. Definite epilepsy excluding acute symptomatic epilepsy; 3 and 5 year remission

When epilepsy is precipitated by an acute insult to the central nervous system it has previously been thought that these patients were at a much lower risk of developing epilepsy, and, indeed, most studies of epilepsy have excluded patients with acute symptomatic seizures. This section shows the remission rates for patients with definite epilepsy, excluding those patients where there was an acute provoking insult, such as hypoglycaemia, or alcohol.

By 9 years 81.4% (95% CI 77.2, 85.7) had achieved a 3 year remission, and 61.7% (95% CI 56.0, 67.4) had achieved a 5 year remission.

These results are shown in tables 41-42.

Table 41 *3 year remission from index seizure excluding acute symptomatic*

Weeks	156	208	260	312	364	416	468
Remission (%)	25.5	48.4	60.0	67.9	73.7	78.9	81.4
95% CI	21.3, 29.7	43.6, 53.2	55.3, 64.7	63.3, 72.5	69.3, 78.1	74.6, 83.2	77.2, 85.7
Number at risk	481	313	209	156	123	82	50
Withdrawals	61	8	8	2	21	18	17

Table 42 *5 year remission from index seizure excluding acute symptomatic*

Weeks	260	312	364	416	468
Remission (%)	21.0	39.7	49.4	55.9	61.7
95% CI	17.0, 25.0	37.0, 42.4	44.0, 54.4	50.7, 61.1	56.0, 67.4
Number at risk	481	313	235	160	106
Withdrawals	85	4	40	36	44

4.1.2.1.6. Definite epilepsy excluding single seizures; 3 and 5 year remission

Single seizures are also not considered by many workers to be epilepsy, and to allow comparisons we have excluded patients who only suffered one seizure. By 9 years 81.8% (95% CI 76.0, 87.1) had achieved a 3 year remission, and 59.7%% (95% CI 52.1, 67.3) had achieved a 5 year remission.

These results are shown in tables 43-46.

Table 43 *Remission excluding single seizures: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	41.2	73.5	82.7	87.5	90.3	91.8	92.9	93.3	94.3
95% CI	46.0, 37.2	69.1, 77.8	78.9, 86.5	84.1, 90.8	87.3, 93.4	89.0, 94.6	90.2, 95.7	90.7, 96.0	91.4, 97.2
Number at risk	237	101	62	44	34	27	18	16	6
Withdrawals	25	11	5	1	0	2	6	1	9

Table 44 *Remission excluding single seizures: 2 year remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	33.4	60.0	71.5	77.4	82.4	85.4	88.0	91.0
95% CI	28.7, 38.1	55.1, 64.9	66.9, 76.1	73.2, 81.7	78.5, 86.4	81.6, 89.2	84.4, 91.7	87.0, 95.1
Number at risk	259	149	102	79	58	39	26	8
Withdrawals	39	10	5	2	3	11	6	1

Table 45 *Remission excluding single seizures: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	29.3	51.1	60.1	67.0	73.0	78.4	81.8
95% CI	24.7, 33.9	46.0, 56.2	62.1, 71.8	62.1, 71.8	68.3, 77.8	73.6, 83.1	76.0, 87.1
Number at risk	265	177	141	111	72	41	13
Withdrawals	53	7	4	6	22	20	24

Table 46 *Remission excluding single seizures: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	23.9	42.3	49.2	53.6	59.7
95% CI	18.7, 29.1	37.1, 47.5	43.8, 54.4	47.9, 59.3	52.1, 67.3
Number at risk	428	195	125	69	22
Withdrawals	72	12	50	48	43

4.1.2.1.7. Definite epilepsy excluding acute symptomatic seizures and single seizures; 3 and 5 year remission

In this section in order to allow comparisons with other studies, all patients with acute symptomatic seizures and those who have only suffered one seizure were excluded. By 9 years 81.6% (95% CI 76.0, 87.1) had achieved a 3 year remission, and 60.3% (95% CI 52.3, 68.2) had achieved a 5 year remission.

These results for 1,2, 3, and 5 year remission are shown in tables 47-50, and summarised in figure 4.

Table 47 *Remission excluding acute symptomatic and single seizures: 1 year remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	40.2	72.92	82.7	87.6	90.1	91.7	92.5	93.9	-
95% CI	35.2, 45.2	68.3, 77.5	78.7, 86.7	84.1, 91.1	86.9, 93.3	88.7, 94.7	89.6, 95.4	90.9, 97.0	-
Number at risk	397	223	95	57	40	32	25	17	-
Withdrawals	24	11	5	1	0	2	6	9	-

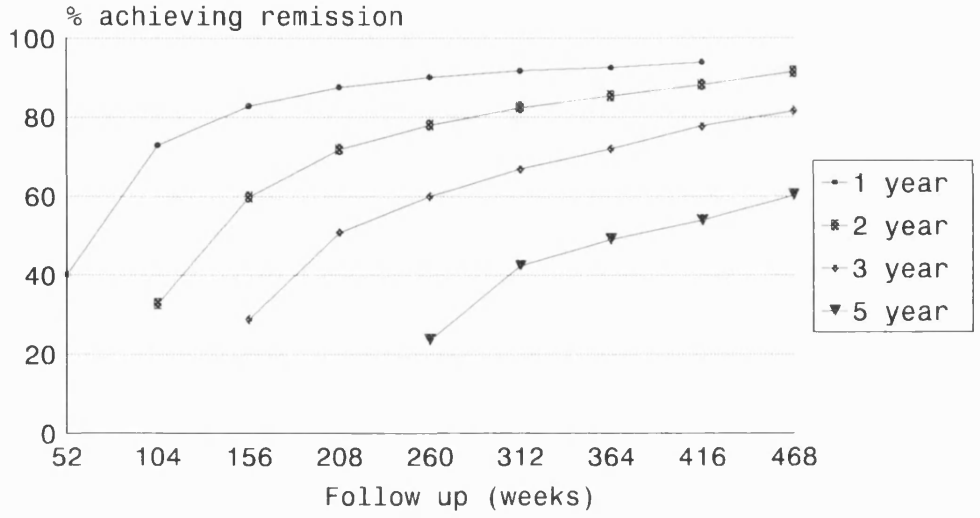
Table 48 *Remission excluding acute symptomatic and single seizures: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	28.9	50.8	59.9	66.8	71.9	77.7	81.6
95% CI	24.1, 33.7	45.5, 56.1	54.7, 65.1	61.7, 71.8	66.9, 76.9	72.7, 82.7	76.0, 87.1
Number at risk	397	246	164	130	102	67	38
Withdrawals	51	8	4	6	22	18	22

Table 49 *Remission excluding acute symptomatic and single seizures: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	23.7	42.4	49.1	53.9	60.3
95% CI	19.1, 28.3	37.0, 47.7	43.5, 54.7	47.9, 59.9	52.3, 68.2
Number at risk	397	251	180	115	64
Withdrawals	68	11	47	43	39

Figure 4 *Remission of patients with definite epilepsy excluding patients with acute symptomatic and single seizures*



4.1.2.1.8. Remission according to aetiological category; 3 and 5 year remission

Aetiology might be expected to be the most important determinate of the probability of entering remission. In this section patients with definite epilepsy were divided up into the categories of idiopathic (which includes those with true idiopathic epilepsy and those patients with no identifiable cause), acute symptomatic, remote symptomatic, and patients with a congenital cause presumed to be present at birth.

By 9 years 86.3% (95% CI 81.1, 91.5) of patients with idiopathic epilepsy had achieved a 3 year remission, and 62.0% (95% CI 56.2, 67.9) a 5 year remission. This compares with patients with remote symptomatic epilepsy of whom 74.7% (95% CI 62.5, 86.9) who achieved a 3 year remission, and 60.5% (95% CI 46.3, 74.8) a 5 year remission. Only the difference between the 3 year remission rates of patients with idiopathic and remote symptomatic epilepsy achieved statistical significance ($p< 0.01$). By 9 years 92.8% (95% CI 86.1,99.5) of patients with acute symptomatic epilepsy achieved a 3 year remission, and 78.2% (95% CI 67.7, 88.6) a 5 year remission. Patients with congenital deficits fared significantly worse, although the confidence limits were wide due to the small numbers.

These results are shown in tables 50-57, and summarised in figures 5 & 6.

Table 50 *Idiopathic: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	41.4	61.0	68.2	74.7	78.4	83.1	86.3
95% CI	36.0, 46.7	55.7, 66.3	63.1, 73.3	62.2, 78.8	73.8, 83.1	78.5, 87.8	81.1, 91.5
Number at risk	345	190	124	100	79	51	29
Withdrawals	21	3	1	3	17	13	18

Table 51 *Idiopathic: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	36.5	44.2	52.8	58.4	62.0
95% CI	31.2, 41.8	38.7, 49.7	47.2, 58.3	52.8, 64.0	56.2, 67.9
Number at risk	345	200	170	142	90
Withdrawals	31	0	0	-	-

Table 52 *Remote symptomatic: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	37.5	47.9	59.4	66.4	68.7	74.7	-
95% CI	26.3, 48.7	36.2, 59.6	47.6, 71.2	54.8, 78.1	57.0, 80.3	62.5, 86.9	-
Number at risk	119	45	34	23	19	14	-
Withdrawals	47	4	4	0	03	5	-

Table 53 *Remote symptomatic: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	33.9	45.8	53.7	60.5	-
95% CI	33.8, 46.0	33.0, 58.5	40.7, 66.7	46.3, 74.8	-
Number at risk	119	39	31	22	-
Withdrawals	60	1	5	10	-

Table 54 *Acute symptomatic: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	70.3	79.7	85.9	90.6	92.8	-	-
95% CI	59.1, 81.5	69.6, 89.6	77.4, 95.4	83.5, 97.7	86.1, 99.5	-	-
Number at risk	83	19	9	6	3	-	-
Withdrawals	19	0	2	3	3	-	-

Table 55 *Acute symptomatic: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	67.7	74.5	78.2	-	-
95% CI	56.1, 79.4	63.5, 85.4	67.7, 88.6	-	-
Number at risk	83	20	15	-	-
Withdrawals	21	1	2	-	-

Table 56 *Congenital deficits: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	28.6	50.0	50.0	62.5	81.3	-	-
95% CI	4.9, 52.2	23.8, 76.2	23.8, 76.2	33.6, 91.4	51.5, 111.0	-	-
Number at risk	16	10	7	5	3	-	-
Withdrawals	2	2	1	2	0	-	-

Table 57 *Congenital deficits: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	15.4	32.7	-	-	-
95% CI	-, 35.0	6.0, 58.7	-	-	-
Number at risk	16	11	-	-	-
Withdrawals	3	2	-	-	-

Figure 5 *Remission according to broad aetiologies: 3 year remission*

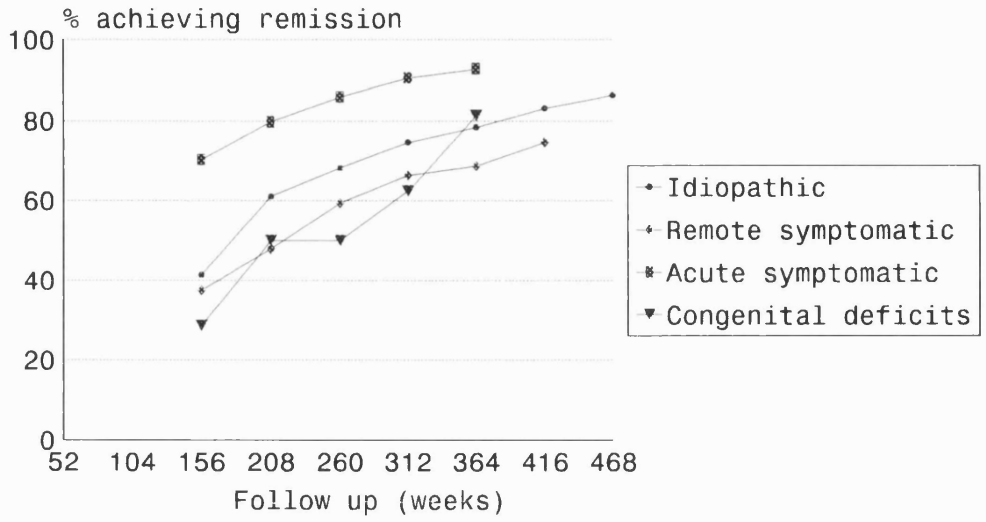
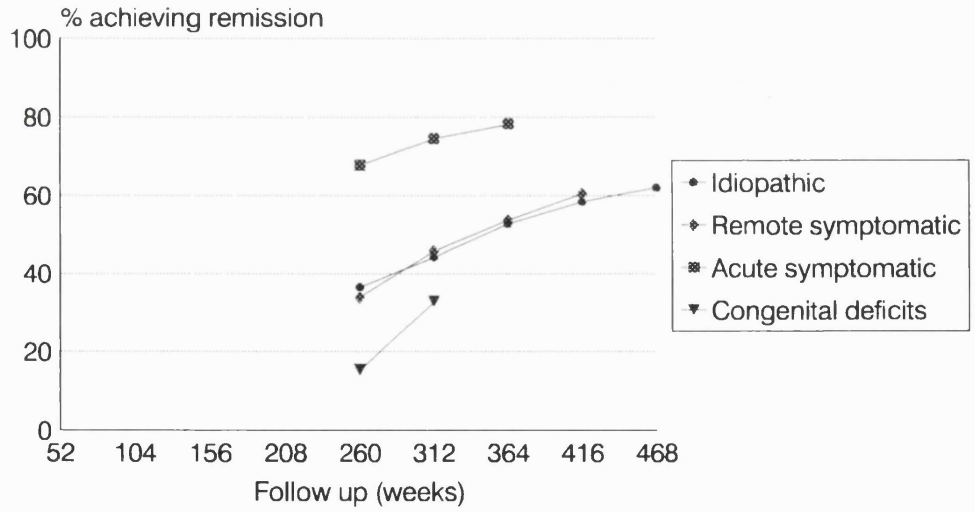


Figure 6 *Remission according to broad aetiologies: 5 year remission*



4.1.2.1.9. Remission according to specific aetiologies

Symptomatic causes of epilepsy account for 39% of patients with definite epilepsy in the NGPSE. The three commonest causes were cerebrovascular disease, tumours, and alcohol. In this section the remission rates for these patients are shown.

70.4% (95% CI 38.2, 102.5) of patients with tumours achieved a 3 year remission, and 42.9% (95% CI 6.2, 79.5) achieved a 5 year remission. 76.6% (95% CI 63.9, 89.3) of patients with vascular causes achieved a 3 year remission, and 77.5% (95% CI 60.3, 94.8) achieved a 5 year remission. 86.8% (95% CI 74.6, 99.0) of patients with epilepsy secondary to alcohol achieved a 3 year remission, and 73.3% (95% CI 57.3, 89.8) achieved a 5 year remission.

The results are shown in tables 58-63, and summarised in figures 7 & 8.

Table 58 *Tumour: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	33.3	44.5	44.5	70.4	70.4	-	-
95% CI	2.54, 64.1	12.0, 80.0	12.0, 80.0	38.2, 102.5	38.2, 102.5	-	-
Number at risk	38	6	4	2	1	-	-
Withdrawals	29	0	1	1	0	-	-

Table 59 *Tumour: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	14.3	28.6	42.9	-	-
95% CI	-, 40.2	-, 62.0	6.2, 79.5		
Number at risk	38	6	5	-	-
Withdrawals	31	0	0	-	-

Table 60 *Vascular: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	38.2	54.2	65.8	73.7	76.6	-	-
95% CI	25.4, 51.0	40.7, 67.7	52.4, 79.3	60.3, 87.2	63.9, 89.3	-	-
Number at risk	90	34	21	13	10	-	-
Withdrawals	35	5	3	0	1	-	-

Table 61 *Vascular: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	42.9	57.1	65.0	77.5	-
95% CI	27.9, 57.8	42.2, 72.1	50.4, 79.7	60.3, 94.8	-
Number at risk	90	24	18	13	-
Withdrawals	24	0	15	8	-

Table 62 *Alcohol: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	70.6	79.4	82.4	86.8	-	-	-
95% CI	52.3, 85.9	65.8, 93.0	69.5, 95.2	74.6, 99.0	-	-	-
Number at risk	35	10	7	5			-
Withdrawals	1	0	1	1	-	-	-

Table 63 *Alcohol: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	64.7	64.7	73.3	-	-
95% CI	48.6, 80.8	48.6, 80.8	57.3, 89.8	-	-
Number at risk	35	12	11	-	-
Withdrawals	1	1	3	-	-

Figure 7 *Remission according to specific aetiologies: 3 year remission*

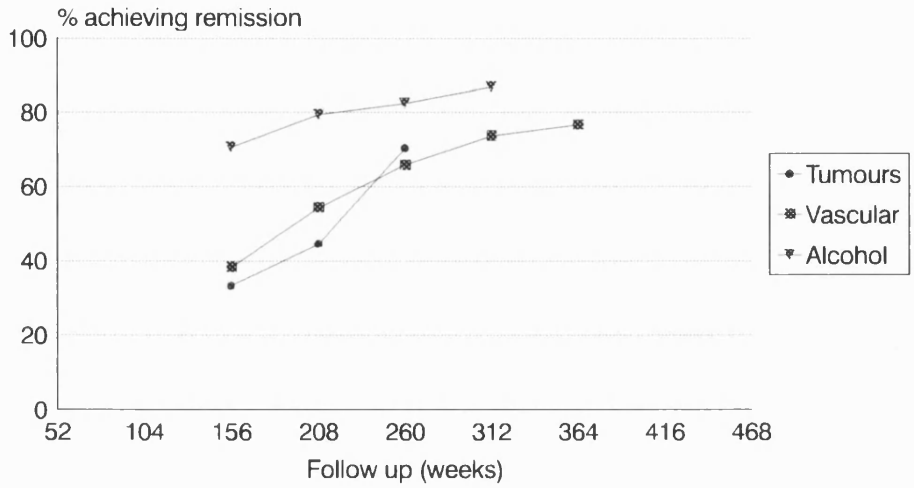
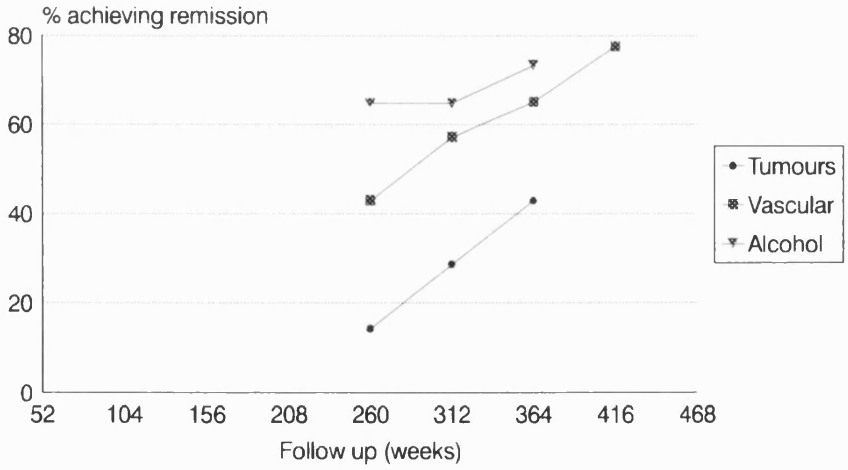


Figure 8 *Remission according to specific aetiologies: 5 year remission*



4.1.2.1.10. Remission according to age; 3 and 5 year remission

There are many reasons to believe that age of onset of epilepsy would have a powerful modulating influence of the chances for achieving remission. Different aetiologies are more common in different age groups, and the brain undergoes maturational changes that alter the susceptibility to the effects of seizures.

The 3 year remission rates stratified by the ages at onset for < 16 years, 16-39 years, 40-60 years, and > 60 years by 9 years were 96.3% (95% CI 88.9, 103.6), 82.0%(95% CI 75.7, 88.4), 90.0% (95% CI 81.5, 98.6), and 84.9% (95% CI 73.4, 96.4) respectively, and the 5 year remission rates by 9 years were 57.2% (95% CI 48.4, 65.9), 72.6% (95% CI 61.5, 83.8), 83.5% (95% CI 67.8, 99.2), and 60.7% (95% CI 45.0, 76.4) respectively.

The results are shown in tables 64-71, and summarised in figures 9 & 10.

Table 64 < *16 years: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	34.5	51.7	64.2	69.8	73.0	81.6	96.3
95% CI	26.7, 42.2	43.6, 59.9	56.4, 72.0	62.3, 77.3	65.7, 80.3	74.8, 88.4	88.9, 103.6
Number at risk	148	95	70	51	43	33	18
Withdrawals	3	0	1	0	6	6	10

Table 65 <*1 6 years: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	29.6	45.3	52.7	57.2	-
95% CI	22.1, 37.1	37.0, 53.5	44.3, 61.2	48.4, 65.9	-
Number at risk	148	100	75	50	-
Withdrawals	21	1	2	-	-

Table 66 *16-39 years: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	47.0	64.0	67.9	73.1	79.5	80.5	82.0
95% CI	39.8, 54.2	57.1, 71.0	61.1, 74.7	66.6, 79.6	73.3, 85.6	74.4, 86.7	75.7, 88.4
Number at risk	193	97	65	58	46	28	18
Withdrawals	10	1	0	3	9	9	5

Table 67 *16-39 years: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	42.9	57.0	61.1	63.2	72.6
95% CI	35.7, 50.1	49.8, 64.2	53.8, 68.3	55.7, 70.7	61.5, 83.8
Number at risk	193	104	74	52	28
Withdrawals	11	5	16	22	25

Table 68 *40-60 years: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	63.8	76.8	81.6	84.1	86.7	90.0	-
95% CI	52.4, 75.1	66.9, 86.8	80.6, 90.8	75.4, 92.7	78.1, 95.3	81.5, 98.6	-
Number at risk	87	25	16	13	11	5	-
Withdrawals	18	16	0	0	5	1	-

Table 69 *40-60 years: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	53.0	65.8	71.0	75.2	83.5
95% CI	41.0, 65.1	54.2, 77.4	59.2, 82.9	62.5, 87.8	67.8, 99.2
Number at risk	87	31	21	11	6
Withdrawals	21	2	8	4	3

Table 70 *>60 years: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	38.5	56.8	66.4	75.4	79.9	84.9	-
95% CI	27.7, 49.3	45.5, 68.1	55.3, 77.7	64.8, 86.0	96.6, 90.2	73.4, 96.4	-
Number at risk	136	48	29	19	13	9	-
Withdrawals	58	6	4	1	2	5	-

Table 71 *>60 years: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	40.0	55.2	60.7	-	-
95% CI	27.6, 52.4	42.5, 67.8	45.0, 76.4	-	-
Number at risk	136	36	26	-	-
Withdrawals	76	1	1	-	-

Figure 9 *Remission according to age: 3 year remission*

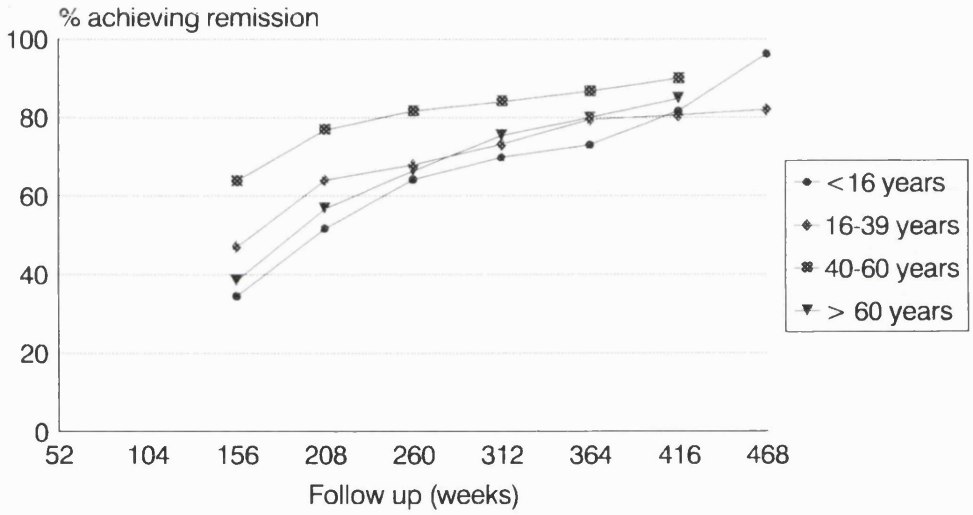
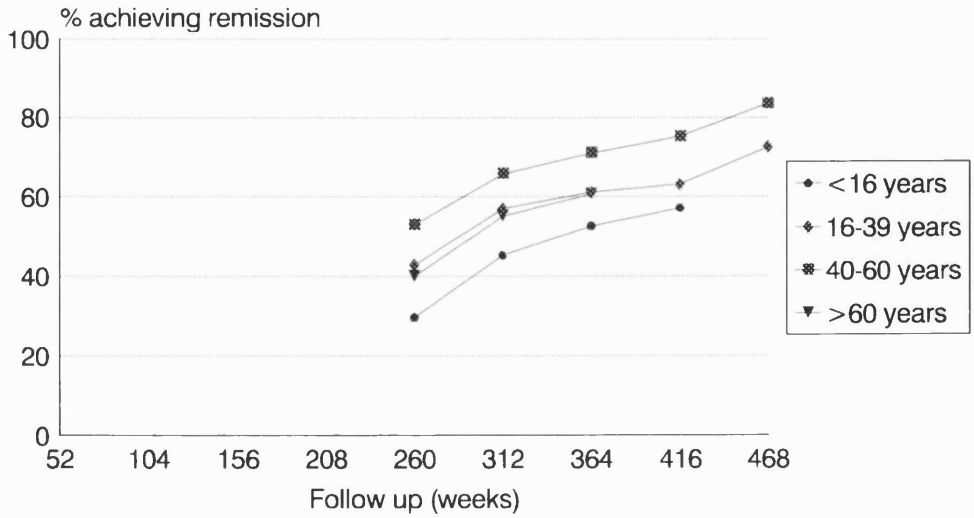


Figure 10 *Remission according to age: 5 year remission*



4.1.2.1.11. Remission according to seizure type; 3 and 5 year remission

Seizure type had a relatively weak influence on remission, and although patients with partial seizures had lower rates than patients with generalised onset seizures this was not statistically significant. From the index seizure by 9 years 80.1% (95% CI 73.9, 86.3) of partial onset, and 71.3% (95% CI 60.9, 81.8) of generalised onset achieved a 3 year remission by 9 years. 63.2% (95% CI 54.7, 71.7) of partial onset, and 71.3% (95% CI 60.9, 81.8) of generalised onset achieved a 5 year remission by 9 years.

The results are shown in tables 73-75 and summarised in figures 11-12.

Table 72 *Generalised onset: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	50.5	64.0	73.2	76.3	81.3	87.5	90.6
95% CI	46.6, 57.4	57.3, 70.6	67.0, 79.4	70.3, 82.2	75.7, 86.9	82.3, 92.7	84.0, 97.1
Number at risk	221	100	52	44	29	14	3
Withdrawals	10	2	1	2	7	7	10

Table 73 *Generalised onset: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	43.4	53.7	61.2	62.8	71.3
95% CI	36.5, 50.3	46.8, 60.7	54.2, 68.3	55.7, 69.9	60.9, 81.8
Number at risk	221	112	88	53	45
Withdrawals	23	4	23	6	34

Table 74 *Partial onset: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	38.7	62.7	68.9	73.7	76.9	80.1	-
95% CI	32.4, 45.0	56.4, 69.0	62.8, 75.0	67.7, 79.7	70.6, 82.9	73.9, 86.3	-
Number at risk	292	141	79	64	42	28	-
Withdrawals	62	9	2	14	10	8	-

Table 75 *Partial onset: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	36.3	52.7	55.6	60.6	63.2
95% CI	29.9, 42.8	46.0, 59.5	48.8, 62.4	53.2, 67.9	54.7, 71.7
Number at risk	292	135	95	66	37
Withdrawals	80	6	24	24	22

Figure 11 *Remission according to seizure type: 3 year remission*

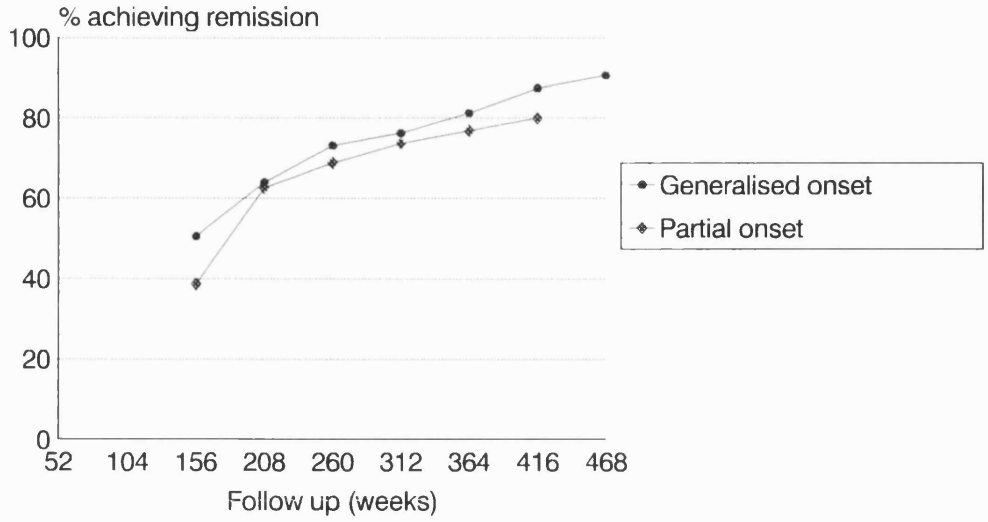
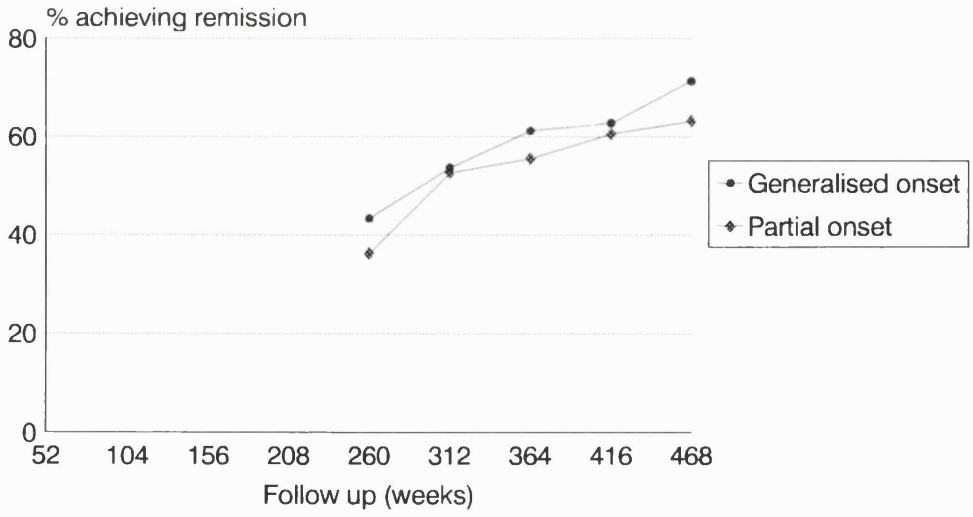


Figure 12 *Remission according to seizure type: 5 year remission*



4.1.2.1.12. The early pattern of seizures

More frequent seizures in the early part of the course of epilepsy may adversely influence outcome. In this section patients with definite epilepsy are stratified by whether seizures were multiple or single at the onset, and by the number of seizures prior to the index seizure.

4.1.2.1.12.1. Single versus multiple seizures at the onset of epilepsy

By 9 years 85.0% (95% CI 80.2, 89.8) of patients with a single seizure within a 24 hour period at the onset achieved a 3 year remission, and 66.6% (95% CI 60.2, 72.9) achieved a 5 year remission. This compares with 77.2% (95% CI 66.5, 87.9) of patients with multiple seizures within a 24 hour period at the onset who achieved a 3 year remission, and 58.8% (95% CI 45.6, 72.1) who achieved a 5 year remission (not significantly different).

These results are shown in tables 76-79.

Table 76 *Single seizure at onset: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	29.8	51.5	61.6	69.5	75.9	81.1	85.0
95% CI	24.6, 34.9	45.8, 57.1	56.1, 67.2	64.2, 74.8	70.9, 80.9	76.3, 86.0	80.2, 89.8
Number at risk	343	141	107	84	55	37	18
Withdrawals	44	5	5	1	13	7	13

Table 77 *Single seizure at onset: 5 year remission*

Weeks	260	312	364	416	468
Remission (%)	27.4	45.6	53.5	60.0	66.6
95% CI	22.2, 32.5	39.8, 51.4	47.6, 59.4	54.1, 66.0	60.2, 72.9
Number at risk	343	154	114	75	37
Withdrawals	58	1	19	25	28

Table 78 *Multiple seizures at onset: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	35.9	53.5	71.7	77.2	-	-	-
95% CI	24.2, 47.7	41.2, 65.8	60.5, 83.0	66.5, 87.9	-	-	-
Number at risk	83	29	17	11	-	-	-
Withdrawals	19	1	0	3	-	-	-

Table 79 *Multiple seizures at onset: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	30.0	46.7	53.6	58.8	-
95% CI	18.4, 41.6	34.0, 59.3	40.9, 66.2	45.6, 72.1	-
Number at risk	83	32	26	13	-
Withdrawals	23	0	2	11	-

4.1.2.1.12.2. Remission stratified by number of seizures prior to the index seizure

The cohort was also stratified by how many seizures occurred between the first and the index seizure. By nine years 81.5% (95% CI 74.6, 88.4) of patients with one seizure between the index and first seizure achieved a 3 year remission, and 70.1% (95% CI 59.1, 81.1) achieved a 5 year remission. For 3 year remission the % of patients achieving remission with 2-3 seizures, 4-9, and >10 seizures by 9 years were 84.4% (95% CI 73.0, 95.9), 77.0% (95% CI 62.5, 91.5), and 81.6% (95% CI 71.2, 92.7) respectively. Similar patterns were observed for 5 year remission, and although there was a tendency for those patients with fewer earlier seizures to have better remission rates, these differences were not significant.

These results are shown in tables 80-87, and summarised in figures 13 & 14.

Table 80 *Single seizure prior to index seizure: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	46.0	60.7	66.7	70.1	76.1	80.2	81.5
95% CI	38.3, 53.7	53.1, 68.3	59.3, 74.0	62.9, 77.3	69.1, 83.2	73.3, 87.0	74.6, 88.4
Number at risk	87	61	49	41	25	16	14
Withdrawals	13	3	3	3	9	5	1

Table 81 *Single seizure prior to index seizure: 5 year remission*

Weeks	260	312	364	416	468
Remission (%)	40.5	53.8	59.8	63.8	70.1
95% CI	32.7, 48.3	45.9, 61.8	51.7, 67.9	55.3, 72.3	59.1, 81.1
Number at risk	183	67	42	25	17
Withdrawals	30	4	18	14	6

Table 82 *2-3 seizures prior to index seizure: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	42.2	55.8	62.6	67.1	72.7	74.6	84.4
95% CI	32.0, 52.4	45.5, 66.1	52.5, 72.7	57.4, 76.9	63.1, 82.2	65.0, 84.2	73.0, 95.9
Number at risk	106	39	33	29	19	12	3
Withdrawals	16	1	0	0	6	6	5

Table 83 *2-3 seizures prior to index seizure: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	32.2	44.0	49.3	51.8	-
95% CI	22.4, 42.0	33.5, 54.5	38.6, 60.0	40.5, 63.1	-
Number at risk	106	47	36	19	-
Withdrawals	19	2	6	6	-

Table 84 *4-9 seizures prior to index seizure: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	27.5	47.6	57.7	66.0	77.0	-	-
95% CI	15.2, 39.7	33.8, 61.4	44.0, 71.4	52.7, 79.2	62.5, 91.5	-	-
Number at risk	61	26	21	16	4	-	-
Withdrawals	10	1	0	1	9	-	-

Table 85 4-9 *seizures prior to index seizure: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	20.8	35.7	41.1	54.1	77.0
95% CI	9.3, 32.3	22.0, 49.3	26.6, 55.6	34.3, 73.9	43.7, 110.4
Number at risk	61	30	18	6	1
Withdrawals	17	1	10	10	4

Table 86 >10 *seizures prior to index seizure: 3 year remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	35.4	64.6	70.8	75.9	81.6	-	-
95% CI	23.8, 47.0	53.0, 76.2	53.0, 76.2	65.4, 86.5	71.2, 92.7	-	-
Number at risk	78	23	19	14	6	-	-
Withdrawals	13	0	0	2	6	-	-

Table 87 >10 *seizures prior to index seizure: 5 year remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	33.3	60.0	64.6	88.2	-
95% CI	21.7, 45.0	47.3, 72.6	51.8, 77.4	68.8, 107.6	-
Number at risk	78	21	13	1	-
Withdrawals	8	6	6	11	-

Figure 13 *Remission according number of seizures prior to index seizure: 3 year remission*

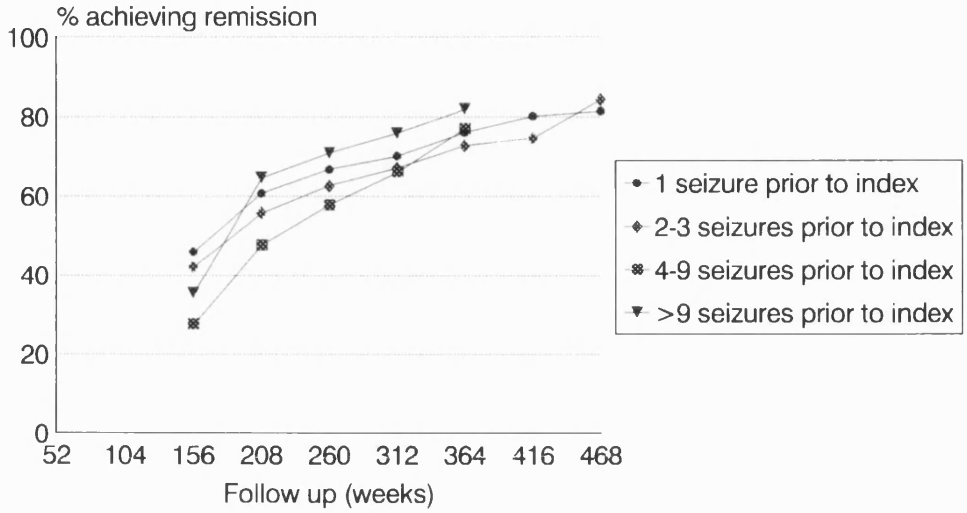
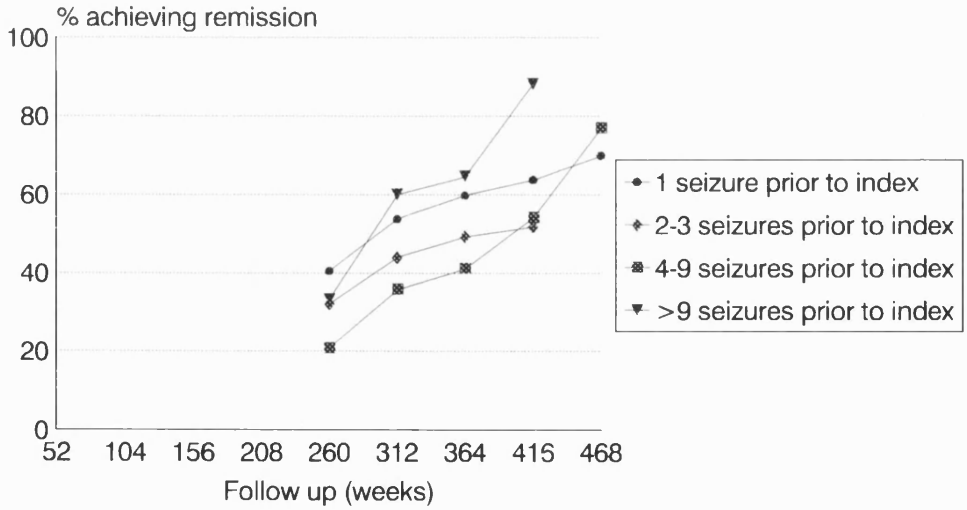


Figure 14 *Remission according number of seizures prior to index seizure: 5 year remission*



4.1.2.1.13. Remission according to interval between index seizure and first seizure

The interval between the index seizure and the first seizure is likely to be affected by the severity and type of the first seizure. The remission when the index seizure was the first seizure has been given earlier.

By 9 years 78.0% (95% CI 70.6, 85.5) whose first seizure was within 6 months of the index seizure achieved a 3 year remission, and 66.9% (95% CI 55.0, 78.9) achieved a 5 year remission. 85.9% (95% CI 77.0, 99.8) of patients where the first seizure occurred between 6 months and 2 years of the index seizure achieved a 3 year remission, and 67.5% (95% CI 50.1, 84.8) achieved a 5 year remission. 88.9% (95% CI 80.9, 96.9) of patients whose first seizure was more than 2 years from the index seizure achieved a 3 year remission, and 72.9% (95% CI 54.3, 90.2) achieved a 5 year remission.

These results are shown in tables 88-93, and summarised in figures 15 & 16.

Table 88 *First seizure occurred within 6 months of the index seizure: 3 year remission*

Weeks	156	208	260	312	364	416	468
Remission (%)	39.0	58.9	64.1	68.4	74.5	78.0	-
95% CI	31.7, 46.2	51.4, 66.3	56.9, 71.4	61.4, 74.5	67.6, 81.3	70.6, 85.5	-
Number at risk	203	72	59	51	31	11	-
Withdrawals	31	3	6	1	12	18	-

Table 89 *First seizure occurred within 6 months of the index seizure: 5 year remission*

Weeks	260	312	364	416	468
Remission (%)	32.5	46.6	53.5	57.4	66.9
95% CI	25.4, 39.7	39.0, 54.24	45.7, 61.4	49.0, 65.8	55.0, 78.9
Number at risk	203	86	54	30	8
Withdrawals	37	3	23	21	19

Table 90 *First seizure occurred between 6 months and 2 years of the index seizure: 3 year remission*

Weeks	156	208	260	312	364	416	468
Remission (%)	37.9	53.6	58.6	67.1	78.9	85.9	-
95% CI	28.5, 47.2	44.0, 63.3	49.0, 68.1	57.8, 76.3	69.5, 88.2	77.0, 99.8	-
Number at risk	121	47	42	29	10	2	-
Withdrawals	18	1	0	5	17	7	-

Table 91 *First seizure occurred between 6 months and 2 years of the index seizure: 5 year remission*

Weeks	260	312	364	416	468
Remission (%)	33.7	47.3,	59.3	67.5	-
95% CI	24.5, 42.9	37.5, 57.2	47.0, 71.7	50.1, 84.8	-
Number at risk	121	47	12	4	-
Withdrawals	20	7	24	7	-

Table 92 *First seizure occurred more than 2 years from the index seizure: 3 year remission*

Weeks	156	208	260	312	364	416	468
Remission (%)	45.7	66.6	74.6	75.8	80.2	86.1	88.9
95% CI	35.5, 55.9	57.0, 76.3	65.6, 83.6	66.9, 84.7	71.7, 88.9	77.9, 92.2	80.9, 96.9
Number at risk	85	30	21	20	13	7	5
Withdrawals	20	1	2	0	4	3	1

Table 93 *First seizure occurred more than 2 years from the index seizure: 5 year remission*

Weeks	260	312	364	416	468
Remission (%)	39.3	57.6	61.8	63.8	72.9
95% CI	28.8, 49.7	47.0, 68.3	51.2, 72.4	53.0, 74.6	54.3, 90.2
Number at risk	104	34	23	18	2
Withdrawals	20	2	8	4	14

Figure 15 *Remission according to interval between the first and index seizure: 3 year remission*

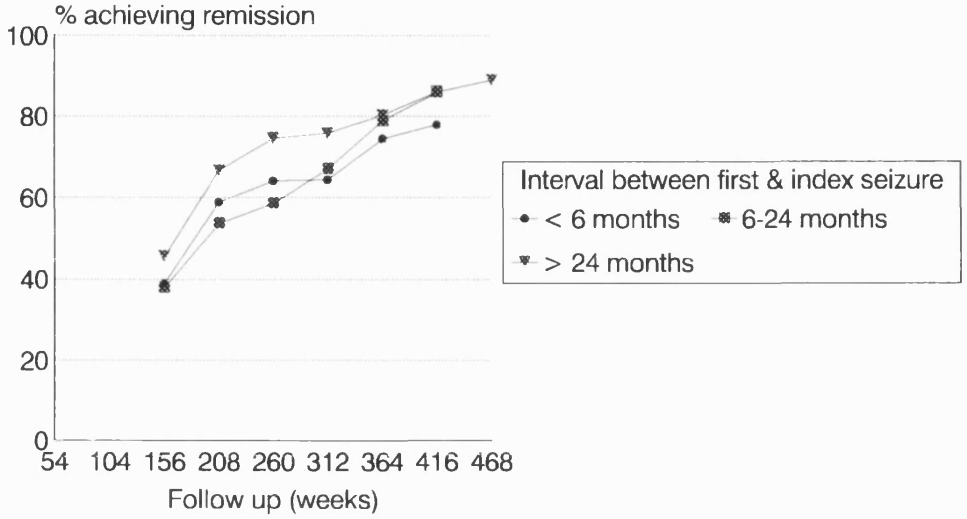
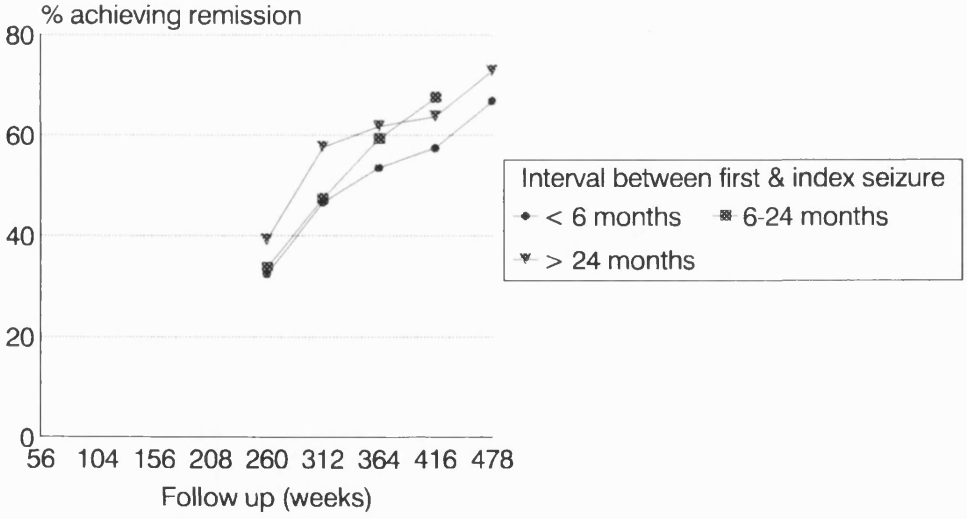


Figure 16 *Remission according to interval between the first and index seizure: 5 year remission*



4.1.2.2. Terminal remission

So far results have been for patients ever achieving remission. In this section the terminal remission is shown. Terminal remission shows the proportion of patients who are in remission at a particular point of follow up. The difference between terminal and cumulative remission will be due to the patients who relapse.

4.1.2.2.1. Overall terminal remission for patients with definite epilepsy and definite combined with possible epilepsy: 1, 2, 3, and 5 year remission

The proportion of patients with definite epilepsy in terminal remission at 9 years follow up from the index seizure was 84.2% (95% CI 77.9, 90.5) for 1 year, 75.9% (95% CI 70.0, 81.8) for 2 year, 67.8% (95% CI 62.3, 73.3) for 3 year, and 54.4% (95% CI 48.9, 59.9) for 5 year remission.

This is shown in tables 94-101, and summarised in figures 17 & 18.

Table 94 *Definite epilepsy: 1 year terminal remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	53.5	70.1	73.5	76.1	78.5	83.9	80.3	82.7	84.2
95% CI	49.3, 57.7	66.1, 80.2	69.6, 77.4	72.2, 80.0	74.7, 82.3	80.5, 87.3	76.3, 84.3	78.1, 87.3	77.9, 90.5
Adjusted number at risk	544	505	486	470	456	442	377	255	127

Table 95 *Definite and possible epilepsy: 1 year terminal remission from index seizure*

Weeks	52	104	156	208	260	312	364	416	468
Remission (%)	57.9	73.0	76.2	77.8	80.2	83.8	81.1	83.2	86.0
95% CI	54.4, 61.4	69.7, 76.3	73.0, 79.4	74.6, 81.0	77.1, 83.3	80.9, 86.7	77.7, 84.5	79.3, 87.1	80.7, 91.3
Adjusted number at risk	766	711	676	645	628	605	514	346	165

Table 96 *Definite epilepsy: 2 year terminal remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	47.3	62.5	66.1	68.2	75.2	73.9	73.5	75.9
95% CI	43.1, 51.5	58.3, 66.7	62.0, 70.2	64.0, 72.4	71.2, 79.2	69.6, 78.2	68.7, 78.3	70.0, 81.8
Adjusted number at risk	541	499	481	466	447	394	324	203

Table 97 *Definite and possible epilepsy: 2 year terminal remission from index seizure*

Weeks	104	156	208	260	312	364	416	468
Remission (%)	46.5	65.5	68.7	70.6	76.1	74.9	74.8	76.5
95% CI	43.0, 49.5	62.0, 69.0	65.2, 72.2	67.1, 74.1	72.7, 79.5	71.2, 78.5	70.8, 78.8	71.5, 81.5
Adjusted number at risk	783	697	668	640	612	542	441	273

Table 98 *Definite epilepsy: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	44.1	57.7	61.0	65.5	66.2	67.6	67.8
95% CI	39.9, 48.3	53.4, 62.0	56.6, 65.4	61.1, 69.9	61.6, 70.8	62.7, 72.5	62.3, 73.3
Adjusted number at risk	537	496	478	458	405	343	280

Table 99 *Definite and possible epilepsy: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	48.6	60.6	64.4	67.5	68.4	69.2	69.4
95% CI	45.0, 52.2	57.0, 64.2	60.8, 68.0	63.8, 71.2	64.5, 72.3	65.0, 73.4	64.7, 74.1
Adjusted number at risk	749	691	664	627	553	471	376

Table 100 *Definite epilepsy: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	39.5	53.3	53.4	52.8	54.4
95% CI	35.4, 43.7	48.8, 57.8	48.7, 58.1	47.8, 57.8	48.9, 59.9
Adjusted number at risk	533	487	438	381	320

Table 101 *Definite and possible epilepsy: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	43.7	55.5	56.5	55.5	57.0
95% CI	40.1, 47.3	51.8, 59.2	52.5, 60.5	51.2, 59.8	52.3, 61.7
Adjusted number at risk	741	676	604	517	431

Figure 17 *Terminal remission for patients with definite epilepsy: 1, 2, 3, and 5 year remission*

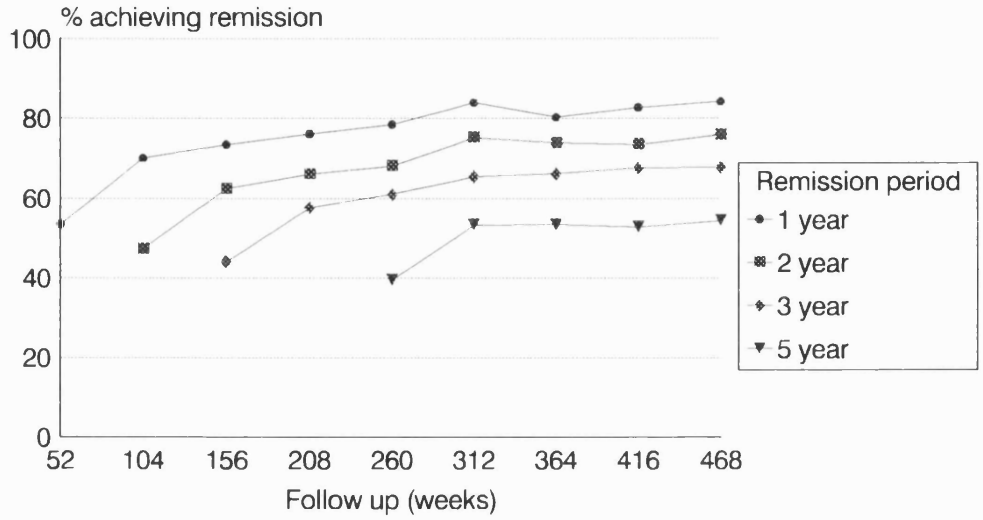
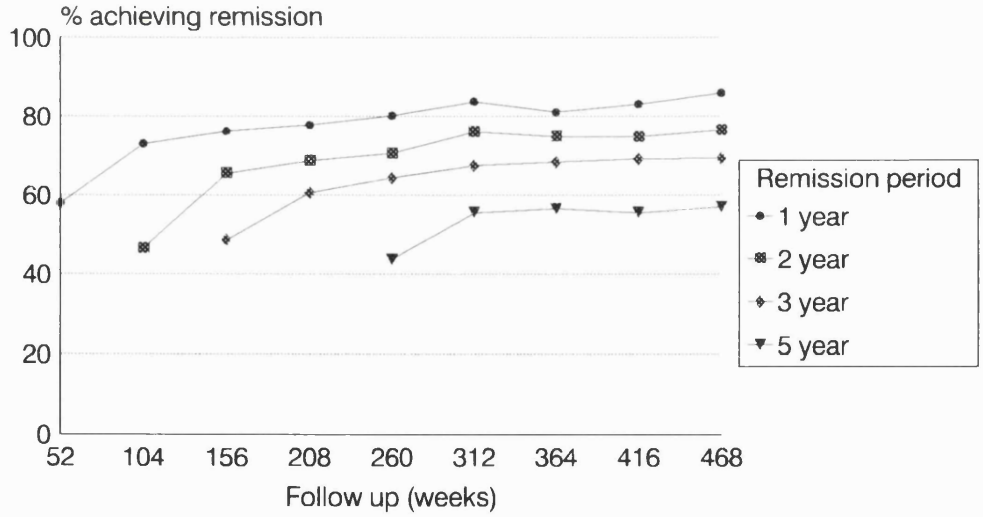


Figure 18 *Terminal remission for patients with definite and possible epilepsy combined: 1, 2, 3, and 5 year remission*



4.1.2.2.2. Stratification of 5 year terminal remission for patients with definite epilepsy

In the following section the results for terminal remission are stratified by aetiology and age of onset. As with cumulative remission, the remission for patients with remote symptomatic causes is similar to that of patients with idiopathic epilepsy, with the worse outcome seen in patients with congenital deficits. Similarly, age, has a weak effect on prognosis.

4.1.2.2.2.1. Terminal remission stratified by aetiology: idiopathic, remote symptomatic, acute symptomatic and congenital deficits

At 9 years 68.8% (95% CI 63.4, 75.2) of patients with idiopathic epilepsy were in 3 year remission, and 53.2% (95% CI 46.7, 59.7) were in 5 year remission. This compares to patients with remote symptomatic epilepsy of whom 58.3% (95% CI 42.2, 74.4) were in 3 year remission, and 50.6% (95% CI 35.9, 65.3) who were in 5 year remission. Patients with acute symptomatic epilepsy had higher rates of remission ($p<0.01$), and those with congenital deficits lower rates ($p<0.01$).

This is shown in tables 102-109, and summarised in figures 19 & 20.

Table 102 *Idiopathic epilepsy: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	48.1	57.2	60.5	64.2	65.3	67.0	68.8
95% CI	42.7, 53.5	51.9, 62.5	55.2, 65.8	58.9, 69.5	59.7, 70.9	61.1, 72.9	63.4, 75.2
Adjusted number at risk	335	332	327	316	283	243	199

Table 103 *Idiopathic epilepsy: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	34.7	52.6	52.3	50.9	53.2
95% CI	29.6, 39.8	47.2, 58.0	46.6, 58.0	44.9, 56.9	46.7, 59.7
Adjusted number at risk	331	327	300	265	225

Table 104 *Remote symptomatic epilepsy: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	43.5	47.8	53.8	63.1	62.5	60.5	58.3
95% CI	33.2, 53.8	36.9, 58.7	42.2, 65.4	51.4, 74.8	49.8, 75.2	45.9, 75.1	42.2, 74.4
Adjusted number at risk	89	81	72	65	56	43	36

Table 105 *Remote symptomatic epilepsy: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	22.5	49.4	45.2	51.4	50.6
95% CI	13.8, 31.2	38.9, 59.9	32.8, 57.6	38.0, 64.8	35.9, 65.3
Adjusted number at risk	89	87	62	54	39

Table 106 *Acute symptomatic epilepsy: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	74.1	74.8	78.1	80.6	86.0	84.3	77.8
95% CI	63.8, 84.4	64.4, 85.2	68.0, 88.2	70.8, 90.4	77.0, 95.0	73.6, 95.0	64.2, 91.4
Adjusted number at risk	70	77	64	62	57	45	36

Table 107 *Acute symptomatic epilepsy: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	64.6	74.0	75.0	72.9	76.9
95% CI	53.0, 70.2	63.4, 84.6	64.0, 86.0	60.3, 85.5	63.7, 90.1
Adjusted number at risk	65	66	60	48	39

Table 108 *Epilepsy secondary to congenital deficits: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	37.5	41.9	31.0	33.3	20.0	41.7	41.2
95% CI	13.8, 61.2	17.3, 66.5	7.2, 54.8	8.2, 58.4	-, 42.2	13.8, 69.5	8.1, 74.3
Adjusted number at risk	16	16	15	14	13	12	9

Table 109 *Epilepsy secondary to congenital deficits: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	13.3	29.0	17.2	18.5	13.0
95% CI	-, 30.5	6.4, 51.6	-, 36.6	-, 39.0	-, 32.4
Adjusted number at risk	15	16	15	14	12

Figure 19 *Aetiological stratification of 3 year terminal remission*

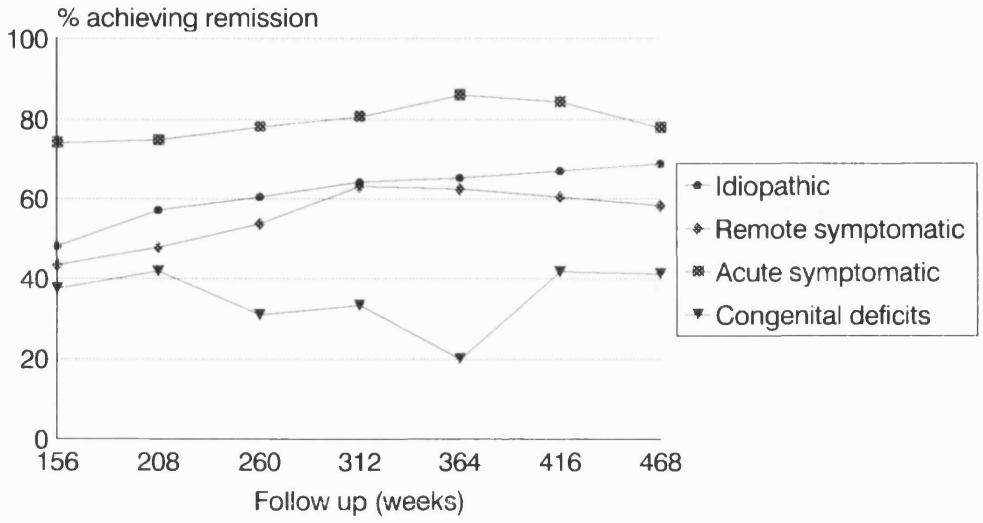
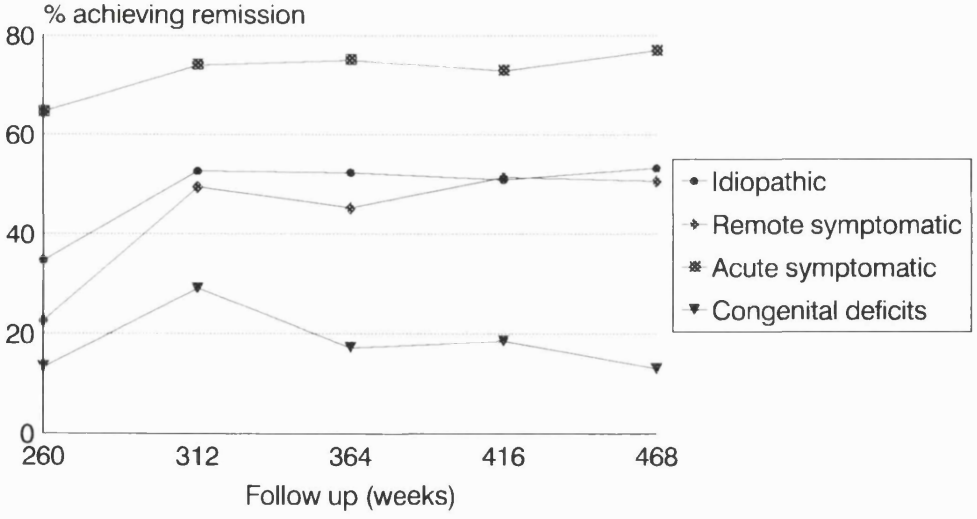


Figure 20 *Aetiological stratification of 5 year terminal remission*



4.1.2.2.2.2. Terminal remission stratified by age grouping: 3 and 5 year terminal remission

As with cumulative remission the effect of age was not statistically different, although trends were observed with age less than 16 years at onset having the worse outcome. The 3 year remission rates at 9 years for the age groups <16 years, 16-39 years, 40-60 years, and > 60 years were: 82.7% (95% CI 75.2, 90.2), 66.7% (95% CI 57.8, 75.6), 75.3% (95% CI 27.2, 53.8), and 67.6% (95% CI 52.5, 82.7) respectively. For 5 year remission the rates at 9 years were: 46.0 (95% CI 36.6, 55.4), 55.1% (95% CI 46.3, 63.9), 66.3% (95% CI 52.4, 80.2), and 60.4% (95% CI 46.2, 74.6)

This is shown in tables 110-116, and summarised in figures 21 & 22.

Table 110 *Definite epilepsy, < 16 years at onset: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	42.6	50.3	44.4	58.3	57.9	63.0	82.7
95% CI	34.6, 50.6	42.2, 58.4	36.4, 52.4	50.2, 66.4	49.4, 66.4	54.1, 71.9	75.2, 90.2
Adjusted number at risk	148	147	147	144	131	114	98

Table 111 *Definite epilepsy, < 16 years at onset: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	28.6	45.9	46.0	44.4	46.0
95% CI	21.3, 35.9	37.8, 54.0	37.7, 54.3	35.7, 53.1	36.6, 55.4
Adjusted number at risk	147	146	137	124	108

Table 112 *Definite epilepsy, 16-39 years at onset: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	52.8	60.6	60.3	64.6	67.5	64.8	66.7
95% CI	45.6, 60.0	53.6, 67.6	53.2, 67.4	57.6, 71.6	60.2, 74.8	56.8, 72.8	57.8, 75.6
Adjusted number at risk	187	186	184	178	68	137	108

Table 113 *Definite epilepsy, 16-39 years at onset: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	41.9	54.9	53.6	53.3	55.1
95% CI	34.8, 49.0	47.7, 62.1	46.0, 61.2	45.0, 61.6	46.3, 63.9
Adjusted number at risk	186	182	166	146	123

Table 114 *Definite epilepsy, 40-60 years at onset: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	64.7	68.1	72.5	74.4	73.7	76.8	75.3
95% CI	54.0, 75.4	57.3, 78.9	62.0, 83.0	63.9, 84.9	62.3, 85.1	64.8, 88.8	27.2, 53.8
Adjusted number at risk	77	72	69	67	57	48	41

Table 115 *Definite epilepsy, 40-60 years at onset: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	47.9	64.8	65.6	63.5	66.3
95% CI	36.4, 59.4	53.7, 75.9	58.4, 72.8	50.4, 76.6	52.4, 80.2
Adjusted number at risk	73	71	61	52	45

Table 116 *Definite epilepsy, > 60 years at onset: 3 year terminal remission from index seizure*

Weeks	156	208	260	312	364	416	468
Remission (%)	44.4	44.8	62.8	73.9	73.9	69.2	67.6
95% CI	34.3, 54.5	34.6, 55.0	52.1, 73.5	64.5, 84.3	62.5, 85.3	55.8, 82.6	52.5, 82.7
Adjusted number at risk	94	92	78	69	58	46	37

Table 117 *Definite epilepsy, > 60 years at onset: 5 year terminal remission from index seizure*

Weeks	260	312	364	416	468
Remission (%)	25.3	53.1	56.5	59.7	60.4
95% CI	16.6, 34.0	42.6, 63.6	45.2, 67.8	47.2, 72.2	46.2, 74.6
Adjusted number at risk	95	88	74	60	46

Figure 21 *Stratification of 3 year terminal remission by age grouping*

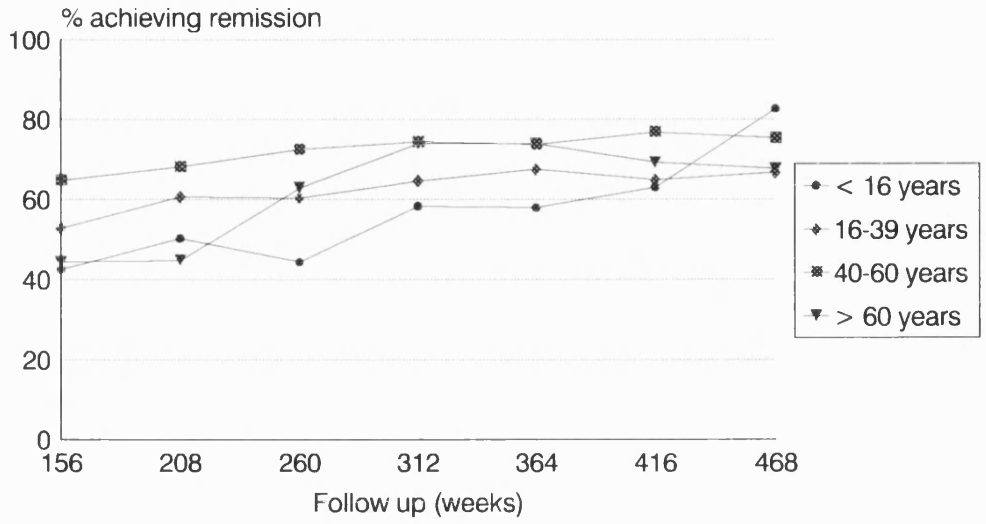
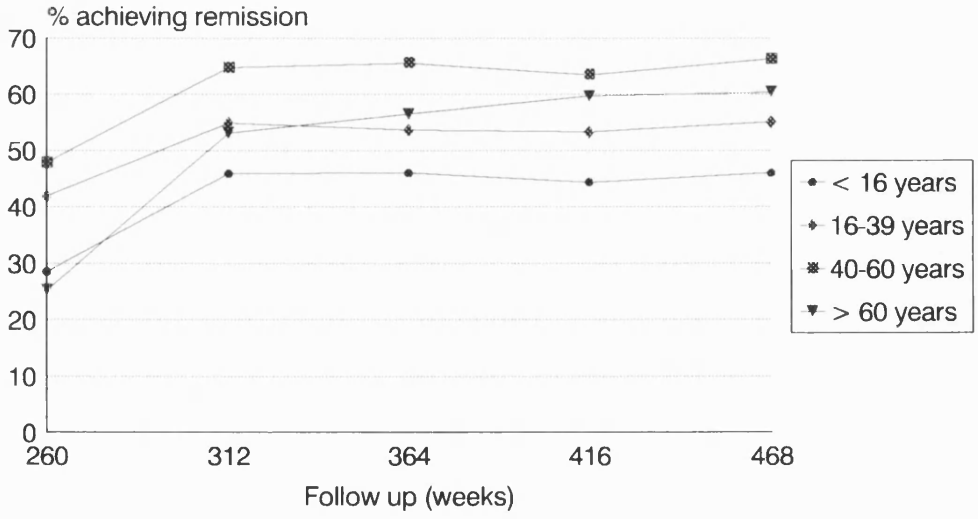


Figure 22 *Stratification of 5 year terminal remission by age grouping*



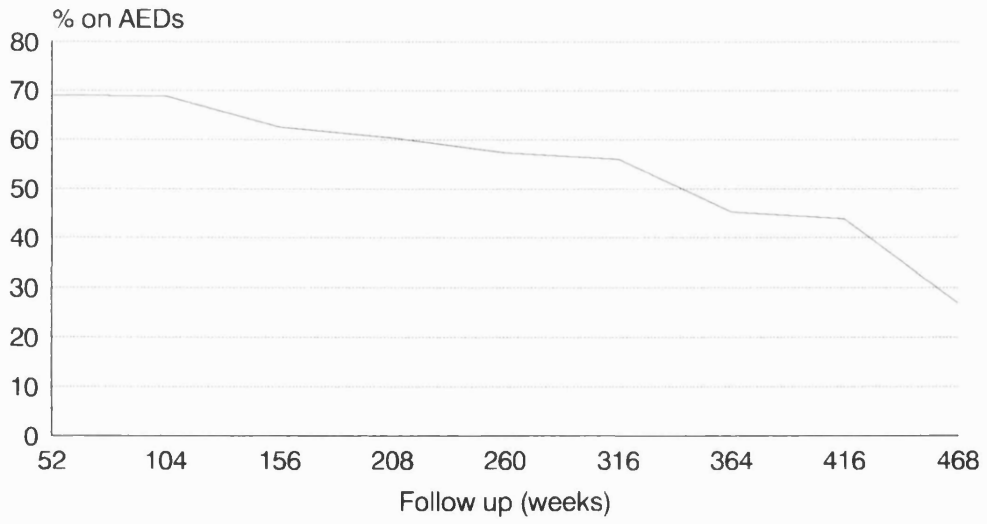
4.1.2.3. Treatment in the NGPSE

Treatment with antiepileptic drugs may influence many aspects of remission. In table 118 and figure 23 the overall treatment of the NGPSE cohort is given. In the first year the majority of patients (68.9%) were on AEDs, but after 9 years this falls to 26.9%. This does not include patients who stopped AEDs for a short period and restarted them later, and the number of patients withdrawing from treatment is likely to be higher.

Table 118 *Percentage of patients with definite epilepsy receiving AEDs*

Weeks	52	104	156	208	260	312	364	416	468
% of patients receiving AEDs	68.9	68.8	62.5	60.4	57.3	56.0	45.3	43.9	26.9
95% CI	65.1, 72.7	64.8, 72.8	58.2, 66.8	56.0, 64.8	52.8, 57.8	51.4, 60.6	40.6, 50.0	38.4, 49.4	20.5, 3.3

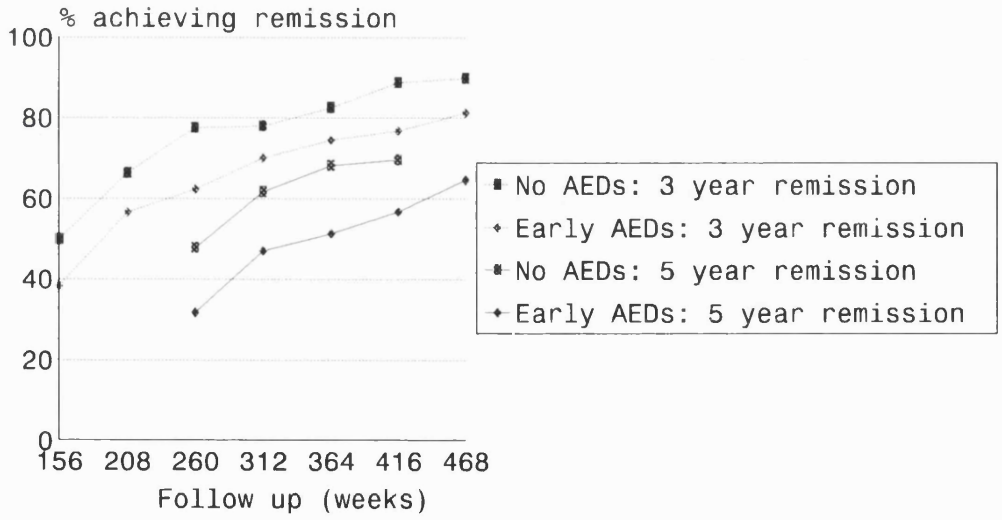
Figure 23 *Percentage of patients with definite epilepsy on AEDs*



The effect of early treatment on remission was also examined. Early treatment was defined as the commencement of AEDs within one month of the index seizure. Treatment had no significant effect, and if anything those patients on early treatment had less chance of achieving remission. By 9 years from the index seizure 89.8% (95% CI 85.1, 94.4) of patients on early treatment, and 81.2% (95% CI 74.4, 87.9) not on early treatment, achieved a 3 year remission. 69.5% (95% CI 63.2, 75.7) on early treatment, and 64.% not on early treatment (95% CI 55.2, 73.9), achieved a 5 year remission by 9 years from the index seizure. These differences did not achieve statistical significance.

This is summarised in figure 24.

Figure 24 *3 and 5 year remission from the index seizure for patients with definite epilepsy stratified according to whether AED treatment was started within one month of the index seizure*



4.1.3 The mortality of epilepsy

Summary

Over a median follow up of 6.9 years, and up to 9 years, the "all cause" SMR for patients with definite or possible epilepsy was 2.5 (95% CI 2.1, 2.9), and 3.0 (95% CI 2.5, 3.7) for those patients who were classified as having definite epilepsy. The SMR was highest in the first year after diagnosis, SMR = 5.1 (95% CI 3.8, 6.5), and declined to 2.5 (CI 95% 1.5, 3.9) at 3 years, and 1.3 (CI 95% 0.7, 0.2) after 5 years. The commonest causes of death were pneumonia (SMR = 7.2), cancer (SMR = 3.6), and strokes (SMR = 3.7). The SMR for patients with idiopathic epilepsy was 1.6 (CI 95% 1.0, 2.4), remote symptomatic epilepsy 4.3 (CI 95% 3.3, 5.5), and acute symptomatic epilepsy 2.9 (CI 95% 1.7, 4.5). Mortality in patients with newly diagnosed epilepsy was consistently raised. This is partly due to the underlying aetiology, however the SMR for idiopathic seizures was also raised, demonstrating that epilepsy per se carries a definite but small risk of premature death.

4.1.3.1 Follow up period

Median (25th, 75th centiles) follow up time for the cohort of 1091 patients was 6.9 (5.8, 7.8) years, and the mortality analysis was carried out up to the date of death or 31 December 1992.

4.1.3.2 Overall mortality

A total of 161 people (75 males, 86 females) died during the follow up period, compared with 69 deaths from all-causes expected from the age, sex, and calendar specific death rates for the population of England and Wales. The main causes were circulatory disorders (ICD codes 410-441) in 58 (36%), neoplasms (codes 162-199) in 48 (30%), and pneumonia (codes 480-486) in 25 (16%); Alzheimer's disease (code 331) was the cause in 6 patients, and fractures of the femur (code 820) and septicaemia (code 038), in 4 each; the remaining 16 patients died from miscellaneous causes including 1 suicide, 3 murders, 1 drowning, and 1 died from burns.

The "all-cause" SMR in the whole cohort was 2.3 (95% CI 1.9, 2.7), indicating highly significant ($p<0.001$) excess mortality over that of the standard population of England and Wales (see table 119).

Table 119 - *All cause mortality for whole cohort and specific sub-groups*

	Number at risk	Number of deaths								
		Males		Females		Totals				
		Obs	Exp	Obs	Exp	Obs	Exp	SMR	(CI 95%)	P*
Definite	564	57	20.9	57	16.6	114	37.4	3.0	(2.5, 3.7)	<0.001
Possible	228	14	8.3	22	14.6	36	22.9	1.6	(1.1, 2.2)	0.014
Sub-total	792	71	29.1	79	31.2	150	60.3	2.5	(2.1, 2.9)	<0.001
NE†	79	4	3.8	7	4.5	11	8.3	1.3	(0.6, 2.4)	0.44
Febrile	220	0	0.4	0	0.2	0	0.5	0	(0, 7.1)	0.80
Total	1091	75	33.3	86	35.9	161	69.2	2.3	(1.9, 2.7)	<0.001

Obs- observed deaths in cohort, Exp- expected deaths in cohort, SMR- standardised mortality ratio
* significance test based on Poisson distribution for SMR different from one (2-sided)
† NE- not epilepsy

4.1.3.3 Mortality in definite epilepsy, possible epilepsy, and febrile seizures

In patients with definite epilepsy the SMR was even higher at 3.0 (2.5, 3.7). There were no deaths in the group with febrile seizures, and in the group who did not have epilepsy, the SMR was not significantly elevated (p=0.22), though the 95% CI does not exclude increased risk (table 119).

4.1.3.4 Mortality in different age groups

Mortality within selected age groups is summarised in table 120 for patients with possible or definite epilepsy; the SMR is highest in patients aged 50-59 years, and declines in the two subsequent decades, but still with a significant (p<0.001) excess in those aged 80 years and over. A similar trend with rather higher SMRs (and wider CIs) was seen in patients with definite epilepsy. The deaths in 16 people aged under 50 years were caused by brain tumours in 5, injuries (ICD codes 800-999) in 5, and myocardial infarction, subarachnoid haemorrhage, cerebral degeneration, viral pneumonia and Huntington's disease in 1 each.

Table 120 *All cause mortality by age-group in patients with definite epilepsy and the combined group with definite or possible epilepsy*

	Number of deaths			
Age (years)	Obs	Exp	SMR	(95% CI)
Definite epilepsy				
0-49	15	2.0	7.6	(4.2, 12.5)
50-59	15	1.8	8.6	(4.7, 14.1)
60-69	21	5.9	3.6	(2.2, 5.5)
70-79	26	13.8	1.9	(1.2, 2.8)
>80	37	14.0	2.6	(1.8, 3.6)
Definite or possible epilepsy				
0-49	16	2.6	6.1	(3.4, 9.9)
50-59	17	2.6	6.6	(3.8, 10.5)
60-69	24	8.1	3.0	(1.8, 4.4)
70-79	38	18.0	2.1	(1.4, 2.9)
>80	55	29.0	1.9	(1.4, 2.5)

4.1.3.5 The time trends of mortality

Mortality in the combined definite and possible epilepsy groups for each year of follow up from the index seizure (date of original diagnosis) is shown in table 121. The SMR was highest at 5.0 during the first year of follow up, approximately halved during the subsequent three years, and then halved again after 4 years; the 95% CI are also consistent with a progressive decline with each year of follow up, to an SMR around one after 4 or 5 years (again a similar pattern with higher SMRs was seen in those with definite epilepsy). Similar results were obtained with the period of exposure to seizures (defined as the interval from first seizure); among those with a history of less than two years the SMR was 5.1 (4.0, 6.3), and then declined to 2.3 (1.5, 3.2) in those having a history of at least two and up to four years, and to 1.3 (0.9, 1.7) in those with a history exceeding four years. These analyses indicate very high mortality soon after diagnosis of epilepsy, which then declines to that in the standard population over a period of about four years. There is no evidence that mortality subsequently increases with the interval from first seizure. This was also borne out by an analysis of mortality stratified by the interval from the first to index seizure, when the index seizure was the first ever seizure the overall SMR was 3.3 (95% CI 2.6, 4.1), and this declined as the interval increased.

Table 121 *Mortality for each year of follow up from index seizure in patients with definite epilepsy and the combined group with definite or possible epilepsy*

Years after index seizure	Number at risk	Number of deaths			
		Obs	Exp	SMR	(CI 95%)
Definite epilepsy					
0-1	564	49	7.4	6.6	(4.8, 8.7)
1-2	515	16	6.1	2.6	(1.5,4.3)
2-3	499	13	5.6	2.3	(1.2, 4.0)
3-4	486	16	5.1	3.1	(1.8, 5.1)
4-5	470	8	4.6	1.7	(0.7, 3.4)
5-6	462	6	3.8	1.6	(0.6, 3.5)
6-8	372	6	4.6	1.3	(0.5, 2.9)
Definite or possible epilepsy					
0-1	792	60	11.8	5.1	(3.8, 6.5)
1-2	732	24	9.7	2.5	(1.5, 3.7)
2-3	708	18	8.6	2.1	(1.2, 3.3)
3-4	690	20	7.9	2.5	(1.5, 3.9)
4-5	670	10	7.7	1.3	(0.6, 2.4)
>5	660	18	14.2	1.3	(0.7, 2.0)

4.1.3.6 Mortality in different aetiological groups

Patients with definite epilepsy were classified by broad aetiology (table 4), and "all cause" mortality was highest in those with remote symptomatic causes (e.g. brain tumours and vascular disease), but was also significantly elevated ($p<0.001$) in those with acute symptomatic (e.g. alcohol and metabolic causes) and in idiopathic cases ($p=0.02$).

Table 122 - *"All-cause" mortality in patients with definite epilepsy according to aetiology*

	At risk	Number of deaths			
Aetiology		Obs	Exp	SMR	(CI 95%)
Idiopathic	346	24	15.0	1.6	(1.0, 2.4)
Remote Symptomatic	119	67	15.4	4.3	(3.3, 5.5)
Acute Symptomatic	83	20	6.9	2.9	(1.7, 4.5)
Congenital Deficit	16	3	0.1	50	(10, 146)

4.1.3.7 The mortality of idiopathic epilepsy

The SMR of patients with idiopathic epilepsy was 1.6, which shows that epilepsy itself carries an increased risk of mortality not related to the underlying cause. The SMR for the idiopathic group did not fall over time during the follow up period. Three deaths in the idiopathic group were due to missing an underlying symptomatic aetiology (primary brain tumours which were unrecognised in life), but even with these deaths excluded the SMR is still 1.4. The causes of death in the idiopathic group were malignant neoplasms (n = 8), strokes and other circulatory disease (n = 4), ischaemic heart disease (n = 2), pneumonia (n = 6), and violent death (n=2), fractured femur (n=1) and drowning (n = 1).

4.1.3.8 Mortality from specific causes of death

Mortality from selected causes of death in those cases with possible or definite epilepsy is presented in table 123. Similar results are obtained when the analysis is restricted to those with definite seizures only, except that the cause specific SMRs are higher and the CIs are wider. There is higher than expected mortality from all neoplasms (also from all neoplasms excluding brain (ICD code 191): SMR 2.5 (95% CI 1.7, 3.5), cerebrovascular disease, and pneumonia. By contrast mortality from ischaemic heart disease (ICD 410-414) did not appear to be significantly higher than in the standard population (SMR= 1.2, 95% CI 0.7, 1.9), though the CI does not exclude elevated risk. Mortality from all causes other than those selected in table 123 was slightly above that in the standard population (SMR= 1.4, 95% CI, 1.0, 1.9; $p<0.025$), but the elevated risk from these other causes was confined to women (men, $p>0.95$, women, $p<0.001$), even in those with definite epilepsy (men; 0.95, 95% CI 0.48, 1.7: women; 2.3, 95% CI 1.4, 3.5).

Table 123 *Selected causes of death for patients with definite, and combined possible or definite, epilepsy*

a) Definite epilepsy

		Number of deaths			
Cause of death	ICD code(s)	Obs	Exp	SMR	(95% CI)
Malignant neoplasms	140-208	43	9.0	4.8	(3.4, 6.4)
Malignant neoplasms excluding primary brain tumour (ICD code 191)	140-208	30	8.8	3.4	(2.3, 4.8)
Neoplasms of lung	162	10	2.4	4.2	(2.0, 7.8)
Ischaemic heart disease	410-414	12	10.0	1.2	(0.6, 2.1)
Cerebrovascular disease	430-438	19	4.4	4.3	(2.6, 6.7)
Pneumonia	480-486	18	1.8	10.3	(6.1, 16.4)

b) Possible or definite epilepsy

		Number of deaths			
Cause of death	ICD code(s)	Obs	Exp	SMR	(95% CI)
Malignant neoplasms	140-208	47	13.5	3.5	(2.5, 4.7)
Malignant neoplasms excluding primary brain tumour (ICD code 191)	140-208	33	13.3	2.5	(1.7, 3.5)
Neoplasms of lung	162	10	3.3	3.0	(1.4, 5.5)
Ischaemic heart disease	410-414	19	15.6	1.2	(0.7, 1.9)
Cerebrovascular disease	430-438	28	7.5	3.7	(2.4, 5.4)
Pneumonia	480-486	24	3.3	7.2	(4.6, 10.8)

4.1.3.9 Specific causes of death in different types of epilepsy

The SMR, where significant, is shown in table 124 for patients with different aetiologies divided up according to broad aetiology. The SMR is raised for cancer, strokes, heart disease and pneumonia in patients with symptomatic epilepsy. However, in patients with idiopathic seizures the SMR for cancer and pneumonia is still raised.

Table 124 - *Mortality by individual cause of death occurring in each aetiological classification*

Cause of death	ICD 9 code(s)	Idiopathic SMR (95%CI)	Remote symptomatic SMR (95%CI)	Acute symptomatic SMR (95%CI)
Neoplasms (all causes)	140-239	2.0 (0.8, 3.9)	9.4 (6.5, 13.2)	-
Neoplasms of bronchus	162	-	10.0 (4.5, 19.0)	-
Ischaemic heart disease	410-414	-	1.91 (0.8, 3.8)	-
Cerebrovascular disease	430-486	-	4.98 (2.38, 9.1)	10.39 (4.49, 20.5)
Pneumonia	480-486	10.1 (3.73, 22.1)	9.5 (4.1, 18.8)	9.7 (1.9, 28.3)

* $p < 0.05$, ** $p < 0.001$

4.1.3.10 Clinical features of patients with definite epilepsy who died

All the patients with definite epilepsy who died were divided up into the broad aetiological categories (idiopathic, symptomatic etc.) and the main clinical features of their epilepsy were looked at. The main feature of patients who died was their age: 69/114 (60.5 %) were over 65 years of age, but the age of death appeared similar in the different aetiological categories. Other features such as sex, specific aetiology of epilepsy, seizure types and total numbers of seizures experienced were not any different to the patients in these categories who did not die.

These results are shown in tables 125-128.

Table 125 *Age at seizure onset, and sex of patients dying, divided up by broad aetiology*

	Aetiology							
	Idiopathic		*Remote symptomatic*		*Acute symptomatic*		*Congenital deficit*	
Age (years)	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
0-10	1	(4)	0	-	1	(19)	2	-
11-20	3	(13)	2	(3)	0	-	0	-
21-40	1	(4)	4	(6)	0	-	0	-
41-60	4	(17)	23	(34)	3	(15)	1	-
> 65	15	(62)	38	(67)	16	(80)	0	-
Sex								
Male	12	(50)	37	(55)	7	(35)	1	-
Female	12	(50)	30	(45)	13	(65)	2	-

Table 126 *Specific causes of epilepsy in each aetiological category of patients dying*

	Aetiology							
	Idiopathic		*Remote symptomatic*		*Acute*		*Congenital deficit*	
Aetiology	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Post-traumatic	0	-	0	-	0	-	0	-
Tumour	0	-	29	(43)	0	-	0	-
Vascular	0	-	34	(51)	19	(95)	0	-
Alcohol	0	-	2	(3)	0	-	0	-
Idiopathic	24	(100)	0	-	0	-	0	-
*Other**	0	-	2	(3)	1	(5)	3	(100)

* Post infection, eclampsia, and specific syndromes such as benign Rolandic epilepsy

Table 127 *Seizure types in patients dying, divided up by aetiology*

	Aetiology							
	Idiopathic		*Remote symptomatic*		*Acute*		*Congenital deficit*	
Seizure type	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Generalised								
Tonic clonic	8	(33)	4	(6)	2	(10)	0	-
Absence	0	(0)	0	-	0	-	0	-
Mixed	3	(13)	0	-	0	-	1	-
Others	0	-	0	-	0	-	0	-
Partial								
Simple	1	(4)	7	(10)	4	(20)	0	-
Complex	4	(17)	8	(12)	2	(10)	0	-
2°generalised	7	(29)	37	(55)	9	(45)	0	-
Mixed	0	-	5	(7)	0	-	2	-
Unclassifiable	1	(3)	6	(9)	3	(5)	0	-

Table 128 *Total number of seizures experienced by patients dying, divided up by aetiology*

	Aetiology							
	Idiopathic		*Remote symptomatic*		*Acute*		*Congenital deficit*	
Number of seizures	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
<11	15	(63)	44	(66)	17	(85)	1	-
11-20	4	(17)	14	(21)	0	-	0	-
21-50	4	(17)	6	(10)	3	(15)	0	-
51-100	1	(3)	1	(1)	0	-	1	-
>100	0	-	2	(2)	0	-	1	-

4.2. RISK FACTORS FOR VASCULAR AND CANCER DEATHS IN THE EPILEPSY POPULATION

Summary

The results from the NGPSE indicate that patients with epilepsy are at higher risk of cancer, vascular deaths, and pneumonia than the general population, and although the bulk of this risk is due to the underlying cause of the epilepsy, there is also an independent risk in patients with idiopathic epilepsy. In order to examine other causes for this increased risk a population-based, and resident-based sample of patients with epilepsy were examined and compared to age and sex matched controls. No significant differences were found between patients in the different categories, although patients in the community with active epilepsy did have a tendency to smoke more than the age and sex matched population.

4.2.1 Patient characteristics

The characteristics of the patients with epilepsy in the community and residential populations in terms of type of seizures, aetiology, and frequency of seizures, are very similar to the patients described before in these populations. (Goodridge & Shorvon, 1983, Klenerman, Sander & Shorvon, 1993)

4.2.2 Results

The comparison of the different epilepsy populations with controls are shown in tables 129-132.

No significant differences were found between any of the variables between patients with epilepsy ever (active, and inactive) and controls, patients with inactive epilepsy (whether on or off treatment) and controls, and patients at the Chalfont Centre and controls. When patients just with active epilepsy were examined no differences were encountered between all the variables, except the number of patients who smoked. 36% of patients smoked compared to 24% of controls, and over 58% of these patients were smoking more than 10 cigarettes per day compared to 50% of controls. In a chi-square analysis comparing the number of patients who smoked against controls this was a significant difference at p=0.0149 (Pearson method, 1DF).

Table 129 *Comparison of all patients with epilepsy, inactive and active, with controls (n-137)*

		Epilepsy	*Controls*
Age	*Mean*	44.6	44.6
	Range	15-85	15-86
Sex	*Males*	43 (31%)	43 (31%)
	Females	94 (69%)	94 (69%)
Mean blood pressure	*Systolic*	128.6	130.9
	Diastolic	77.9	78.9
Number with Bp > 140/90		25 (18%)	41 (30%)
Mean BMI		26.6	26.2
Number with BMI > 25		53 (39%)	66 (48%)
Number on antihypertensives	*Yes*	18 (13%)	17 (12%)
	Unknown	4 (3%)	5 (4%)
Smokers	*No*	91 (66%)	94 (69%)
	Yes	32 (23%)	39 (28%)
	Unknown	14 (11%)	4 (3%)
No of cigarettes per day	*<10*	15 (47%)	16 (41%)
	10-20	12 (38%)	20 (51%)
	21-40	5 (15%)	3 (8%)
	>40	0	0
Alcohol intake	*Nil*	40 (29%)	39 (28%)
Units per week	*<1 unit*	9 (8%)	4 (4%)
	1-9	56 (60%)	66 (70%)
	10-21	11 (11%)	21 (22%)
	>21	3 (4%)	3 (4%)
	Unknown	18 (16%)	4 (4%)

Table 130 *Comparison of patients with active epilepsy with controls (n-33)*

		Epilepsy	*Controls*
Age	*Mean*	45	45
	Range	15-82	15-82
Sex	*Males*	10 (30%)	10 (30%)
	Females	23 (70%)	23 (70%)
Mean blood pressure	*Systolic*	133.9	133.6
	Diastolic	79.4	80.4
Number with Bp > 140/90		9 (27%)	11 (33%)
Mean BMI		25.8	25.3
Number with BMI > 25		11 (33%)	15 (45%)
Number on antihypertensives	*Yes*	7 (21%)	8 (24%)
	Unknown	4 (12%)	0
Smokers	*No*	17 (52%)	25 (76%)
	Yes	12 (36%)	8 (24%)
	Unknown	4 (12%)	0
No of cigarettes per day	*<10*	5 (42%)	4 (50%)
	10-20	5 (42%)	3 (38%)
	21-40	2 (16%)	1 (12%)
	>40	0	0
Alcohol intake	*Nil*	9 (27%)	8 (24%)
Units per week	*<1 unit*	1 (5%)	2 (8%)
	1-9	13 (68%)	19 (76%)
	10-21	3 (16%)	4 (16%)
	>21	2 (11%)	0
	Unknown	5 (24%)	0

Table 131 *Comparison of patients with inactive epilepsy, but on AEDs, with controls (n-41)*

		Epilepsy	*Controls*
Age	*Mean*	53	53
	Range	17-86	17-86
Sex	*Males*	15 (37%)	15 (37%)
	Females	26 (63%)	26 (63%)
Mean blood pressure	*Systolic*	132.4	138.9
	Diastolic	77.8	81.9
Number with Bp > 140/90		17 (41%)	24 (59%)
Mean BMI		25.9	26.5
Number with BMI > 25		11 (27%)	19 (46%)
Number on antihypertensives	*Yes*	9 (22%)	6 (15%)
	Unknown	0	0
Smokers	*No*	36 (88%0	26 (63%)
	Yes	3 (7%)	15 (37%)
	Unknown	2 (5%)	0
No of cigarettes per day	*<10*	1 (33%)	5 (33%)
	10-20	1 (33%)	9 (60%)
	21-40	1 (33%)	1 (7%)
	>40	0	0
Alcohol intake	*Nil*	14 (34%)	10 (24%)
Units per week	*<1 unit*	4 (18%)	1 (3%)
	1-9	17 (74%)	22 (71%)
	10-21	1 (4%)	6 (19%)
	>21	1 (4%)	2 (7%)
	Unknown	4 18%)	0

Table 132 *Comparison of patients with chronic intractable epilepsy resident at the Chalfont Centre with controls (n-128)*

		Epilepsy	*Controls*
Age	*Mean*	55.6	55.6
	Range	28-100	28-100
Sex	*Males*	93 (73%)	93 (73%)
	Females	35 (27%)	35 (27%)
Blood pressure	*Systolic (mean)*	127.3	134.1
	Diastolic (mean)	80.1	80.8
BMI	*Mean*	25.3	25.6
Number on antihypertensives	*Yes*	7 (6%)	12 (88%)
	Unknown	0	3 (3%)
Smokers	*No*	107 (84%)	93 (73%)
	Yes	21 (16%)	27 (21%)
	Unknown	0	8 (6%)
No of cigarettes per day	*<10*	4 (19%)	6 (22%)
	10-20	12 (57%)	18 (67%)
	21-40	4 (19%)	3 (11%)
	>40	0	0
Alcohol intake	*Nil*	40 (31%)	28 (22%)
Units per week	*<1 unit*	77 (89%)	1 (1%)
	1-9	9 (10%)	66 (72%)
	10-21	1 (1%)	21 (223%)
	>21	0	4 (4%)
	Unknown	1 (1%)	8 (8%)

4.3. SECULAR TRENDS IN THE EPIDEMIOLOGY OF EPILEPSY: THE TONBRIDGE 6000

Summary

A population of 6000 persons was studied ten years apart to determine secular trends in the prevalence and prognosis of epilepsy. The lifetime prevalence of all patients with one or more afebrile seizures was 20.3/1000 (95% CI 16.9, 24.3) in 1983 and 21.0/1000 (95% CI 17.6, 25.1) in 1993. The prevalence of active epilepsy was 5.3/1000 (95% CI 3.6, 7.5) in 1983 and 4.3 (95% CI 2.8, 6.3) in 1993. To assess trends in incidence rates we measured the annual first attendance rates from 1964 to 1993. Annual first attendance rates in children (age < 20 years) have declined, from 152.4/100,000 (90% CI 106.0, 212.9) in the years 1974-83, to 60.9/100,000 (90% CI 33.0, 103.3) in the years from 1984-93, suggesting that the true incidence of epilepsy in children is falling. Also noteworthy was the first attendance rates for epilepsy in the elderly (61-80 years) in the years 1984-93, which was 82.0 (90% CI 38.5, 154.0), higher than in any other age band. This increase in the number of elderly patients with epilepsy is important, and has health planning implications, especially with the overall increase in the total elderly population. There was, however, no evidence that prognosis has significantly altered in the last forty years.

4.3.1 Demographic features

The age structure of the population of the Tonbridge 6000 back to 1948 is shown in table 133. The age structure of the Tonbridge 6000 in the two survey years, 1983 and 1993, is shown in table 134. The social structure of the population of the town of Tonbridge is shown in table 135.

Table 133 Age adjusted population of the 6000 from 1948-1993 based on OPCS census data for years 1951, 1961, 1971, 1981, and 1991

Age	1948-1953	1954-1958	1959-1963	1964-1968	1969-1973	1974-1978	1979-1983	1984-1988	1989-1993
0-20	1620	1776	1776	1974	1974	1668	1612	1612	1672
21-40	1644	1542	1542	1656	1656	1638	2065	2065	1697
41-60	1614	1578	1578	1350	1350	1506	1335	1335	1492
61-80	1014	948	948	822	822	1014	799	799	910
81+	108	156	156	198	198	174	189	189	229
Total	6000	6000	6000	6000	6000	6000	6000	6000	6000

Table 134 *The age and sex of the of the Tonbridge 6000*

a) 1983

Age	Persons	Male	Female	%
0-10	744	393	351	12.4
11-20	868	456	412	14.5
21-30	988	484	504	16.4
31-40	1077	516	561	17.9
41-50	742	402	340	12.4
51-60	593	319	274	9.9
61-70	456	221	235	7.6
71-80	343	149	194	5.7
81+	189	60	129	3.2
Total	6000	3000	3000	100

b) 1993

Age	Persons	Male	Female	%
0-10	787	406	381	13.1
11-20	885	465	420	14.8
21-30	841	439	402	14.0
31-40	856	438	418	14.3
41-50	865	444	421	14.4
51-60	627	320	307	10.5
61-70	512	241	271	8.5
71-80	398	165	233	6.6
81+	229	82	147	3.8
Total	6000	2986	3014	100

Table 135 *Social class and ethnic origin of Tonbridge*

a) Social class of persons resident in Tonbridge compared to whole UK

Social class	Tonbridge (%)	UK (%)
I	9	7
II	45	30
III	24	40
IV	11	14
V	6	5
Other	6	4

b) *Country of origin of persons resident in Tonbridge urban districts in 1981*

Country	(%)
England	93
Rest of UK	3
Irish Republic	0.1
Africa	0.5
Caribbean	0.2
Indian subcontinent	0.5
Far East	0.4
Mediterranean	0.3
Other	2

4.3.2 Prevalence

4.3.2.1 Overall prevalence rates

In 1983 a total of 122 patients with definite epilepsy were ascertained, and in 1993 we identified 178 patients with possible epilepsy of whom 126 were classified as having definite epilepsy. 64 patients currently in the practice in 1993 were in the 1983 survey, and 62 were new patients to the practice. 58 patients had moved away or died from the original 1983 6000.

The prevalence of all patients with one or more afebrile seizure was 20.3/1000 (95% CI 16.9, 24.3) in 1983 and 21.0/1000 (95% CI 17.6, 25.1) in 1993, or 16.7 /1000 (95% CI 13.5, 20.4) for patients with two or more attacks in 1983, and 17.0/1000 (95% CI 13.9, 20.7) in 1993. The prevalence for those with active epilepsy was 5.3/1000 (95% CI 3.6, 7.5) in 1983 and 4.3/1000 (95% CI 2.8, 6.3) in 1993. The prevalence of unprovoked seizures (non acute symptomatic) was 17.2/1000 (95% CI 14.1, 20.9) in 1983, compared to 17.7/1000 (95% CI 14.6, 21.5) in 1993.

4.3.2.2 Age and sex specific prevalence

The age and sex specific rates are shown in table 131. The overall prevalence rate for men was 13.7/1000 (95% CI 9.8, 18.6) and for women 27.0/1000 (95% CI 21.4, 33.5) in 1983, and 15.4/1000 (95% CI 11.3, 20.5) for men and 26.5/1000 (95% CI 21.0, 32.9) for women in 1993. For patients with active epilepsy in the 1993 survey (n =26) the age specific rates were: 4.8/1000 0-20 years, 2.7/1000 21-60 years, and 6.1/1000 over 60 years.

Table 136 *Age and sex distribution of patients in 1983 and 1993*

a) Age and sex distribution at onset of seizures in populations of 1983 and 1993

	1983				1993			
	Male	Female	Total	%	Male	Female	Total	%
0-10	14	24	38	31	20	28	48	38
11-20	8	22	30	25	8	20	28	22
21-30	7	16	23	19	7	12	19	15
31-40	2	2	4	3	4	4	8	6
41-50	4	5	9	7	3	6	9	7
51-60	1	4	5	4	3	4	7	6
61-70	5	5	10	8	1	1	2	2
71-80	0	3	3	3	0	5	5	4
81+	0	0	0	0	0	0	0	0
Total	41	81	122	100	46	80	126	100

b) Age and sex distribution at time of survey in populations of 1983 and 1993

	1983				1993			
	Male	Female	Total	%	Male	Female	Total	%
0-10	3	3	6	5	3	1	4	3
11-20	7	11	18	15	5	8	13	10
21-30	9	12	21	17	8	10	18	14
31-40	7	17	24	20	11	19	30	24
41-50	4	13	17	14	6	13	19	15
51-60	4	5	9	7	7	13	20	16
61-70	5	9	14	11	4	6	10	8
71-80	2	8	10	8	2	9	11	9
81+	0	3	3	3	0	1	1	1
Total	41	81	122	100	46	80	126	100

c) Age and sex specific prevalence rates per 1000 persons for 1983 and 1993

	1983				1993			
Age	Male	Female	Total	95% CI	Male	Female	Total	95% CI
0-10	7.6	8.5	8.1	3.0, 17.7	7.4	2.6	5.1	1.4, 13.1
11-20	15.4	26.7	20.7	12.3, 32.7	10.8	19.0	14.7	7.8, 25.1
21-30	18.6	23.8	21.3	13.2, 32.6	18.2	24.9	21.4	12.7, 33.8
31-40	13.6	30.3	22.3	14.3, 33.2	25.1	45.5	35.0	23.6, 50.1
41-50	10.0	38.2	22.9	13.3, 36.6	13.5	30.9	22.0	13.2, 34.3
51-60	12.5	18.2	15.2	7.0, 28.9	21.9	42.3	31.9	19.5, 49.1
61-70	22.6	38.3	30.7	16.8, 51.6	16.6	22.1	19.5	9.4, 35.9
71-80	13.4	41.2	29.2	14.0, 53.7	12.1	38.6	27.6	13.8, 49.4
81+	-	23.3	15.9	3.3, 46.4	-	6.8	4.4	0.1, 24.5
Total	13.7	27.0	20.3	16.9, 24.3	15.4	26.5	21.0	17.6, 25.1

4.3.2.3 Seizure type and aetiology

This is shown in tables 137 and 138. 35% of patients had partial seizures in 1983 compared to 39% in 1993. 48% had generalised onset seizures in 1983 compared to 51% in 1993. 17% were unclassified in 1983 and 14% in 1993. 74% had epilepsy of unknown origin in 1983, and 76% in 1993.

Table 137 *Seizure classification of epilepsy in populations of 1983 and 1993*

	1983		1993	
Seizure type	No.	%	No.	%
Partial				
Simple	1	1	1	1
Complex	10	8	15	12
Secondary generalised	18	15	11	9
Partial and SG	14	11	22	17
Generalised				
Tonic clonic	50	41	46	37
Absence	4	3	9	7
More than one type	5	4	9	7
Unclassifiable	20	17	17	14
Total	122	100	126	100

Table 138 *Aetiology of epilepsy in populations of 1983 and 1993*

	1983		1993	
Aetiology	No.	%	No.	%
Unknown	90	74	96	76
Acute symptomatic				
Trauma	7	6	3	2
Vascular	3	2	1	1
Metabolic	0	0	2	2
Infection	1	1	4	3
Alcohol	4	3	3	2
Other‡	4	3	7	6
Remote symptomatic				
Tumours	1	1	2	2
Vascular	9	7	5	4
Trauma	2	2	1	1
Other†	1	1	2	2
Total	122	100	126	100

† Eclampsia, drugs, hypoxia ‡ Associated with progressive neurological degenerative disease or severe neurological deficit present at birth

4.3.3 First attendance rate trends

4.3.3.1 Overall rates calculated from 1983 and 1993

The average mean first attendance rates were calculated from patients ascertained in the 1983 survey population, and from those ascertained in the 1993 survey population. The rates calculated from 1948-1983, and from 1948-1993, are shown in table 139.

From the 1983 survey the mean annual first attendance rate was 56.5/100,00 (95% CI 47.1, 67.7) from 1948-1983, and from the 1993 survey it was 45.7/100,000 (95% CI 38.2, 54.6) from 1948 to 1993. The overall annual sex specific rates were 33.3/100,000 (95% 24.4, 44.3) for men and 58.0/100,000 (95% CI 46.0, 71.9) for women for 1948-93 when calculated from the 1993 survey.

4.3.3.2 Age specific first attendance rates in children 1964-93

Retrospective calculation of first attendance rates will only correlate with the true incidence rates when the death rates are low, and this is situation exists for children (under 20 years) back to 1964 where the maximum age by 1993 is 49 (see discussion). The age specific rates (calculated from the 1993 survey population) for persons under 20 years are shown in table 140. Annual first attendance rates in children (age < 20 years) declined, from 152.4/100,000 (90% CI 106.0, 212.9) in the years 1974-83, to 60.9/100,000 (90% CI 33.0, 103.3) in the years from 1984-93. This difference was significant (Chi squared $p< 0.01$).

4.3.3.3 Age specific rates 1983-1993

Calculation of first attendance rates in the years immediately preceding the survey dates are less prone to distortion than the rates further back in time (see discussion). The age specific first attendance rates for the most recent years, 1984-93 are shown in table 141. The most important finding was first attendance rates for epilepsy in the elderly (61-80 years which was 82.0 (90% CI 38.5, 154.0), higher than any other age band.

Table 139. *Number of new cases between 1948-1993 and average annual first attendance rate per 100,000*

a) Calculated from 1983 survey

Age	1948-1963			1964-1973			1974-1983			Total (mean)		
	No.	Rate	95%CI	No.	Rate	95%CI	No.	Rate	95%CI	No.	Rate	95%CI
0-20	20	72.5	44.3, 111.7	22	111.4	69.8, 168.2	19	115.9	69.8, 180.8	72	112.4	87.9, 141.6
21-40	7	27.8	11.1, 57.3	14	84.5	46.1, 142.0	6	32.4	11.9, 70.6	27	44.3	29.2, 64.2
41-60	8	31.4	13.5, 61.9	8	59.3	25.6, 116.8	5	35.2	11.4, 82.0	21	40.1	24.9, 61.4
61-80	0	-	-	2	24.3	2.9, 87.7	11	121.4	60.6, 217.3	13	40.2	21.4, 68.7
81+	0	-		0	-		0	-		0	-	
Total	35	36.5	25.4, 50.7	46	76.7	56.1, 102.0	41	68.3	49.0, 92.9	122	56.5	47.1, 67.7

b) Calculated from 1993 survey

Age		1948-1963			1964-1973			1974-1983			1984-1993			Total (mean)		
		No.	Rate	95%CI	No.	Rate	95%CI	No.	Rate	95%CI	No.	Rate	95%CI	No.	Rate	95%CI
0-20	93	16	58.0	33.2, 94.0	26	131.7	86.0, 193.6	25	152.4	98.6, 225.6	10	60.9	29.2, 112.1	76	94.7	74.6, 118.4
21-40	93	5	19.8	6.4, 46.1	12	72.5	37.5, 126.9	3	16.2	3.3, 47.3	7	37.2	14.9, 76.6	27	33.7	22.2, 48.9
41-60	93	1	3.9	0.1, 21.7	6	44.4	16.3, 96.8	3	21.1	4.3, 61.6	4	28.3	7.7, 72.4	16	24.0	13.7, 38.9
61-80	93	0	-	-	0	-	-	0	-	-	7	82.0	32.9, 168.9	7	17.1	6.9, 35.2
80+	93	0	-		0	-		0	-		1	47.8	1.2, 266.2	1	11.9	0.3, 66.3
Total	93	22	22.9	14.4, 34.6	44	73.3	54.7, 100.5	31	51.7	35.1, 73.4	29	48.3	32.4, 69.6	126	45.7	38.2, 54.6

Table 140 *Secular trends in first attendance rates in children. Number of new cases between 1964-1993 and annual first attendance rate per 100,000 in children*

Age	1964-1973				1974-1983				1984-1993			
	No.	Rate	90%CI	95%CI	No.	Rate	90%CI	95%CI	No.	Rate	90%CI	95%CI
0-20	26	131.7	92.3, 182.8	86.0, 193.6	25	152.4	106.0, 212.9	98.6, 225.6	10	60.9	33.0, 103.3	29.2, 112.1
All ages	45	75.0	57.6, 96.2	54.7, 100.5	31	51.7	37.4, 69.7	35.1, 73.4	29	48.3	34.6, 65.9	32.4, 69.6

Table 141 Age specific first attendance rates in last decade. Number of new cases and annual first attendance rates per 100,000 between 1984-93

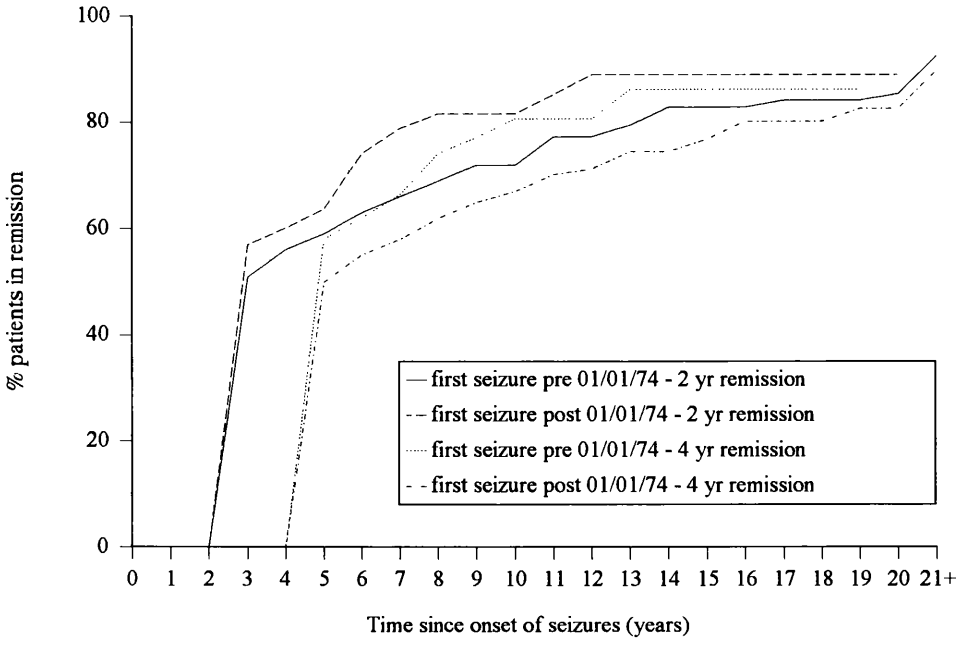
Age	No.	Rate	90% CI	95%CI
0-20	10	60.9	33.0, 103.3	29.2, 112.1
21-40	7	37.2	17.5, 69.9	14.9, 76.6
41-60	4	28.3	9.7, 64.7	7.7, 72.4
61-80	7	82.0	38.5, 154.0	32.9, 168.9
81+	1	47.8	2.4, 227.0	1.2, 266.2
Total	29	48.3	34.6, 65.9	32.4, 69.6

4.3.4 Prognosis

Over 65% of patients responded to the questionnaire and this enabled clarification of the seizure onset and remission dates in 20% of patients where this was not clear from the notes. 3 patients denied all knowledge of their epilepsy despite convincing documentation to the contrary. The life tables and remission curves are shown in figure 25.

The number of patients with active epilepsy in this population were 32 in 1983 and in 26 in 1993, suggesting that the prognosis has not changed significantly between the two points. The survival curves indicate that for all the cases combined 61% achieved 2 year remission at 4 years, 81% at 10 years, and 74% achieved 4 year remission by 10 years. The curves for the 1983 and 1993 populations are shown, and also for patients with onset pre 1974 (n=100) and post 1974 (n=84). There were no significant statistical differences between these analyses, or when performed for idiopathic or symptomatic, age, sex, or seizure type.

Fig 25 *Remission in all patients (n=184), comparing those diagnosed before and after 1 January 1974*



4.3.5 Treatment

In 1983 47 patients (38.5%) were receiving AEDs, compared to 47 (37.3%) in 1993. 96 patients (78.7%) from the 1983 survey had received AEDs at some time compared to 93 (73.8%) in 1993.

4.4. THE ECONOMIC COST OF EPILEPSY

Indirect and direct costs were assessed in the NES, and direct costs in the NGPSE. A longitudinal cost profile of epilepsy was calculated, with an average initial direct cost of £611 per patient per annum which decreased after 8 years of follow up to £169 per patient per annum. The cost to the UK of newly diagnosed epilepsy in the first year of diagnosis was £18 million. The total annual cost of established epilepsy to the UK was estimated at £1930 million, over 69% of which was due to indirect costs (unemployment and excess mortality). The cost of active epilepsy per patient was approximately £4167, and inactive £1630 per annum.

4.4.1. The NES

The basic demographic features of the denominator population (1628 cases) were similar to the UK population as a whole (Hart, 1992). The characteristics of the patients in terms of age, sex, type of seizures and seizure severity were also similar to other studies of epilepsy in the community (Goodridge and Shorvon, 1993), 64% had active epilepsy and 36% inactive epilepsy. At the time of the survey, 81% had attended a hospital out-patients, and 28% of the patients were under hospital follow up (36% by a neurologist), and in the previous year 9% had been an in-patient. 74% had an EEG and 50% had a CT scan, at some point in time, and 65% of patients were on monotherapy. Indirect costs calculated for excess mortality, and unemployment, totalled £ 5.1 million per annum, and the transfer payments were £2 million (table 137). The total of the direct medical costs comprising: anti epileptic drugs (AEDs), hospital care and GP care, was £650,000, and non-medical direct costs: residential care, special schooling was £1.6 million (table 138 and 139). The total cost for the 1628 patients was £7.4 million (excluding transfer payments). Extrapolating to the whole UK, the medical costs alone of epilepsy was £170 million per annum, and the total costs, including direct and indirect was £1930 million (table 140).

Table 142 *Indirect costs and transfer payments of active and inactive established epilepsy (Derived from the NES)*

	Active epilepsy*			Inactive epilepsy*			Combined cost (£)	
Type of cost	No.	%	Cost (£)	No.	%	Cost (£)	No.	
A Indirect costs								
Unemployment	297	82	3,800,000	54	18	900,000	351	4,700,000
Excess mortality	-	-	-	-	-	-	6	400,000
						Total		5.1 million
B. Transfer payments								
Attendance allowance	159	86	344,000	25	14	56,000	184	400,000
Mobility allowance	93	83	56,000	19	17	11,000	112	67,000
Sickness benefit	31	78	67,000	9	12	19,000	40	86,000
Invalidity pension	164	84	460,000	30	16	90,000	194	550,000
Severe disablement allowance	107	82	180,000	23	18	40,000	130	220,000
Unemployment benefit	297	82	550,000	54	18	110,000	351	670,000
Total			1,700,000			300,000		2 million

* *Sub-division was not performed for excess mortality*

Table 143 *The cost of antiepileptic drugs (AEDs) in patients with active and inactive established epilepsy in the NES*

	Active epilepsy (n=1046)			Inactive epilepsy (n=582)			Total (n=1682)
AEDs	No.	%	Cost (£)	No.	%	Cost (£)	Total (£)
Carbamazepine	417	79	36,000	113	21	14,000	50,000
Phenytoin	416	55	8,300	284	41	6,700	15,000
Sodium Valproate	364	76	43,000	112	24	14,000	57,000
Phenobarbitone	123	44	400	158	56	560	1,000
Primidone	55	53	670	47	47	630	1,300
Clonazepam	31	88	3,900	4	12	600	4,500
Ethosuximide	16	62	1,900	10	38	1,100	3,000
Other	34	25		104	75	-	-
Total			94,000			36,000	130,000

Total costs to nearest hundred £

Table 144 *The direct cost of established active and inactive epilepsy per annum: medical and non-medical costs in the NES*

A Medical costs

Hospital care-

	Active epilepsy (n=1046)			Inactive epilepsy (n=582)			Total (n=1682)
Out-patient	398	87	80,000	59	13	2,600	83,000
In-patient	152	99	380,000	2	1	5,000	385,000
CT$^{\infty}$	43	70	4,000	20	30	2,000	6,000
EEG$^{\infty}$	57	70	6,000	34	30	2,600	8,600
Total			470,000			13,000	480,000
AEDs-							
Total			94,000			36,000	130,000
GP care-							
Total							37,000
Total medical costs			560,000*			49,000*	650,000

B Non medical costs$^{\propto}$				Total no.	Cost (£)			
Special schooling	-	-	-	-	-	-	30	870,000
Residential care	-	-	-	-	-	-	32	700,000
Total non medical cost								1,570,000

∞ Number of new patients having these investigations, and so are minimum estimates of no. per year

* Not including GP costs

$\propto$ Sub-division was not performed for special schooling or residential care

Table 145 *The total annual cost per patient and to the UK of active and inactive established epilepsy, and newly diagnosed seizures (Derived from the NES and NGPSE)*

A Established epilepsy (NES)

	Active		Inactive		Total	
	Per patient	Total UK	Per patient	Total UK	Per patient	Total UK
Direct costs-						
Medical (Hospital & drug costs)	£535	£147 M	84	£13 M	£374	£ 160 M
Medical (primary care)	-	-	-	-	£22	£10 M
Non medical	-	-	-	-	£964	£415 M
Indirect costs-						
Unemployment	£3632	£997 M	1546	£242 M	£2887	£1239 M
Mortality	-	-	-	-	£245	£106 M
(Transfer payments)	£1625	£446 M	515	£80 M	£1226	£526 M
Total (excluding transfer payments)	£4167*	£1144 M	1630*	£255 M	£4492	£1930 M

B Newly diagnosed seizures (NGPSE)

	Per patient	UK
Total direct costs in first year	£611	£18 M

M - Millions

* GP costs, non medical direct costs, and mortality costs not sub-divided for active and inactive epilepsy which thus do not appear in sub-totals

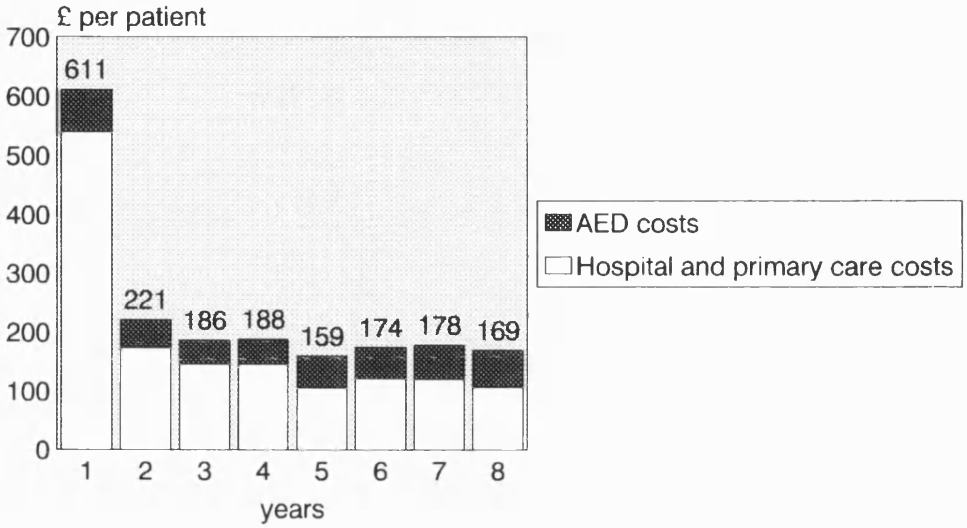
4.4.2. The NGPSE

The features of the NGPSE cohort have been described in earlier sections. The mean time of follow up was 6.6 years. 114 patients had died during the period. Follow up data was available on all but 18 patients. 92% of patients had an initial hospital assessment as an in or out patient. 21% were still under hospital review by year 2, and 7% by year 8 (65% had an EEG, and 39% of patients had a CT scan, in the first year, 81% in those below the age of 16 and 39% above the age of 60 years). The AED treatment of the cohort over the 8 years is shown in table 5, and the costs of the cohort and the total average medical costs per patient per annum over 8 years of follow up are shown in figure 26. The average medical cost per patient was £611 in the first year of diagnosis, £188 in the fourth year, and £169 in the eighth year. This gives a projected annual figure for the total cost in the UK of seizure disorders in their first year of £18 million (Table 145).

Table 146 *Percentages of patients in the NGPSE cohort on each AED per year (to nearest 1%)*

AED	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Lamotrogine	0	0	0	0	1	1	1	2
Vigabatrin	0	0	0	0	1	1	2	2
Diazepam	2	1	1	1	1	0	0	0
Ethosuximide	1	1	1	1	0	0	0	0
Clobazam	1	1	1	1	1	1	1	1
Clonazepam	3	3	2	2	1	1	1	1
Phenobarbitone	3	1	1	1	1	0	0	0
Primidone	0	0	1	1	1	1	0	0
Valproate	27	16	14	14	14	13	12	9
Phenytoin	27	19	19	18	17	14	12	10
Carbamazepine	29	20	18	20	19	21	19	13

Fig. 26 *Total medical costs of newly diagnosed patients with seizures up to 8 years after diagnosis, per patient per annum (derived from the NGPSE)*



SECTION 5

DISCUSSION

5.1. THE PROGNOSIS OF EPILEPSY

5.1.1 The NGPSE cohort

The NGPSE cohort has been described previously.(Sander, et al. 1992) Over 60% of patients had idiopathic epilepsy. Over 35% of patients were under 20 years of age, and 25% were over 60 years. The cohort is representative of newly diagnosed patients at the population level, and the features of the NGPSE cohort are comparable to incident studies of epilepsy in Western populations. (Goodridge & Shorvon, 1983, Hauser & Kurland, 1975) The NGPSE diagnostic review panel reassessed the patients after 5 years to compare the results with the 6 month follow-up. The major change was the increase in the number of patients diagnosed as having definite epilepsy, but 176 patients remained classified as having possible epilepsy even after 5 years. A considerable bias may in theory arise from this form of retrospective classification as patients with repeated attacks will be more liable not to have a diagnosis made, and patients who die before 5 years (such as the elderly) are not then able to have a diagnosis made.

5.1.1.1 The advantages of the NGPSE study design

The incorrect application of epidemiological techniques has detrimentally influenced our understanding of many aspects of the epidemiology of epilepsy, including the prognosis. (Sander & Shorvon, 1987, Shorvon, 1984) For instance, early ideas of the poor prognosis of epilepsy were due to a failure to appreciate the importance of the population from which patients were drawn. (Shorvon, 1984) A study from a general practice population in the UK was one of the first to question the intractability of epilepsy, when it was calculated that the development of active epilepsy was a relatively rare event. (Crombie, Cross, Fry, Pinsent & Watts, 1960) Data from retrospective population-based studies later confirmed this and found that about 70% of patients could be expected to achieve a worthwhile remission, (Annegers, Hauser & Elveback, 1979, Goodridge & Shorvon, 1983) and a similar figure was also reported in prospective hospital-based studies. (Elwes, Johnson, Shorvon & Reynolds, 1984) Despite this consensus there has been a pressing need to establish the prognosis of epilepsy in a truly population-based study that has identified a

Addendum (page 182)

An important aspect of epidemiological research is the ethics of data collection and storage. When patient data is collected by research studies it is important that the data is kept securely and confidentially so that outside agencies are unable to gain access to it. The NGPSE has always been fully aware of its responsibilities and has striven to maintain patient anonymity. Recently, the European Union has ruled that patients must also have given permission for their data to be used. This means that each of the 1091 patients in the NGPSE would ideally have given individual consent to be included in the study. The logistic problems this would entail and the likelihood of exclusions of patients who would not co-operate would seriously have jeopardised the viability of the study. Most workers feel that confidential patient data can be gathered when this is for the overall good and where individual patients will not suffer. For instance, it has always been seen as ethical practice to collect population data on HIV status, vaccination uptake, as well as more formal studies of disease frequency, mortality and outcome, without needing the individual patient consent. In the NGPSE it was therefore felt to be ethical not to inform the patient. Only, one problem was encountered when a GP mentioned to a patient that he was collating his data and sending it on as part of a research study. The patient then declined to have this done and I was unable to pursue follow up with this patient. If the GP had followed our advice and not told the patient then this problem would not have arisen.

reasonable number of incident cases, and that is referable to the whole population, rather than the population of small towns in Minnesota or South East England. The NGPSE was specially designed to accommodate the lessons learnt from previous studies. The NGPSE is prospective and population-based. This means that milder cases, patients with fewer seizures, and certain sub-groups of patients such as the elderly, will all be included. The NGPSE system of active follow up allows for a good estimation of current seizure status. Most studies have judged the year to year seizure status of patients by retrospectively scrutinising hospital notes. This method is unreliable, as patients will tend to forget the number and timing of seizures that they have had in the past. For example, in the Rochester studies the timing of remission was assessed by examining patient records going back in many cases to over 10 years previously.

5.1.2 Remission

5.1.2.1 Overall 1, 2, 3, and 5 year remission

The overall chances of patients with definite epilepsy achieving remission was high and by 9 years was: 95.5% for a 1 year remission, 92.9% for a 2 year remission, 85.7% for a 3 year remission, and 68.1% for a 5 year remission. These good remission rates are in agreement with data from other population-based studies. (Annegers et al., 1979, Goodridge & Shorvon, 1983) In the British Tonbridge study at 5 years from onset, over 50% had entered a remission of 2 or more years, and slightly less entered a remission of 4 or more years. At 15 years from onset nearly 70% had achieved a 2 year remission. (Goodridge & Shorvon, 1983) After 10 years the 5 year remission rate from Rochester was 65%, although no confidence limits were calculated, and single and provoked seizures excluded. (Annegers et al., 1979) The NGPSE thus confirms that epilepsy is generally a benign condition and that prolonged remission is the norm rather than the exception. It might be expected that the success with which the NGPSE was able to identify patients at the population level would relatively increase the numbers of patients with less severe seizure disorders, and so it is somewhat surprising that the findings from our prospective study are in such close agreement with retrospective data. However, as discussed, in the NGPSE seizure status on a year to year basis was accurately assessed, and this will tend to increase the chances of seizure

detection, thus lowering the overall number of patients thought to be in remission.

The temporal trends of remission are also of interest. The chances of achieving a remission increase in the first five to seven years, but after this the cumulative and terminal remission curves flatten out, suggesting that if remission is not achieved in the early period then later remission becomes less likely. The follow up was only for nine years and further follow up may reveal a different pattern, although the Rochester studies showed that remission is relatively rare if not achieved in the first ten years. (Annegers et al., 1979)

5.1.2.2 Remission from index compared to first seizure

Remission when calculated from the first seizure was slightly less than when calculated from the index seizure (remission by 9 years from first seizure: 94.5% for 1 year, 89.9% for 2 year, 82.7% for 3 year, and 64.3% for 5 year remission). The NGPSE ascertained patients with new onset epilepsy, which is not necessarily the same as from the first seizure. Whilst the identification immediately after the first seizure is an ideal, it is also an impossible task as most patients have had a second seizure prior to any medical contact, and the relatively small differences observed suggests that the NGPSE approach was not unduly biased.

5.1.2.3 Remission of possible epilepsy

A particular aim of the NGPSE was to address the problems encountered in studies of epilepsy prognosis by the difficulties of epilepsy diagnosis. Anecdotal experience indicates that patients with epilepsy are not easy to diagnose with complete certainty and to make matters harder, patients with epilepsy may even conceal the diagnosis. (Beran, Hall & Michelazzi, 1985, Cockerell, Sander & Shorvon, 1993) The diagnosis rests on a clinical description of the seizures and therefore there is little room for improving the diagnostic validity without some form of gold standard test. As discussed in the introduction, inter-observer reliability is low even among trained neurologists with a Kappa value of 0.58, (Van Donselaar, Geerts, Meulstee, Habbema & Staal, 1989) and many patients, even with definite epilepsy, are probably often misdiagnosed. (Betts, 1983) The difficulty of making a diagnosis, and the time this often takes, means that if

studies do not include patients with possible seizure disorders there will be tendency to exclude specific subgroups of patients in whom the diagnosis is particularly difficult, for instance, patients with infrequent seizures, or patients who live alone, such as the elderly. All these patients have a lower chance of having one of their seizures witnessed and therefore achieving an accurate and early diagnosis. All the studies to date have largely ignored this problem, and the NGPSE is the first study to include patients with only a possible diagnosis of epilepsy. When patients with possible seizures are combined with the definite epilepsy group this increases the remission rates after 9 years of follow up to 87.2% for 3 year remission, and 71.3% for 5 year remission. This reflects the inclusion of patients who are less severely affected, as well as those who turned out later not to have epilepsy. Interestingly, the combined rates are not greatly different from the definite epilepsy group alone, probably because the majority of patients with definite epilepsy enter remission anyway.

5.1.2.4 Remission of epilepsy excluding single seizures, and provoked seizures

Previous studies have excluded patients with single seizures and provoked seizures. In the first instance it may be difficult to make the distinction between provoked seizures, and "epilepsy", and some patients with epilepsy syndromes are often brought out by provoking situations such as alcohol in Juvenile Myoclonic Epilepsy. (Janz, 1990) It is also difficult to justify the distinction of single seizures from epilepsy, both on purely pathophysiological terms, and because the majority of patients with one seizure will go on to have further seizures. (Hart, Sander, Johnson & Shorvon, 1990) This approach is largely vindicated by the finding that when patients with single seizures, or when those with acute symptomatic seizures were excluded this only decreased the remission rates by a few percent. When all patients with either single or acute symptomatic seizures were excluded the overall remission rates were still similar, and by 9 years they were 81.6% for 3 year remission, and 60.3% for 5 year remission.

5.1.2.5 Effect of aetiology on remission

Epilepsy is not a single disease but a symptom of cerebral dysfunction and therefore the strongest influence on remission should be the underlying

aetiology. A striking finding from this study is the relatively small degree to which the underlying cause does influence the long term outcome. This is true either when divided up into broad aetiological categories of idiopathic, and remote symptomatic, or into specific categories such as tumour or vascular aetiologies, and the remission rates are surprisingly similar. Patients with underlying structural causes did have lower remission rates, however, this was only significantly different for 3 year remission (86.3% for idiopathic and 74.4% for remote symptomatic). There were exceptions, and patients with congenital neurological deficits do have a worse outlook, although the numbers were small and the confidence intervals wide. Also, patients with alcohol induced seizures and other acute symptomatic causes, did fare significantly better. One would expect that patients with tumours and other structural causes would have lower chances of entering remission than the more "benign" idiopathic generalised epilepsies and the other epilepsies in the idiopathic group. This study suggests that epilepsy behaves in the same way no matter what the cause, and that the brain may have a natural tendency to inhibit seizure activity after a certain period (6 months to 2 years), even if there is a structural lesion present. It should be noted that there may be factors that also could account for the relatively small effect aetiology exerts on remission, and this could be partly due to a dilution effect where specific syndromes and aetiologies are occurring in too small numbers to have any discernible influence. The other reason may be that mortality rate is much higher in the symptomatic group with over 67 deaths in the first 8 years, and that the patients who survived presumably suffered from less severe epilepsy, and thus experienced higher remission rates.

Other studies have reported that the probability of attaining a 5 year remission after 20 years was 74% for patients with idiopathic epilepsy, compared to a slightly lower rate for symptomatic epilepsy in the early years, but which evened out later on. (Annegers et al., 1979) Similarly to the NGPSE, only 46% of patients with neurological dysfunction from birth achieved a 5 year remission after 20 years. (Annegers et al., 1979) Two other studies have shown a significantly better outcomes for patients with idiopathic epilepsy, (Okuma & Kumashiro, 1978, Shorvon & Reynolds, 1982) but most studies have not. (Collaborative Group for the Study of Epilepsy, 1992, Goodridge & Shorvon, 1983)

It should also be remembered that some conditions with specific prognostic patterns are not included in the NGPSE to any great degree, and so little information is gained on the prognosis of certain specific syndromes, such as juvenile myoclonic epilepsy, benign epilepsy with centerotemporal spikes, and cryptogenic and symptomatic generalised epilepsy. Nevertheless these syndromes are uncommon at the population level, and make up less than 10% of patients in the NGPSE.

One conclusion from this study is that more work is clearly needed on the rarer syndromes and aetiologies which do have different outcomes. All studies to date have been hospital-based, and work on the prognosis of such syndromes as juvenile myoclonic epilepsy would benefit from a population-based approach, a formidable task if the methods of the NGPSE are to be utilised.

5.1.2.6 Effect of seizure type on remission

Similar effects are observed when remission is stratified by seizure type. There is a tendency for patients with partial onset seizures to have a lower chance of remission than patients with generalised onset seizures, largely due to patients with partial onset seizures having underlying structural disease. Most previous studies have also shown that there is a worse prognosis for patients with partial seizures, (Goodridge & Shorvon, 1983, Okuma & Kamashiro, 1981, Rodin, 1972) although one study did report that patients with complex partial seizures had a similar outcome to patients with other seizure types. (Ramsay, Wilder, Berger & Bruni, 1983)

5.1.2.7 Effect of age on remission

The affect of age on remission in the NGPSE is rather complex. The age group 40-60 appears most favourable for 3 and 5 year remission, then 16-39 years, > 60 years, and finally < 16 years was least favourable. However, after 8 years the 3 year remission for the < 16 year age group increases dramatically to become better than the other age groups. Overall, age probably does not greatly effect the chances of achieving remission, however these data show that patients with seizures under 16 years appear to do worse than many of the older patients. This may be due to aetiology, with the older, more severely affected patients dying sooner leaving less severely affected patients alive who are well able to

enter remission. Also, some of the childhood onset epilepsies may remit in adolescence, and 9 years of follow up may be insufficient for the better 5 year prognosis of the childhood syndromes to be determined, which does, however, becomes evident for the 3 year remission.

Other studies have usually found that youth is a predictor of a better outcome, (Annegers et al., 1979, Hauser & Kurland, 1975, Ramsay et al., 1983) although this was not always confirmed. (Collaborative Group for the Study of Epilepsy, 1992, Goodridge & Shorvon, 1983)

5.1.2.8 The early pattern of seizures

There has been considerable interest concerning the epileptogenic nature of seizures themselves with suggestions that frequent seizures in the initial early period of the history may adversely influence the long term prognosis. (Elwes, Johnson & Reynolds, 1988, Reynolds, 1988) This is of particular interest because if the frequent early seizures are treated effectively, this may effect the long term outcome. The findings from our study show that patients who had more than one seizure in the first 24 hours (termed multiple onset), then the remission rates are lower than for those with only one seizure in the first 24 hours. However, the differences are not great and probably simply a reflection of the severity of the disorder. The results are more complicated when the number of seizures between the first and index seizure were examined and no clear patterns emerge. For example, even patients with more than 10 seizures prior to index seizure still have an excellent chance of eventually achieving remission. The time interval between the first and second seizure is also of interest, with the longer interval being proportional to good outcome. This may be due to the patients with numerous early seizures having a worse outlook, but again the differences are not as marked as one might expect, and it is difficult to disentangle cause and effect.

5.1.2.9 Early treatment and remission

Treatment with antiepileptic drugs has a powerful modifying influence on seizure frequency and the chances of successful withdrawal. However, there is no good evidence that early treatment will reduce the chances of a patient becoming intractable in the long term. The NGPSE was an observational study

and patients were not randomised to specific antiepileptic drugs, or even to no treatment at all. Patients with more severe seizures will be more likely to receive treatment, and the decision to treat will also be affected by other factors such as age, and individual patient circumstances, such as the importance of driving. In the NGPSE patients who were treated within one month of the first seizure, or within one month of the index seizure, actually had a poorer long term outcome. This must be because patients with worse epilepsy were more likely to receive treatment. It is difficult to make conclusions regarding treatment from the NGPSE, however, if treatment had a major curative action then better results would surely have been observed. The effect of early treatment on long term remission can only be addressed by a proper randomised trial, and one has recently been set up in Europe. (Chadwick, 1994)

Long term treatment also affects remission. Most patients who achieve remission are still on treatment, and other studies have shown that many patients who attempt withdrawal will relapse. Sustained remission is thus partly reliant on continued AED treatment and 5 year remission rates will thus be partly dependent on the numbers of patients who withdraw from treatment, either voluntarily or under physician supervision.

5.1.2.10 Terminal remission

The chances of patients being in terminal remission in the NGPSE are consistently 10% lower on average for the 1, 2, 3, and 5 year periods than for the cumulative remission rates. This difference is due to patients who have entered remission later relapsing. In the only other study to look at the difference between cumulative and terminal remission, the rates for 5 year remission were 4% less at 10 years, and 6% less by 20 years. (Annegers et al., 1979) In the same study the chances of relapse from a 5 year remission was 15% by 10 years. In the MRC drug withdrawal study, patients on continued treatment had a relapse rate of 22% by 2 years, compared to 41% for patients who had undergone slow withdrawal. (Medical Research Council Drug Withdrawal Trial, 1991, Overweg, Binnie, Oosting & Rowan, 1987) There are two possible reasons for the larger difference between the NGPSE terminal and cumulative remission rates. The first is, as discussed above, that because to the design of the NGPSE with the system of active follow up every year, patients who relapse are more liable to be identified. The second is that more patients in

the NGPSE underwent drug withdrawal than in the USA, and there is a fairly large decrease in the percentage of patients who are continuing to receive AEDs between the 7-9 year follow up. No data on the number of patients who were on treatment was given by the USA study. (Annegers et al., 1979)

SUMMARY AND CONCLUSIONS

- Epilepsy has an excellent prognosis with over 95.5% of patients with definite epilepsy experiencing a 1 year remission by 9 years, and 68.1% experiencing a 5 year remission by 9 years.

- The inclusion of patients with possible epilepsy raises the remission rates to 95.7% and 71.3% for 1 and 5 year remission respectively.

- Patients with idiopathic epilepsy have a similar chance of achieving a remission as patients with remote symptomatic seizures caused by tumours and strokes. However, the high mortality rate of the symptomatic seizures influences this finding, as patients with more severe seizures die, mostly within one year of onset.

- Patients with acute symptomatic seizures have an excellent chance of achieving remission, and patients with congenital deficits from birth have a low chance.

- Age had a complex influence on remission, and epilepsy acquired in the middle years fares better than in children or the elderly.

- Seizures types only weakly affect remission, although partial seizures do slightly worse than generalised onset seizures.

- The early pattern of seizures is related to long term remission with fewer and more infrequent seizures being related to better outcome. However, cause and effect are difficult to disentangle.

- The chances of patients with epilepsy achieving a terminal remission at any particular time of follow up is about 10% less than the corresponding cumulative remission rate. This is due to relapses, which in the later years (7-9) are possibly due to AED withdrawal.

- Early treatment had no detectable effect on long term remission.
- Further work should be directed into the remission of specific defined syndromes and aetiologies in population-based studies.

5.1.4. The mortality of epilepsy in the NGPSE

Previous studies of the mortality of epilepsy have been hindered by important methodological problems, for example, some studies have not specified the case definition for epilepsy, (Rodin, 1968, Zielinski, 1974) and most have been in selected populations, such as in special institutions, (Klenerman, Sander & Shorvon, 1993, White, McLean & Howland, 1979) or in populations of insured patients. (Livingston, 1963) The application of such results to the wider, and usually less disabled epilepsy population is of doubtful validity. Ascertainment has also often been inadequate, particularly so in studies which identify cases from death certificates; (Schwade & Owen, 1954) a method which is unreliable as death certificates do not often state that the patient had epilepsy. (Hauser, Annegers & Elveback, 1980) Another difficulty is the determination of the cause of death when the contribution of epilepsy is often highly subjective. (Bradford-Hill, 1984) Post mortem records are often the most accurate method of determining the cause of death, but again, used in isolation may not contain the relevant circumstantial evidence that may be important, for instance, that a person who drowned did so during a generalised seizure. New cases of epilepsy are often not ascertained in cross-sectional studies which will not account for the impact of time trends, and will fail to determine the large initial mortality rate in epilepsy and will also misrepresent particular causes of death. For example, patients with brain tumours will have a high death rate in the first year of diagnosis. The errors that are due to biased patient selection can be eliminated by a population based study. Two previous studies have been carried out in unselected groups of patients. (Hauser et al., 1980, Zielinski, 1974) Both studies were retrospective, with the potential to miss mild cases, or particular patient groups such as the elderly, the very young, and solitary individuals where seizures were not witnessed. Also by only including patients with definite epilepsy, milder cases or those with a delayed diagnosis may be missed. The study design of the NGPSE, by including patients who had definite or possible seizures , allows us to be confident that no patients with epilepsy were missed, even where the diagnosis was not at first clear (an important issue in epilepsy as death rates are highest in the periods immediately after presentation). In the study, therefore, maximum case ascertainment was achieved and also the accurate reporting of death. A SMR of 3.0 in patients with definite epilepsy was

found, and 2.5 for definite and possible epilepsy combined. Thus epilepsy has a high mortality rate, even when the whole range of patients are considered.

This study includes patients with single seizures who are often not included in the definition of epilepsy. The NGPSE has already shown that the majority of patients with single seizures go on to experience further seizures (about 80%), and that there is no pathophysiological difference between patients who have single seizures and patients who have more than one seizure and that exclusion of these patients would be artificial.

5.1.4.1. Mortality rate from seizure onset as opposed to index seizure

A particular concern in the NGPSE has been the effect of the interval from first seizure to the time of the first medical consultation and registration (index seizure). Patients with new onset epilepsy were included, not necessarily after the first seizure, and so the death rate may be underestimated because other patients could have been excluded who had their first seizure in the same time period, but who had died prior to ascertainment. This was examined by calculating the SMRs for patients according to whether the interval between first seizure and index seizure was within 6 months, or not. The SMR is highest where the index seizure was also the first seizure (SMR = 3.30), 2.73 if the first was within 6 months of the second, and 1.44 if it was not. Part of the explanation is that patients with milder epilepsy such as absence seizures, will consult their doctor later than a patient with seizures secondary to a stroke or brain tumour. These results may however still slightly underestimate the death rate and should be taken as minimum estimates, although if this is so, the effect will be probably more pronounced for symptomatic rather than idiopathic epilepsy.

5.1.4.2. Mortality in different aetiologies

When the causes of death are examined in the definite epilepsy group subdivided by broad aetiology (idiopathic, remote symptomatic, acute symptomatic, and seizures associated with severe congenital neurological deficit) the SMR is highest in the remote and acute symptomatic cases. This is largely because of the underlying lesion such as tumours and strokes, which are the commonest cause of death in these groups. Patients with congenital deficits

have a very high mortality which again is largely a result of severe underlying neurological disease.

5.1.4.3. The mortality of idiopathic epilepsy

Perhaps of greater interest is the mortality rates of patients with idiopathic epilepsy, the SMR of which was also raised at 1.6, which shows that epilepsy itself carries an increased risk of mortality not related to the underlying cause. Three deaths in the idiopathic group were due to missing an underlying symptomatic aetiology (primary brain tumours which were unrecognised in life), but even with these deaths excluded the SMR is still 1.4. The prospective nature of the NGPSE means that patients with all types of aetiology have to be ascertained to avoid selection bias, so that the numbers of patients with an unknown aetiology is less, and further follow up to examine less common causes of death is required. However, it is safe to conclude that no single cause accounts for the elevated death rate in the idiopathic group in the first 9 years from diagnosis.

5.1.4.4. Temporal trends in the mortality rate

The death rate is highest in the first year (SMR 6.6, CI 95% 4.8, 8.7).and then decreases progressively. Even after 6 years the death rate is still raised, though not significantly so, at 1.3. These findings are similar to the only other study to examine the mortality rate over time. (Hauser et al., 1980) with the majority of these deaths occurring in the first 2 years. However in patients with idiopathic epilepsy the deaths were spread out evenly over the follow up period, and the SMR for the idiopathic group did not fall over time during the follow up period. These trends are largely the result of the early death of patients with underlying lethal causes such as strokes and tumours in patients with symptomatic epilepsy, whereas the causes of death which kill patients with idiopathic epilepsy occur at any time during the course of the disease, and indeed might be expected to become more frequent with time as patients with active epilepsy start to become more affected by long term effects of seizures and AED side affects.

5.1.4.5. The mortality rate in differing age groups

The SMR declined with increased age. Although over 70% of the deaths occurred in people over the age of 60, the SMR is highest in the younger age groups because of the low numbers of expected deaths in younger persons.

5.1.4.6. The mortality rate from different causes of death

In agreement with other studies there was a raised SMR for cancer, strokes, and pneumonia. (Annegers, Hauser & Shirts, 1984, Klenerman et al., 1993, White et al., 1979, Zielinski, 1974) After excluding primary brain tumours there still is an excess cancer mortality over that which could be accounted for by cerebral metastases. The SMRs for cancer and strokes are highest in the remote and acute symptomatic aetiological groups. The cause of the high cancer risk is unknown. Previous speculation that patients with epilepsy are at risk from AED induced liver cancer or via lymphoma induction, (Jancar, 1980, White et al., 1979) was not substantiated as the NGPSE cohort has had a relatively short lived exposure to AEDs: there was only one death from liver cancer, and none from lymphoma. It is possible that other cancer risk factors, such as increased smoking or alcohol intake, were operating in the cohort, although other studies have not suggested any difference between the smoking habits of people with epilepsy and the general population. (Klenerman et al., 1993) There has also been speculation about other possible effects of AEDs on patients with epilepsy which might influence the mortality rate, because of their antiarrythmic effect, (Annegers et al., 1984) or the effect of raised plasma lipids. (Muuronen, Kaste, Nikkila & Tolppanen, 1985) In this study the SMR for ischaemic heart disease was normal for the whole cohort, and only raised in the remote symptomatic group (SMR 1.9, 95% CI 0.8, 3.8), probably due to the association with the high rate of cerebrovascular disease.

Pneumonia has been noted as a common cause of death in patients with seizures since 1910. (Munson, 1910) One hypothesis concerning a possible damaging effect of AEDs on pulmonary function has not been substantiated. (Moore, 1959) A high rate for pneumonia deaths was found across the aetiological groups in the sample. Detailed evidence from the GP and / or hospital failed to find an underlying cause for the pneumonia, such as cancer, or status epilepticus. The mean age of patients who died of pneumonia was 81.3 years

(SE 3.6), and thus elderly patients with epilepsy must carry an increased susceptibility to pneumonia which is probably multi-factorial, because of higher rates of associated diseases, worse mobility, and the heightened dangers of accidents and aspiration following seizures.

Only two patients had epilepsy related deaths, one drowned in the bath and the other suffered severe burns consequent of a seizure. A higher accident rate has previously been reported in patients with epilepsy, although this risk is still low for the whole epilepsy population. (Hauser et al., 1980) Suicide may be more common in patients with epilepsy, (Barraclough, 1987) but only one patient committed suicide in the study and the raised suicide rate was thus not confirmed. Previous studies of suicide in epilepsy have been in patients with chronic intractable epilepsy which is different from the NGPSE cohort of incident cases with relatively few severely affected patients. No patients suffered sudden unexpected deaths (SUD), although one patient was found dead after an unexplained fall from a tower block. The rate of SUD is reported to lie between 1:370 and 1:1,100 per year, (Klenerman et al., 1993) but in patients in the general population it is at the upper end of this limit, being most prevalent up to the age of 45 years. Also all data on SUD in epilepsy come from patients with active epilepsy. In the NGPSE approximately 1000 person years have been observed of active epilepsy in persons up to 45 years, so none or only one death would have been expected, and further follow up may be more informative. Of some concern were the 3 violent deaths in patients with definite epilepsy, but because the numbers were small the significance of this is unknown.

SUMMARY AND CONCLUSIONS

- Patients with epilepsy carry a significant risk of premature death, and this is so even when patients with milder epilepsy are included, such as single seizures and patients with possible seizures. Over a median follow up of 6.9 years, and up to 9 years, the "all cause" SMR for patients with definite or possible epilepsy was 2.5, and 3.0 for those patients who were classified as having definite epilepsy.

- The raised SMR for patients with newly diagnosed epilepsy is mainly due to the underlying aetiology, however the SMR for idiopathic seizures was also

raised, demonstrating that epilepsy per se may carry a definite but small risk of premature death.

- The death rate showed a steady decline from the time of diagnosis. The mortality rate was highest in the first year after diagnosis, SMR = 5.1, and declined to 2.5 at 3 years, and 1.3 after 5 years. This is due to patients with symptomatic epilepsy dying of the lethal causes, such as brain tumours and strokes. The death rate for patients with idiopathic epilepsy remained constant over the 9 year follow up period.

- The commonest causes of death were pneumonia (SMR = 7.2), cancer (SMR = 3.5), and stroke (SMR = 3.7). In patients with idiopathic epilepsy violent death was much more common than expected, although the numbers were too small to allow for calculation of SMRs.

- Although the majority of patients with epilepsy who die are over 65 years of age, the mortality rate is highest in young patients and progressively declines with advancing age. The elderly patient is at most risk of death from pneumonia whilst brain tumours are the most important cause of death in the younger age groups.

5.2. RISK FACTORS FOR VASCULAR AND CANCER DEATHS IN PATIENTS WITH EPILEPSY

Previous studies have shown that patients with epilepsy carry a significant excess risk of cancer, stroke and pneumonia deaths compared to the general population, and this has been shown in the NGPSE, and for patients at the Chalfont Centre (in three studies of almost identical populations of patients). (Cockerell, Sander, Klenerman & Shorvon, 1993, Klenerman, Sander & Shorvon, 1993, White, McLean & Howland, 1979)

It is possible that the increased number of cancer and stroke deaths observed in patients with epilepsy is due to a bias introduced because both cancer and vascular disease may also be the underlying cause of the epilepsy. For instance, in a recent study Ng et al examined the relationship between hypertension and new onset epilepsy, and found that hypertension was an independent risk factor for unprovoked seizures. (Ng, Hauser & Brust, 1993) However, there was probably a failure to exclude patients with strokes, and the population was totally hospital based. (Bladin, 1993) Nevertheless patients with idiopathic epilepsy still have a higher risk of dying from strokes, and cancer, (Hauser, Annegers & Elveback, 1980, Zielinski, 1974) and pneumonia is also more common than expected, even allowing for the increased rate in patients debilitated by terminal or frequent seizures. (Zielinski, 1974) The use of anti epileptic drugs (AEDs) has been implicated as a possible aetiological factor for all these causes of death. (Clemmensen, 1974, White et al., 1979) Liver or immune system damage by AEDs has been suspected of causing carcinogenesis, (Clemmensen, 1974) or by raising lipid levels leading to increased atherosclerotic disease, (Berlit, Krause & Schellenberg, 1982) and even by decreasing lung elasticity so increasing susceptibility to pneumonia. (Moore, 1959)

Patients were not matched to controls of a similar social class. There is some evidence that patients with epilepsy come from lower social classes, (Scambler & Hopkins, 1980) that persons in social class III-V are predisposed to carry more risk factors. (Bottiger & Carlson, 1980) However, this potential bias is

obviated by the finding the same level of risk factors in patients with epilepsy as the GP population.

This study shows that patients with epilepsy do not significantly differ in terms of BMI, blood pressure, or alcohol intake from other members of the population. Patients with active epilepsy in the community have a greater tendency to smoke. This, however, is unlikely to account for the increase in the SMR due to cancer and vascular disease because the increase in smoking behaviour (12%) is only marginally increased and would not account for the two to three times increased risk of lung cancer or other disorders. In the population of 300,000 persons with active epilepsy in the UK, this difference in smoking behaviour would produce an SMR for lung cancer of 1.2. (Samet, 1993)

This study will not account for the number of cancer deaths observed in a newly diagnosed population. The highest death rate is seen in patients with symptomatic seizures and secondary neoplasms are certainly an important contributor to deaths, and many of these cases may have been connected with smoking. Patients dying of such causes will then only make up a small proportion of the prevalent epilepsy population.

SUMMARY AND CONCLUSIONS

This study suggests that the mortality of patients with a past history of epilepsy, active epilepsy, or intractable institutionalised epilepsy, can not be explained on the basis of a different risk factor profile for cancer or vascular deaths. The causes of the increased mortality risks in patients with epilepsy needs further investigation which will require further prospective trials with correlation of the causes of death in relation to the various risk factors.

5.3. SECULAR TRENDS IN THE EPIDEMIOLOGY OF EPILEPSY

This study again highlights the advantages the general practice (GP) system in the UK has for studying the epidemiology of epilepsy. (Cockerell, Sander & Shorvon, 1993) There is high coverage of the population with over 98% registered with a GP, and the GP initiates and documents all hospital contacts, including those that occurred without his or her initial knowledge. The GP is responsible for all long term prescribing, as well as keeping the medical notes going back to 1948, containing a patient's lifetime medical history with information on investigations, and hospital care. The complete medical notes are transferred with the patient should they move. In the UK, the Office of Population Census and Survey (OPCS) keeps detailed data on population demographics and social structure down to the town level, and records go back to the beginning of the century.

In this study medical records review was utilised and correlated with information from the 1983 study, and a questionnaire was used to obtain data on each patient. In 1993 over 96% of patients had been referred to a neurologist or other physician and the notes gave a clear account of the seizures in letters, hospital summaries, or from the original notes written by the GP. The majority (over 75%) of patients had EEGs, and in recent years, CT or MRI scans (52% of new onset cases in the last 10 years had CT). The absence of a patient interview may have meant that in some patients the determination of the exact number of seizures was inaccurate. The exact numbers of seizures, or patient attitudes to their treatment, were not being examined in this study, so that the lack of an interview does not detract from the validity of the data. It is also felt that there is no real merit in distinguishing single seizures from epilepsy, (Hart, Sander, Johnson & Shorvon, 1990) and so a failure to identify the number of patients with single seizures will not adversely affect the results.

5.3.1. The population of Tonbridge

The population of the town of Tonbridge is relatively homogenous compared to the rest of the UK. There are higher proportions of the higher social classes and

the bulk of the population was born in the UK. Over the last fifty years the population has undergone some alteration. After the second world war the proportion of men between 20-40 years was significantly less than women and the proportions under 10 years of age was 15.6%. This changed in the sixties with an increase in the young male population together with a rising birth rate (over 18% in the under 10 age group). This then gradually fell to a level of 13% in the last two decades. Against this there has been a marginal increase in the number of elderly, with 8.7% over 71 in 1951, and 8.8% in 1992, although the percentage over 81 has risen, especially in women. The population of the practice 6000 very closely mirrored the age and sex distribution of the town and is likely to be representative of the town of Tonbridge, and also the whole of the UK. It should be remembered that the population of the 6000 is in essence a window into the whole UK and is a dynamic population with in and out migration. There is no evidence from OPCS that there is a tendency for different types of people to move in or out of the town and the population is reasonably representative of the whole UK. It is unknown whether ethnicity or social class have any influence on the epidemiology of epilepsy in the UK, as in the USA. (Haerer, Anderson & Schoenberg, 1986)

5.3.2. The 1983 and 1993 prevalence surveys

The lifetime prevalence of 20.3/1000 in 1983 and 21.0/1000 in 1993 is not significantly different. This is important from a health planning perspective, but as pointed out elsewhere, (Hauser, Annegers & Kurland, 1991) similar prevalence results may mask more significant trends in mortality and incidence. The prevalence rates are higher than other studies in the developed world which have calculated lifetime prevalence rates, (De Graaf, 1974, Hauser et al., 1991, Juul-Jensen & Foldspang, 1983, Sato, 1964, Tsuboi, 1984) and also higher than prevalence studies which relied on field surveys. (Haerer et al., 1986) Even when single seizures and unprovoked seizures are excluded the rates are still significantly higher at 14.5/1000 and 14.6/1000, in both the 1983 and 1993 survey dates. This probably reflects the success with which long-standing inactive cases were identified using the GP system, compared to the rates for active epilepsy which were in the same order of magnitude as other studies. (Brewis, Poskanzer & Miller, 1966, Granieri et al, 1983, Gudmundsson, 1966, Pond, Bidwell & Stein, 1960)

5.3.2.1. Age and sex distribution

The age and sex distribution in the two prevalence surveys were similar, both in terms of age of onset and age at time of survey. There is a small decrease in the prevalence of children under 20 years in the 1993 (10.2/1000, 95% CI 5.9, 16.3) compared to the 1983 survey (14.9/1000, 95% CI 5% CI 8.3, 24.6). Lifetime prevalence is reasonably proportional to cumulative incidence in children, (Hauser et al., 1991) and this fall in the age specific lifetime prevalence rate may be due to a fall in the incidence of epilepsy in children, however the numbers were small and the confidence limits quite wide. This will be discussed when first attendance rates are considered. The female to male preponderance which was at odds to other prevalence studies continued in 1993. (Granieri et al., 1983, Hauser et al., 1991) The proportion of cases is also highest in the middle years of life. This it at variance to other workers who found a higher prevalence in the elderly, (Hauser et al., 1991) or in the second decade of life. (De Graaf, 1974, Granieri et al., 1983, Sato, 1964) The USA studies from Rochester are alone in finding a higher rate in the elderly, which has been ascribed to better identification of more elderly cases in the latter studies. (Hauser et al., 1991) There has been a tendency for the number of elderly cases to rise over the last 10 years, and the National General Practice Study of Epilepsy (NGPSE) found that over 25% of new onset cases were over 65 years. (Sander, Hart, Johnson & Shorvon, 1990) As pointed out, prevalence data does not mirror incidence data, and although epilepsy is becoming more common in the elderly, it is usually caused by more lethal processes and is associated with a much reduced life span, (Cockerell, Sander, Slok & Shorvon, 1993) making it less likely that cases will then feature in prevalence statistics. There is no reason to suspect trans-Atlantic differences in longevity of patients with epilepsy and it is not clear why this pattern is not also present in Rochester.

5.3.2.2. Seizure types

Again there is little variation between 1983 and 1993. The number of partial seizures is dependent on whether symptoms or partial onset are documented and the level of investigations performed. (Sander & Shorvon, 1987) This probably explains any inter-study variation. More information is liable to be gained where patients have been classified syndromically, (Commission on

Classification and Terminology of the International League Against Epilepsy, 1989) or by using aetiology.

5.3.2.3. Aetiology

In agreement with other studies the aetiology is unknown in over 70% of patients. (Hauser et al., 1991) Again, this will depend on the sophistication and degree to which investigations are applied, (Sander & Shorvon, 1987) and would be expected to decrease with the introduction of CT and MRI. The prevalence population includes a high number of inactive cases who do not warrant any investigation, and it will take many years before the improved investigation of new onset, and the few intractable, cases feeds through into the prevalence population. In the NGPSE which identified patients at the population level in the UK between 1984-1987, the number of unknown aetiologies was considerably less. (61%) (Sander et al., 1990) There is no apparent difference in the type of aetiologies in the 1983 and 1993 surveys, except that the number of traumatic seizures has fallen. This may be related to an overall significant decrease in fatal road accidents in the UK with the introduction of new motorcycle and car safety laws. (Office of Population Census and Surveys, 1991)

5.3.3. First attendance rates and incidence

First attendance rates are a measure which was first used by Zielinski. (Zielinski, 1974) He calculated the first attendance rates of patients attending a specialist neurological hospital and found these rates to be considerably lower than incidence rates estimated from a population-based survey, and concluded that first attendance rates were a poor guide to incidence. Hospital attendance is a poor way of ascertaining epilepsy, but attendance rates that utilise GP-based populations are, as discussed, a good method of ascertaining cases of epilepsy in a defined population. First attendance can therefore be used as an estimate of the incidence of epilepsy, but rates calculated retrospectively from a cross-sectional population may not be proportional to the incidence and there are four main factors that may affect the relationship between the two measures. (Bradford-Hill, 1984, Hauser et al., 1991, Zielinski, 1974) *i)* Patients with epilepsy may move away from the population being surveyed and will therefore be missed in any retrospective method. However, in the study population,

patients with epilepsy who moved away were then replaced in the surgery list by patients with epilepsy who moved into the area, and so the two forces will cancel each other out unless one predominates. For instance, patients may perceive that the practice offers advantages to patients with epilepsy (there is no evidence for this occurring in the Tonbridge practice). *ii)* Patients with epilepsy may die and will be missed in retrospective surveys (unless accurate death registers are kept). In an identical population in the UK, the NGPSE has recently reported on the mortality rate of patients with epilepsy. (Cockerell et al., 1993) The rate was highest in the first few years, and after five years was little different from the standard population. Thus, in an incident cohort of epilepsy in a GP population about 20% of patients with epilepsy die in the first five years, and thereafter about 1% die per year. The deaths mostly occurred in elderly patients and less than 5% of deaths occurred in patients under 24 years, and all these occurred in the first two years. This means that first attendance rates for patients in the younger age bands will be very close to the true incidence rates and are not significantly affected by mortality rates. *iii)* Retrospective analysis is prone to miss patients as the data becomes more incomplete and past occurrences get lost in time. This is not likely to have a significant affect in the study where all the patient's lifetime history was well documented in the GP notes, and even single seizures are likely to have been recorded, as evidenced by the high lifetime prevalence rates. *iv)* Epilepsy is often difficult to diagnose and in the NGPSE, diagnosis of patients with new onset epilepsy was delayed for more than 6 months in 20% of cases. (Sander et al., 1990) This is most likely to affect the relationship between first attendance rates and incidence in the five years prior to the survey dates. This should mean that the first attendance rates for the period 1974-1983 will be lower when calculated from the 1983, as compared to the 1993, survey populations. When this was done there was no major difference between the two calculations.

There are two important findings from the calculation of first attendance rates in this study. Firstly, that there has been a steady decrease in the first attendance rates in children (persons under 20 years) over the years from 1964-1993, with the biggest fall in the last decade, which provides strong evidence for a corresponding decrease in the number of incident cases. As discussed earlier, there have only been a few studies which have looked at the influence of time trends on the incidence of epilepsy. (Granieri et al., 1983, Hauser, Annegers &

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It should be born in mind that the changes in the incidence of epilepsy that we have found will not be immediately apparent in the prevalence data. As discussed above, prevalence data may mask more significant incidence trends, and indeed, despite the changes in incidence, no major differences were observed between the two prevalence surveys. The reasons for this are that the prevalence population is only composed of a small number of annual incident cases, and therefore many years will have to elapse (about 20-40 years), before any incidence trends are manifest in the prevalence populations.

Kurland, 1993, Sidenvall, Forsgren, Blomquist & Heijbel, 1993) In Rochester, USA, from 1935 to 1984 there was no significant difference in overall incidence rates, but this masked strong underlying trends. (Hauser et al., 1993) The incidence in children declined by 40% between the earliest and latest time interval, whereas the incidence in the elderly population almost doubled. In the Italian study, the rate varied from 30.5 to 36.6 /100,000 and no significant time trends were observed between 1964 to 1978, although the age specific rates were not given. (Granieri et al., 1983) However, as the death rate was not taken into account, a similar number of new cases in the period 1964-68 compared to 1974-78 may have been significant, as the further from the survey date so the number of cases ascertained should fall (it is more difficult to ascertain cases when recall of events and records become more sketchy), and the number of cases dying rises. A study recently carried out in Northern Sweden found that the incidence of childhood epilepsy (0-15 years) was 89/100,000 in the period 1985-87, (Sidenvall et al., 1993) which compared to 134/100,000 when measured by a previous study in 1975. (Heijbel, Blom & Bergfors, 1975) However, this represents only two incidence periods, and the differences could have been due to sampling error or different effectiveness of case ascertainment (no confidence limits were calculated).

The second important finding from the study is the high first attendance rates for elderly cases in the last ten years from 1984-1993. As discussed, the likelihood of elderly patients with epilepsy dying in the first five years is high, so that the first attendance rates in this age group are likely to be an underestimate of the true incidence, which may be up to 25-50% more than this. This is the first study in which estimates of the incidence of epilepsy in the elderly has exceeded that of children. This has important health service planning implications with epilepsy services at the primary care, and specialist levels, needing to be more geared up to this age group. The cause of the rise in the number of epilepsy cases in the elderly has often been ascribed to the incidence of cerebrovascular disease in this age group, however, this is not reflected in the data above, where the aetiology of epilepsy throughout the age groups is unknown in over 70%.

5.3.4. Prognosis

Any analysis of the secular trends in the prognosis of epilepsy is hampered by the same handicaps that were found when looking at incidence and prevalence: different populations studied with different methodologies. The prognosis of epilepsy prior to the 1970s was held to be poor, with less the 20% entering remission, (Sander, 1993) with more recent evidence showing that at the population level over 80% probably enter long term remission. (Annegers, Hauser & Elveback, 1979) This difference is of course nothing to do with the changing fortunes of people with epilepsy, but rather the different results evinced from hospital, as opposed to population based studies. However, an improvement in the remission rates has been suggested by Okuma. (Okuma & Kumashiro, 1978) He drew attention to early studies prior to the introduction of phenobarbitone (1912) and phenytoin (1938), which indicated that remission rates were as low as 2-30%, (Habermas, 1901, Turner, 1907) whereas studies in Japan in 1940 and 1952 reported rates of 27% and 22%, compared to later studies in 1963 and 1969 where the rates increased to 41% and 45%. (Fukishima, 1969, Wada, 1963) The only data on secular trends of prognosis in a single population comes from the Rochester series. From 1935 and 1974 no difference in remission rates was observed between patients diagnosed in the first decade as compared to the last. (Annegers et al., 1979) The authors, however, highlighted the effect of possible confounding factors. For instance, in the first 25 years and in the last 15 years there may have been different mechanisms which were underlying the group classified as "idiopathic" and more successful treatment in the latter years may have been masked by the appearance of a more aggressive "idiopathic" form of epilepsy. The other important point is that the incidence of epilepsy in children appears to have fallen, and as this group has the highest remission rates this would lead to a more pessimistic overall view. Despite commenting on this the authors did not then give the age specific remission rates for the earlier, as compared to the later decades. One more definite indication of improved prognosis in the Rochester series is shown in the relative decline in the total epilepsy population against the increase in the number of patients with single seizures. (Annegers et al., 1979) This may thus be due to earlier and more effective treatment of patients after their first seizure preventing patients from going on to have further seizures. This would also have the effect of decreasing the number of

milder cases of epilepsy in the overall epilepsy series and so lower the later overall remission rates.

In this study the overall good prognosis of patients with epilepsy was confirmed with over 80% entering a 2 year remission by 10 years. (Goodridge & Shorvon, 1983) No differences were found between the chances for remission for more recent cases, although the proportion achieving 2 year remission for epilepsy which started after 1.1.74 was 64% at four years, compared to 59% for cases which started prior to 1.1.74. For four year remission at 10 years the proportions were 70% for pre 1.1.74 and 80% for cases post 1.1.74. Only 30 cases for the post 74 group were followed for more than 10 years, so the level of error is likely to be higher. It is possible that these results may be masking more significant trends that will become more apparent with a longer follow up, or by surveying larger numbers. Further work to definitively follow the incidence and prognosis of epilepsy to document secular trends are needed before it is possible to say that modern medicine has truly advanced the lot of patients with epilepsy.

SUMMARY AND CONCLUSIONS

- Despite minor changes to the demography of the base population in Tonbridge, as well as changes that may have affected the prevention and treatment of epilepsy, there is no evidence for any major alterations in the prevalence of epilepsy. This has important implications for service provision.

- Most patients with a history of epilepsy, or with active epilepsy are in the middle years of life, and this study did not report a peak in the prevalence of elderly patients with epilepsy. This may be because, as the NGPSE pointed out, elderly patients who develop epilepsy have a high mortality rate.

- The aetiologies and the seizure types in the two prevalence populations are broadly similar. About 40% had partial seizures compared to 50% with generalised seizures. Over 70% of patients did not have an identified cause for their epilepsy. The only noteworthy changes was a fall in the number of cases of epilepsy secondary to trauma, from 8 to 3%.

- There is no strong evidence for any alteration in the prognosis of patients with epilepsy over the last 40 years. The proportion of patients with active epilepsy did fall in the last decade, from 32/122 (26%) in 1983, to 26/126 (21%) in 1993. However, actuarial analysis of patients with onset of seizures prior to the 1970s, compared to after this date, did not find any significant differences. This lack of difference may be related to the problems of retrospective analysis and comparisons between prospective studies are needed.

- First attendance rates are reasonable approximations to incidence rates, especially in the younger age groups. This study showed that the annual first attendance rates in the 0-20 age band fell from between 111.5 and 131.8 in the decade 1963-73, and 115.8 to 140 in the decade 1974 to 1983, to 67.0 from 1984-1993. This suggests that the incidence of epilepsy in children is falling. Formal longitudinal incidence studies are needed to determine this.

5.4. THE ECONOMIC COST OF EPILEPSY

5.4.1. The NGPSE and NES

The NGPSE and the NES overcome problems of patient selection bias by ascertaining patients and accumulating clinical data at a population level. The initial average direct medical cost of £611 per patient in the first year of diagnosis calculated from the NGPSE does not seem excessive. However, this figure represents the overall cost of care of all the seizure disorders in the cohort and there is a wide variation within the overall cost. In the first 3 years of follow up 33% of patients had a single seizure only, and many doctors thought investigation and treatment unnecessary in this group, and furthermore in the first year 25% of the cohort received no treatment. Conversely 11% required admission to hospital in the first year, and 14% were taking more than one AED. The estimated costs from the time of diagnosis in the NGPSE cohort shows an unsurprising decline over the years after diagnosis. The bulk of the initial costs were made up of investigations and hospital follow up, but as time passed the major costs were those of drug treatment. Although the total number of patients receiving treatment fell, costs increased because of the more expensive second line drugs such as lamotrogine (LTG) and vigabatrin [GVG]. After 8 years 2% of patients being followed were on LTG and 3% were on GVG, with the cost of a years treatment over £840, and £670 respectively, compared to £93 for carbamazepine and £22 for phenytoin. The high cost of these new drugs means that the average drug costs of the cohort actually starts to increase at 8 years, LTG and GVG accounting for over 60% of the AED costs, although only 5% of patients were taking these drugs.

The direct cost of established epilepsy to the UK of £170 million per year calculated from the NES is similar to the only other UK estimate of £109 million. (Griffin & Wiles, 1991) However, when the indirect (and transfer) costs are included the overall cost is considerably greater, although similar in magnitude per patient to the Dundee study. (Davidson, Swingler & Moulding, 1992) The scale of the indirect costs of epilepsy, and the cost of unemployment in particular, emphasises the importance of the non-medical when compared to the medical costs, a fact which should not be forgotten when planning health care. The total cost (direct and indirect) of active epilepsy to the UK was £1144

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The NES has been described previously (Hart, 1992), and the demographics and clinical features of the patients were similar to other prevalence surveys.

million, and £255 million for inactive epilepsy (these breakdowns exclude mortality costs, residential care, and special schooling), or £4167 compared to £1630 per patient per annum respectively. The indirect costs (i.e. unemployment) formed over 80% of the overall total cost of active epilepsy (£3632 per patient), and 77% of inactive epilepsy (£1546 per patient). The largest component of the medical costs of active epilepsy was hospital care (67% of £535 per patient), whilst the major medical cost of inactive epilepsy was AED costs (72% of £84 per patient).

The cost for excess mortality is less than in previous studies. Non-epilepsy related deaths were not costed, and although the death rate of epilepsy is 2 to 3 times that of the population, the deaths directly attributable to epilepsy form a small part of the total. (Klenerman, Sander & Shorvon, 1993) This cost was calculated using the discounting method which heavily weighs against the capital cost of death. (Robinson, 1993b)

5.4.2. Possible sources of error

A number of assumptions were made in this study in extrapolating costs from the study cohorts to the general population. These included for instance; cost of unemployment based on average wage; the incidence, prevalence, and mortality figures for epilepsy based on published literature; the individual resource costs based on mean data from a single health authority and central government health service figures; the cost of residential care and special schooling from mean figures from single institutions; and the drug costs based on minimum dosages. The derived figures can therefore be considered approximations only; nevertheless they are the most accurate estimates currently available. In addition there are five other sources of possible error. Firstly, in the NES only 4% of subjects were institutionalised. This is may be an underestimate because only patients in social service institutions will be registered with a GP (and thus registered with the study), and not those in mental handicap hospitals. Data for the UK is sparse, but by comparison with the only detailed study (from Sweden), 50% of those with severe mental handicap and epilepsy were in special institutions. (Forsgren, Edvinsson, Blomquist, Heijbel & Sidenval, 1990)

Secondly, the NES only included patients who were on AEDs who had definite epilepsy. This will exclude patients not taking AEDs who are in remission, or

who are undiagnosed but still have seizures, and these patients can be expected to incur some direct and indirect costs, albeit small. (Gloag, 1985, Scambler & Hopkins, 1980) The US commission study estimated, on rather limited evidence, that these groups accounted for 33% of the total epileptic population. (US Commission for the control of Epilepsy, and its consequences., 1978)

Thirdly, since 1990 when the NES data was collected some of the benefits have changed in form and payment scale, for example, the attendance allowance has been replaced by the disabled living allowance. However the figures still provide estimates of transfer costs that are not likely to have changed dramatically for the overall group.

Fourthly, in accord with convention the costs of unemployment, and excess mortality were measured. However, the cost of under-employment was not, because of the difficulty in assessing this, and the inadequate evidence for its significance in patients with epilepsy.

Finally, certain other indirect costs were also omitted. Two of these, the cost of patient's or relative's travel to and from hospital, and the cost of lost production due to days off sick, are unlikely to result in a serious difference to the figures. However one cost that may be much more significant is the cost incurred by informal carers. This is the cost due to patients, relatives, or friends not being able to work to their full economic potential. Figures for this cost are not available, partly due to the difficulties involved in collecting such data. About 5% of patients are probably heavily dependent on formal carers in the community, and although a small number, the attributable cost may be very high.

5.4.3. Indirect costs of epilepsy and the cost of active epilepsy

A number of important findings are raised by this study. Firstly, where indirect costs are measured adequately the cost of epilepsy is very high, and are disproportionately more than the direct costs. Whilst there may be methodological problems as discussed, it still suggests that the economic impact of epilepsy due to unemployment is significant and that measures to reduce this will help to offset treatment costs. The second point is that the cost of active epilepsy is far greater than that of inactive epilepsy or newly diagnosed epilepsy.

Again this is largely due to the indirect costs, but with these excluded there are still heavy direct costs, which although only affecting a relatively few individuals have a disproportionate impact on the overall cost. For instance the cost of institution care per patient at about £28,000 per annum greatly outweighs the cost of GP care at only £36 per annum. Ways of reducing such costs thus have a large savings potential.

5.4.4. Limitations of cost of illness studies

A main aim of health economic research is economic appraisal, to provide evidence of the potential costs and benefits of health care intervention. Cost of illness studies are only one way of assessing the cost of an illness. The rationale behind cost of illness studies is that resources should be channelled into alleviating those diseases that cost the most, and in reducing particular aspects of costs alluded to above. This approach has been advocated by a recent government document. (Secretary of state for health., 1991) However, just because a disease costs more doesn't mean that increasing expenditure on the disease is going to save money, and in fact the reverse can be envisaged. Economists have therefore argued that what is needed is more goal-directed economic evaluation which is not met by cost of illness analysis, and there are four alternative approaches: cost effectiveness, cost minimisation, cost utility, and cost benefit analysis. In epilepsy, such studies are in their infancy and there is a pressing need for such work, for instance, with the introduction of expensive new AEDs and other treatments. The cost of the newly introduced drugs, lamotrogine, vigabatrin, and gabapentin, for example, is 120-140 times more expensive than the cost of phenobarbitone. Studies of cost effectiveness or cost benefit ratios are warranted in order to justify their use. Similarly, epilepsy surgery costs about £20,000 per procedure. Although less than 200 operations are performed in the UK per annum, (British Branch of the International League Against Epilepsy., 1991) at a total cost of £4 million, this is a small fraction only of the total UK epilepsy budget. Surgical therapy is gaining in popularity and economic appraisal is important, which should rely as much on measures of social rehabilitation as on seizure frequency, which is currently the usual outcome measure. (Gumnit, 1991, Primrose & Ojemann, 1991) Similar considerations can be applied to the introduction of new investigations, such as video-telemetry, magnetic encephalography, or brain

mapping. With increasing pressure on health care resources, economic appraisal studies to provide tangible evidence of cost benefit are essential, and will require a more sophisticated application of economic theory than is currently often applied. (Robinson, 1993a)

SUMMARY AND CONCLUSIONS

- The majority of patients who develop epilepsy do not incur significant economic costs to society, in the order of £600 in the first year, and patients who enter remission and who are able to stop AEDs incur minimal costs.

- On the other hand, patients who do not enter remission and have established epilepsy, which is either active or inactive but still requiring treatment, do pose a large a economic burden: over £1930 million to the whole UK per annum.

- Patients with continued seizures who have active epilepsy are considerably more costly than patients whose seizures are well controlled. This difference per year to the whole UK is £1144 million for active epilepsy, and £255 million for inactive epilepsy, or £4167 compared to £1630 per patient per annum respectively.

- The annual indirect costs (i.e. unemployment) formed over 80% of the overall total cost of active epilepsy (£3632 per patient), and 77% of inactive epilepsy (£1546 per patient).

- The largest component of the medical costs of active epilepsy was hospital care (67% of £535 per patient), whilst the major medical cost of inactive epilepsy was AED costs (72% of £84 per patient)

- The prevention of the transformation from a patient with newly diagnosed epilepsy into a patient with established active epilepsy would have a large potential for cost savings. However, this way forward in economic evaluation is best achieved by more goal directed cost studies, such as cost benefit studies between different AEDs, or between surgery and AEDs.

SECTION 6

APPENDICES

APPENDIX 1

LITERATURE SUMMARY

Selected studies of remission

(Alstrom, 1950)

An early retrospective study of the prognosis of epilepsy. 897 patients were identified from the out- and in- patients records in the Karolinska Institute Neurological Clinic. Large number of untraceable patients were not included. Information was obtained by a home visit. 29% of patients with an unknown aetiology, 23% with a probable aetiology, and 14% with a definite aetiology, were seizure free for more than 5 years. No relationship to time of onset was given.

(Strobos, 1959)

A retrospective clinic-based study which reported on the prognosis of 228 patients who were followed from 2-15 years. Inclusion criteria were "idiopathic" seizures and two or more abnormal EEGs. End-point was "100% controlled" which was curiously defined as seizure freedom for one year and prior seizure frequency was more than one per week, or seizure freedom for two years if less frequent seizures. 38% of patients were 100% controlled. Adverse factors were seizure onset of less than one year old, or abnormal neurological signs or cognitive status.

(Kiorbie, 1961)

Another hospital-based study of patients attending the County and City Hospital of Odense, in Denmark. Patients identified between 1948-52. 156

patients identified who had epilepsy of short duration, which was under 5 years and patients had the first seizure over 17 years of age and were followed for up to 7 years. 32% were seizure free, 14% had only occasional seizures. No differences between idiopathic and symptomatic epilepsy. Grand mal seizures fared better than "psychomotor" seizures (58% compared to 21% seizure free). 99 patients were also identified who had epilepsy that started under 17 years of age. 43/99 were seizure free. No factors were identified that predicted prognosis.

(Juul-Jensen, 1964)

A retrospective study of patients at the Arhus Kommunehospital. 1020 patients were identified between 1959-61. Follow up was for a minimum of 2 years, although a maximum of 4 years. Patients with tumours were excluded. Only 49% had epilepsy of unknown cause (not including petit mal and other identifiable syndromes).At end of study 32% were seizure free for more than 2 years, and 68/311 were off treatment. Poor prognosis of petit mal. Good prognosis for vascular disease and patients with normal EEGs. Drug withdrawal was attempted on patients who were seizure free for more than 2 years.

(Kuhl, Kiorboe & Lund, 1967)

216 patients identified from the County and City Hospital of Odense (same patients as reported in 1961), and patients from the Glostrup hospital in Copenhagen. Patients with no EEG or single seizures excluded. Follow up information obtained on 173 patients. 59% of patients had onset of seizures before 35 years of age. Prognosis difficult to asses as length of remission not examined. 50% of patients had a favourable course (no seizures in observation time, or seizures in only one of the observation years). 50% had an unfavourable course (seizures in more than one observation year). An inverse relationship was seen between seizure duration and prognosis. Patients with tumours had worse outlook, otherwise aetiology not significant. Psychomotor seizures did worse than other seizure types.

(Rodin, 1968)

Important work and summarised the literature to date. Actual evidence presented was based on three main studies. i) Retrospective study of 32 patients less than 10 years old and seen more than 5 years previously at the Michigan Epilepsy Centre. Definition of epilepsy was more than 3 seizures. Only 44% were in remission of 1-9 years duration. 33% in 2 year terminal remission. Poor prognosis in mental retardation, and patients with an abnormal EEG ii) Best analysis was carried out on 222 patients, also at Michigan Centre, but without an age limitation, and different to original study population. Over 86/222 patients lacked good follow up information. Only 32% were seizure free for more than 2 years, and 17% more than 5 years. Worse prognosis for psychomotor seizures, if patients had more than one seizure type, a history of status, or an abnormal EEG. iii) 122 patients attending the Laffayette clinic followed for more than 2 years, up to 7. Only 26% achieved a remission of 2 years of more than 6 months.

(Currie, Heathfield, Henson & Scott, 1971)

Limited study because only patients with temporal lobe epilepsy were identified from a hospital-based population. Nevertheless, it is an important study as it was one of the first to examine the clinical features and outcome of this type of epilepsy which is particularly amenable to surgery. 603 patients included from the London Hospital. Esoteric exclusion criteria: long-standing epilepsy, late-developing temporal lobe focus with no clinical features, patients with psychiatric disease, and patients with late onset TLE secondary to tumours. 40% of patients achieved a remission of more than one year. More than 50% of these were still in remission after 5 years.

(Zielinski, 1974b)

312 patients randomly identified from a hospital-based sample, and 98 patients found in a field survey. 25% of the hospital-based and 75% of the population-based sample were not currently on treatment. over 30% of the population sample had never received treatment. Over 30% of untreated patients had been seizure free for more than 5 years, supporting the premise that AED treatment is not required in order to achieve long-term prognosis.

(Morikawa, Ishihara, Kakegawa, Seino & Wada, 1977)

This was a retrospective follow-up study on the prognosis of 90 patients with epilepsy above 40 years of age. The findings were: 1. In the aged patients, the duration of epilepsy (mean: 23 years) was longer than the period of treatment they underwent (mean: 14 years). The delayed commencement and/or interrupted medication along with the patients' non-compliance of taking drugs accounted for the main reasons for at least 70% of the patients. 2. Partial epilepsy (80%) especially with complex symptomatology (55%) predominated in the aged group. And also, that the tonic-clonic seizures were liable to convert to the complex partial seizures in their thirties and forties, was found in this study. 3. Although almost all the patients (97%) had more or less clinical attacks at the time of survey, 75% or more decreased in seizure frequency for one and a half years, regardless of the seizure types.

(Fukushima, 1977)

631 epileptic patients were identified from a seizure clinic in the period between January 1961 and December 1966. 97 (15.4%) were treated until September 1976, when the long-term prognosis was evaluated. The "good prognosis (completely controlled)" were found in 59% of grand mal, in 55% of focal motor seizure, in 42% of psychomotor and in 33% of the mixed seizure in which more than two types of seizures were combined; in 49% (48 cases) on the average. Seventy-nine percent of the cases of the mixed seizure were combined with psychomotor seizures. In the psychomotor and the mixed seizure groups, the presence of personality disorders tended to lead them to "poor prognosis" which meant that the seizures were not well controlled.

Twelve cases manifested psychotic (paranoid) state: a schizophrenic, a case with chronic paranoid-hallucinatory state, and 10 patients with episodic paranoid state, whose episodes may be identified with the paranoid reactions. Out of the 49 "poor prognosis" cases, 17 (35%) had had seizure-free periods for more than three years in the past course of their treatment.

(Blom, Heijbel & Bergfors, 1978)

This study from Sweden with a first seizure (not well specified) identified 74 children, who were then examined 3 years later. 24.74 were seizure free for more than one year. Risk of recurrence of seizures was highest in patients with neurological deficits, or partial seizures.

(Harding, Herrick & Jeavons, 1978)

This study was limited to the prognosis of photosensitive epilepsy. The range of flash rates of intermittent photic stimulation to which patients were sensitive (photosensitive range) was tested prior to treatment, and the reliability of this measure established by repeated tests on 70 patients. The photosensitive range was measured on 50 patients prior to and during treatment with sodium valproate. In 27 patients photosensitivity was abolished and in a further 12 patients photosensitivity was significantly reduced. A group of 167 patients followed without treatment did not show significant improvement over a 7 year period. Sixteen patients had drug treatment withdrawn, and in 7 months their photosensitive range had returned to its predrug level.

(Sofijanov, 1982)

Five-hundred twelve epileptic children were identified at the Paediatric clinic of the University of Skopje and followed longitudinally for several years (the exact number was difficult to determine). The 2- and 4-year remission status at the latest examination were 50.6 and 44.2%, respectively. For the different age groups: onset of seizures in infancy or at 2-3, 4-7, 8-10, or 11-14 years, the

remission rates were: 48.5, 67.6, 49, 46, and 33.3%, respectively. The rates of remission of generalised and focal epilepsies were similar (52.9 and 49.7%, respectively; chi 2 = 0.293; p greater than 0.5). The earlier the onset of seizures, the higher was the probability of their association with mental sub normality and neurological deficits. Generalised epilepsies were more strongly associated with mental sub normality (40.1%) than are the focal epilepsies (13%), and the focal epilepsies were associated with neurological deficit almost twice as frequently as are the generalised epilepsies (12.2 vs. 7.3%). The EEG was of little prognostic importance.

(Lindsay, Ounsted & Richards, 1979)

This was another important paper to examine the prognosis of temporal lobe epilepsy, and has often been cited in the argument for early epilepsy surgery. One-hundred children, diagnosed as having temporal lobe epilepsy in 1966, were followed up to 1977. They were coded into four social outcome categories, A, B, C and D. A: 33 per cent are found to be seizure-free and independent; B: 21 per cent are socially and economically independent but are receiving anticonvulsant treatment and are not necessarily seizure-free; C: O9 per cent are dependent either on their parents or in institutions; D: 5 per cent died under the age of 15. Various factors were ascertained and coded in childhood and were related to adult outcome. Eight adverse factors emerged: an IQ below 90, onset of seizures before 2 years 4 months, five or more grand mal attacks, temporal lobe seizure frequency of one per day or more, a left-sided focus, the hyperkinetic syndrome, catastrophic rage and special schooling. The presence of first-degree relatives with seizure disorders was a good prognostic sign. In general, the prognosis for children with limbic seizures was apparent before the end of adolescence.

(Ross, Peckham, West & Butler, 1980)

1043 children (6.7%) under 11 years were identified in an unselected national sample, and who had a history of seizures or other episodes of loss of consciousness; 322 (20.8/1000) had a history of febrile convulsions without

other epileptic problems. A clear-cut diagnosis of non-febrile epilepsy was established in 64 children (4.1/1000) by the age of 11 on the basis of confirmatory information supplied by family doctors and paediatricians. A further 39 (2.6/1000) were reported as having epilepsy but did not fulfil the study criteria. The progress of 59 of the 64 children with established epilepsy was reviewed again when they were aged 16. Of the 37 educated in normal schools eight (22%) had one or more seizures in their 16th year compared with 13 out of 22 (59%) who received special education. A possible cause for epilepsy was found in 17 of the 64 (27%) children, but for the majority there was no obvious reason.

(Sofijanov, 1982)

Five-hundred twelve epileptic children were followed longitudinally for several years. The 2- and 4-year remission statuses at the latest examination were 50.6 and 44.2%, respectively. Dividing the sample into groups showing onset of seizures in infancy or at 2-3, 4-7, 8-10, or 11-14 years, the remission rates were: 48.5, 67.6, 49, 46, and 33.3%. The rates of remission for generalised and focal epilepsies were similar (52.9 and 49.7%, respectively; chi 2 = 0.293; p greater than 0.5). The earlier the onset of seizures, the higher the probability of their association with mental subnormality and neurological deficits. Generalised epilepsies were more strongly associated with mental subnormality (40.1%) than were the focal epilepsies (13%), and the focal epilepsies were associated with neurological deficits almost twice as frequently as were the generalised epilepsies (12.2 vs. 7.3%). Epidemiologically, the EEG is of little prognostic importance. The combined percentage of normalised (19%) and stabilised (17%) EEGs was lower than the percentage of remission.

(Loiseau, Dartigues & Pestre, 1983)

This was a retrospective study of the notes of 235 patients having a partial seizure for the first time between the ages of 12 and 18 years to establish the best predictive indicators of outcome. Among the factors considered to affect significantly the outcome were the seizure type (elementary or complex symptomatology), the initial EEG, the seizure frequency, the aetiological

factors, and an association with generalised seizures. Sex, age of onset, and topography of EEG paroxysmal abnormalities had no significance.

(Todt, 1984)

This was study was held to be a prospective study, but in reality was a study of relapse after discontinuation of antiepileptic drug treatment. 433 children with epilepsy and 40 patients who were treated after the first seizure were reported. Independent of the electroencephalographic findings, the age of the patients, and other factors, the antiepileptic drugs were reduced during 1, 3, 6, and 12 months after 2, 3, and 4 seizure-free years; and in children with absences after 1, 2, 3, and 4 seizure-free years. The observation period after stopping therapy was at least 3 (on average, 5-6) years. In 157 of 433 children (36.3%) and 5 of 40 patients (12.5%), relapses occurred during this time. More than half (61.8%) of the relapses occurred during the withdrawal period or within 3 months: altogether, 86% within 1 year after discontinuation of therapy. Eighty-six percent of these patients again became free from seizures on administration of the original therapy. The chances of relapse were dependant on the duration of the seizure-free period, the duration of the withdrawal period, the length of illness, the frequency and duration of seizures, and the presence of paroxysmal activity in the EEG at the start of the discontinuation of antiepileptic drug treatment.

(D'Alessandro, Pazzaglia, Timuper, Ferrara, Fabbri & Lugaresi, 1986)

This study reported on the electroclinical features and prognosis of 103 patients with tonic-clonic seizures alone. Patients were classified into three groups according to seizure semiology and interictal EEG: primary grand mal, focal grand mal and indeterminate grand mal. Discriminant analysis showed that a number of other electroclinical features had no significant classificatory power. Patients were followed for 2-10 years. 40% of patients were free from tonic-clonic seizures (not specified for how long) and 23% had fewer than 1 seizure a year, without differences among the three groups. The appearance of 'minor' (absence or partial) seizures during follow-up occurred

in 12 patients and did not change the prognosis of tonic-clonic seizures. At the end of follow-up, 96% of patients had a normal social adjustment. The authors concluded that grand mal epilepsies appeared to have a good prognosis.

(Deonna, Ziegler, Despland & van Melle, 1986)

This study was principally a clinical and electroencephalographic study of 107 neurologically normal children with partial seizures, which was undertaken to verify the existence and determine the frequency of epileptic syndromes reported in selected populations. Sixty-three children had simple partial seizures, 39 had complex partial seizures, and 5 children were unclassifiable. The syndrome of benign partial epilepsy of children with Rolandic spikes (BPEC, 38 cases) was clearly identified and its uniformly benign final prognosis was confirmed even if some of these children had at times severe or poorly controlled seizures. Among the children with simple partial seizures outside the BPEC (25 cases) and complex partial seizures (39 cases), no homogeneous clinical or electroclinical subgroup could be found. Two children with benign partial epilepsy and myoclonic-astatic seizures ("atypical benign partial epilepsy of childhood") and one child with "benign epilepsy with occipital spike-waves" were identified. 74% of children with epilepsy with complex partial seizures had a 1-year seizure-free interval, and many children with epilepsy with simple partial seizures outside the BPEC group (ESP) had no more than two seizures. The conclusion was that a benign course was not limited to the BPEC.

(Luhdorf, Jensen & Plesner, 1986)

251 patients were identified with seizures over the age of 60 years, who had been admitted to the county hospital of Frederiksberg during the period 1979-1983, 163 had not received anti-epileptic treatment prior to admission, of these 151 had been admitted with their first seizure, 88 had established epilepsy at the time of admission. Of patients not previously treated and observed for at least 12 months, 62% remained seizure-free throughout the study, while 47% with established epilepsy were seizure-free. Of those not

previously treated, 72% entered remission within the first year with a slight increase during the subsequent years. The first year was crucial in determining the long-term prognosis. Compared to previous studies on the prognosis of epilepsy the study concluded that prognosis in the elderly is as good or even better. The presence of paroxysmal activity in the EEG was significantly correlated to seizure recurrence. Thirty-three patients entered nursing homes during the study period. Deterioration in residence status was correlated to degree of dementia and to the presence of focal neurological signs but not to age or to the severity of epilepsy.

(Brorson & Wranne, 1987)

All children aged 0-19 years who had active epilepsy in a defined Swedish population were traced and given a clinical and psychometric investigation. This report summarised the results 12 years later. Eleven of the 194 children had died, 8 of whom had signs of neurodeficits, i.e., abnormal neurology and/or mental retardation. A long-standing remission of seizures occurred in 124 of the 194 children. Signs of neurodeficits, frequent seizures, and many types of seizures were negative prognostic factors. The presence of all these factors carried a bad prognosis, seizures persisting during 12 years in greater than 80%. For those who were mentally and neurologically normal and had low seizure frequency, prognosis was excellent, only 11% still having active epilepsy after 12 years. A study of the annual remission rate showed that each year approximately 13% of the children without neurodeficits had remission from epilepsy the next year. This rate appeared to be stable over the 12 years studied. Among those children with neurodeficits, the annual remission rate was high only during the first years after onset, later falling to 3% a year.

(Ehrhardt & Forsythe, 1989)

640 children with grand mal seizures were identified from a hospital based survey. 187 became seizure-free for three consecutive years on monotherapy which was then discontinued have been followed for between one and 14 years. Relapse occurred in 22 children (12 per cent) and was related to age at

presentation: only four of 89 children with primary grand mal seizures who had presented after the age of three years relapsed, compared with 12 of 45 who had presented before their third birthday. Children who had had more seizures were at greater risk of relapse. EEGs were not useful in predicting prognosis, whether taken at presentation or before withdrawal of treatment.

(Oka, Yamatogi, Ohtsuka & Ohtahara, 1989)

This was a hospital-based study of childhood epilepsy at the Okayama University Hospital. Ten to 15 years of follow-up was possible in 730 of 1,295 patients who were first diagnosed at ages below 15 years, from 1968 to 1971. The 3-year remission rate amounted to 82.0% and 5-year remission was obtained in 79.1%. The authors concluded that these high rates of remission indicated the favourable prognosis of childhood epilepsy, but that "cases of intractable epilepsy also amounted to a considerable number".

(Fish, Miller, Roberts, Blackie & Gilliatt, 1989)

A small study in which 29 patients with late-onset epilepsy were followed prospectively for a mean period of 4.9 years; 14 had CT evidence of occult cerebral infarction and 15 had normal scans. The prognosis was similar in the 2 groups; 57% and 53% respectively became seizure-free. One patient in each group had a myocardial infarction and one patient with occult cerebrovascular disease had a stroke. A separate study was made of the prognosis of 24 patients with epilepsy following stroke (mean follow-up 5.9 years). Twelve of 12 patients with seizure onset within 2 weeks of the stroke became seizure-free, compared with 7/12 with more delayed onset. It was concluded that late-onset epilepsy has a favourable prognosis, and excellent control should be expected if seizures commence within 2 weeks of stroke.

The Rochester studies

The Rochester record linkage system has resulted in a number of important studies in the epidemiology of epilepsy. Three papers have been produced with examined the remission of epilepsy.

i) (Hauser & Kurland, 1975)

As part of a larger analysis of the epidemiology of epilepsy in Rochester, 346 patients with new onset epilepsy (defined as two or more unprovoked afebrile seizures) were ascertained between 1935-67. Life-table analysis showed that 40% of patients were seizure free for more than 2 years after 10 years follow up, 49% by 15 years, and 55% by 20 years.

ii) (Annegers, Hauser & Elveback, 1979)

In a larger study of patients with epilepsy in Rochester, Minnesota, 618 patients were ascertained between 1935-74. The probability of being in remission (at least 5 consecutive years seizure-free, and continuing) at 20 years after diagnosis was 70%. The rates for remission were generally higher than those previously reported. The authors believed that the better prognosis in this series resulted from inclusion of all incidence cases in a defined population, beginning at the initial diagnosis of epilepsy. Prognosis for remission of epilepsy was poor in patients with associated neurological dysfunction identified from birth. Patients with idiopathic seizures and survivors of postnatally acquired epilepsy had a better prospect for eventual remission. The probability of remission was highest in patients with generalised-onset seizures diagnosed before 10 years of age. Prognosis was less favourable for those with partial complex seizures and adult-onset epilepsy.

iii) (Shafer, Hauser, Annegers & Klass, 1988)

A more limited analysis of the Rochester epilepsy population ascertained from 1935-78. The study looked at 306 patients who had lived in the region for more than 5 years, had not moved away from the area, and had EEGs, as well as the total 432 new cases, 122 of whom did not have EEG data. More sophisticated statistical analysis was applied using Cox modelling. The overall probability of achieving 5 years seizure free by 20 years was 75%. The most

important predictors of poor prognosis were early brain damage, partial EEG activity, generalised tonic-clonic seizures, and age over 16 years at diagnosis.

The Rochester system also facilitated a number of other studies looking at the chances of epilepsy following certain cerebral insults.

i) (Annegers, Grabow, Groover, Laws, Elveback & Kurland, 1980)

In this study of 2747 patients with head injuries the risk of post-traumatic seizures after severe injury was 7.1% within 1 year and 11.5% after 5 years, 0.7% and 1.6% after moderate injury, and 0.,1% and 0.6% after mild injury which was not any greater than the risk in the general population.

ii) (Annegers, Shirts, Hauser & Kurland, 1986)

The risk of developing epilepsy after meningitis or encephalitis was over 6% after 20 years and was proportional to the severity of the infection, although even aseptic meningitis was associated with a small risk of producing epilepsy.

The Group for the study of prognosis of epilepsy in Japan

This group produced a number of reports, the latter Epilepsia report summarising the study results.

(Okuma & Kamashiro, 1981, Okuma & Kumashiro, 1978)

Patients were ascertained from 20 institutions in Japan. The study was clinic-based although the authors claimed good population level cases ascertainment. The study was carried out between 1975-77 and retrospectively ascertained a total of over 1868 patients whose seizures had begun 10 years previously (i.e. between 1964-67), 5 years previously and 3 years previously. 58% of patients achieved a 3 year remission, and a only about 13% of patients seizures deteriorated or remained unchanged. The other patients seizures decreased in frequency. This rate did not vary at the different end point times. Seizure control was more favourable for idiopathic seizures, patients with

seizures which started under 10 years of age, patients with infrequent seizures, patients who started treatment within one year of onset, patients with a single seizure type, and patients without neurological or psychological handicaps.

The King's group studies

The King's group were responsible for a number of important studies which examined the prognosis of patients with epilepsy, in newly diagnosed hospital populations, and an important study of epilepsy at the population level. The first two studies reported on a basic population of 106 patients with new onset epilepsy, defined as two or more untreated seizures, with tonic-clonic seizures, or partial seizures needing treatment.

i) (Shorvon & Reynolds, 1982)

In 94 previously untreated new referrals to a neurological clinic with tonic-clonic or partial seizures or both the failure rate for optimum single-drug treatment with phenytoin or carbamazepine after a median of 32 months was 17%. Failure of single-drug treatment was associated especially with the presence of additional neuropsychiatric handicaps but also with partial or mixed seizures, symptomatic epilepsy, and a higher number and frequency of tonic-clonic or partial seizures before treatment. Analysis of the recurrence of seizures suggested that the first year of treatment may be crucial in determining the long-term prognosis. The authors suggested that these findings were in keeping with the concept that seizures may predispose to further seizures, and imply that early, effective treatment may be important to prevent evolution into chronic and more intractable epilepsy.

ii) (Elwes, Johnson, Shorvon & Reynolds, 1984)

In the second study the 106 patients were followed prospectively for a median of 66 months (range, 6 to 96). Twenty-six patients remained completely free of seizures for as long as they were followed. Actuarial analysis showed that 35 per cent of patients could be expected to enter a seizure-free period of at least two years at the start of treatment, 73 per cent would have had a two-year seizure-free period at the end of four years, and 82 per cent would have had a

two-year seizure-free period at the end of eight years. Of 79 patients whose seizures were completely controlled for at least two years, 51 subsequently remained seizure-free. If seizures continued for up to two years after the start of treatment, the probability of subsequent seizure control fell by half. The presence of partial seizures; a high frequency of tonic-clonic seizures before treatment; a neurological, social, or psychiatric handicap; and a family history of epilepsy each indicated a worse prognosis. This study reinforced the idea that the long-term pattern of seizure control is largely established during the first two years of treatment.

iii) (Elwes, Johnson & Reynolds, 1988)

In this study different patients were identified from the same clinic from 1981. The time intervals between untreated tonic clonic seizures were examined retrospectively in 183 patients presenting to the department having had two to five seizures. After the first seizure a second attack had occurred within one month in 56 patients, within three months in 93, and within one year in 159. The median interval between the first two seizures was 12 weeks (95% confidence interval 10 to 18 weeks), between the second and third eight weeks (four to 12 weeks), between the third and fourth four weeks (two to 20 weeks), and between the fourth and fifth three weeks (one to four weeks). When patients who had three, four, or five untreated seizures were considered separately a similar pattern of decreasing intervals was seen. Successive intervals between seizures could be compared in 82 patients. In 48 the interval decreased, in 16 it did not change, and in 18 it increased. These results suggested that in many patients there is an accelerating disease process in the early stages of epilepsy.

iv) (Goodridge & Shorvon, 1983)

In this study from the same group, treatment and prognosis were studied in 122 patients with non-febrile seizures in a population of 6000. This was an important study as it was population-based, and patients with single and provoked seizures were included, so that the full range of patients with both severe and milder epilepsy were included. Phenytoin and phenobarbitone were the most commonly prescribed drugs, although the popularity of phenobarbitone had declined over time. The average duration of treatment was

relatively short, and most patients received single drug treatment. Treatment patterns were erratic, and the surveillance and audit of treatment generally poor. Recurrence after a first attack was found in four fifths of the patients. Generally the total number of seizures suffered by each patient was small, the period of active epilepsy short, and remission when it occurred was usually permanent. The cumulative probability of continuing activity fell and the proportion of patients in remission rose over time. Overall nearly 80% of patients achieved a 2 and 4 year remission period. Patients with partial or mixed seizure types had a poorer overall prognosis. The course of the epilepsy in the early years of treatment proved to be a useful guide to the long term prognosis, and the possibility that effective treatment might influence long term prognosis was raised.

The Collaborative Group for the Study of Epilepsy

This Italian group lead by Beghi carried out a large multi-centre prospective study which was the subject of two main reports.

i) (Beghi & Tognoni, 1988)

283 patients were ascertained at the time of first antiepileptic treatment for afebrile seizures. Each patient started with monotherapy at standard daily doses. Data were collected at admission, at scheduled 6-month exams, and at unscheduled exams and included age, sex, general profile of the disease, and treatment. Prognosis of epilepsy was evaluated by actuarial methods using first seizure relapse after onset of treatment to indicate unfavourable prognosis. In addition, a maximum interval of complete seizure control was calculated and related to length of follow-up in order to grade the severity of the disease (defined as mild, moderate, or severe). The average length of follow-up was 21.6 months (range 2-40). Seizure relapse occurred in 52% of cases during follow-up (36% by 3 months, 43% by 6 months, and 49% by 12 months). A larger number of seizures before therapy and the presence of combined seizure patterns were the variables most commonly associated with relapse. In general, epilepsy was mild in 65% of the cases, moderate in 28%, and severe in 7%. The earlier the first relapse the higher the risk of developing

more severe disease. A larger number of seizures before treatment, combined seizure types, earlier age at onset, and prolonged disease duration (1 month to 1 year) seemed to be more frequently associated with the development of moderate-to-severe epilepsy. This paper can be most criticised because the length of follow up was less than 2 years in the majority of patients, making meaningful conclusions about remission difficult.

ii) (Collaborative Group for the Study of Epilepsy, 1992)

This report of the same cohort of 280 (mysteriously three patients were lost from the prior report) patients were followed for a median period of 48 months. The cumulative probability of achieving 1-year remission was 62% by 1 year after onset of treatment, 81% by 2 years, 92% by 3 years, and 98% by 5 years. The corresponding figures for 2- and 3-year remission at 5 years were 92 and 78%, respectively. Sixty-two patients (22.1%) had no remission period with monotherapy. Remission rates were significantly lower among patients with two or more seizure types and were inversely correlated to the number of seizures before treatment. The rate of seizure relapses during the first year of follow-up appeared to correlate with the risk of developing refractory epilepsy (i.e., with no remission).

The Turku cohort

This cohort was ascertained between 1961 and 1964 and comprised all children with seizures in this period from a specified area in south-western Finland. Patients with situation related, non-convulsive, associated with a progressive brain disease, or who had less than 3 seizures were excluded. All the patients had been personally seen by Dr Sillanpaa and the study represents a considerable personal achievement.

Four main reports were produced.

i) (Sillanpaa, 1973)

In this study 245 patients were identified and the overall chances for remission appeared favourable, and the results were better presented in the subsequent reports.

ii) (Sillanpaa, 1983)

This report examined the prognosis for epilepsy with a childhood onset by means of a follow-up study with a twenty-year follow-up period. All patients were initially under 16 years of age and who had recurrent, non-sporadic seizures not caused by an acute infection or a progressive cerebral disease. The original series consisted of 245 patients, followed up retrospectively for approximately ten years. The first prospective follow-up evaluation was carried out in 1977 and the second in 1982. The method used in these two follow-ups was that of a mail inquiry. By 1982, 29 patients had died, ten were not reached and two refused to participate. The group studied in 1982 consisted of the remaining 204 patients. The shortest follow-up period was 17 years (mean 21.16 +/- 24 years). At the end of the follow-up the age of the youngest was 17 years and that of the oldest 34 years (mean 24.74 +/- 0.33 years). The seizure outcome was considered good if three years or more had elapsed from the last seizure. In 1982 such patients accounted for 60% of all cases. Stepwise logistic regression analysis showed that good seizure outcome is best explained by the occurrence of one seizure type only and good short-term treatment outcome. The non-occurrence of status epilepticus, normal psycho neurological development status and the occurrence of grand mal only also contributed to the explanation.

iii) (Sillanpaa, 1990)

This report examined the cohort after 23-39 years. At the end of the follow-up period, 55.5% of the original sample, i.e. 63.2% of the subjects who participated in the last follow-up evaluation, or 76.4% of those who were alive at that time, had not had epileptic attacks for at least the previous three years. A total of 60% lived independently; 21% of subjects, on the other hand, were not gainfully employed and lived in institutions. The intermediate group was the smallest (less than 18%); these were receiving a disability pension but had not been institutionalised. The author pointed out that a certain polarisation had taken place with the patient who was able to lead a normal life or was in

institutional care. The intermediate group showed a steady decline in size in the course of the follow-up.

iv) (Sillanpaa, 1993)

This latest report of this impressive series looked at the same data as the 1990 report, but compared the clinical features of the 40 patients with refractory drug resistant epilepsy with the rest of the cohort who had entered remission. The factors most strongly associated with AED resistance were symptomatic aetiology, abnormal neurological development, high initial seizure frequency, occurrence of status epilepticus, and poor initial AED response. Patients with more than one of these risk factors had the highest risk of being drug resistant. The author concluded that AEDs had little effect on long-term prognosis and that aetiology was the most important predictor of outcome, so that epilepsy surgery should be considered earlier.

Selected studies of mortality

(Zielinski, 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 or mortality rates due to ischaemic heart disease among men or women with epilepsy. The

numbers 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 thought 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--1976, 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 phenobarbitol 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 phenobarbitone 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, 1982)

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 seizure 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 than 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 phenobarbitone, phenytoin and carbamazepine were found in subtherapeutic drug levels in half of the cases and "lethal" concentrations, mainly of phenobarbitone, 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 mortality 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 relation 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 nontraumatic 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 nontraumatic 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 number 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 tumors all but one died within the first year. Mortality among patients with postapoplectic 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 postapoplectic 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 one case, indicating that the frequency of sudden, unexpected death among epileptics could easily be underestimated.

(Wolfersdorf & Froscher, 1987)

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, pharmacogenically, 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 pharmacogenetic depressive moods, which occur in phenobarbitone treatment. Help is often possible by change of medication.

(Satishchandra, Chandra & Schoenberg, 1988)

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 1978 were 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.

(Keeling & 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 death were monitored by the Office of the Medical Examiner of Cook County (Chicago), Illinois in a year-long prospective study. It 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, 1991)

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 1-2/1,000 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 modes 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 the 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 diseases (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.

Selected studies of incidence and prevalence

(Pond, Bidwell & Stein, 1960)

This was another incidence and prevalence study which utilised the UK GP system, in a review of the case notes of 39,500 persons from 14 practices. Positive cases were interviewed. Case definition not totally clear and included provoked seizures and single seizures as well as some febrile seizures. Incidence was 70/100,000, which was calculated for the cases occurring over the previous year. The prevalence was 6.2/1000.

(Crombie, Cross, Fry, Pinsent & Watts, 1960)

An example of the power of using a GP population to identify cases of epilepsy in a defined population. 67 GP practices serving a population of 288,830 persons were surveyed. Febrile seizures were included. The definition of epilepsy was not clear, although "inactive" cases were not included. Incidence was 63/100,000 and prevalence was 4.2/1000.

(Gudmundsson, 1966)

Must be one of the few studies which ascertained all the cases occurring in a single country, although the population of Iceland then was 190,000. Ascertainment, which was probably sub-optimal, used a system of passive reporting from local doctors, and a review of the medical records. Single seizures and inactive cases were included. There were 987 patients with epilepsy in Iceland which gave an incidence rate of 26/100,000 and a prevalence of 5.2/1000.

(Brewis, Poskanzer & Miller, 1966)

This was an important study as it was the only incidence study in the UK which did not just rely on GP records. Patients were ascertained in the population of Carlisle which had 67,798 inhabitants. Epilepsy was surveyed along with all other neurological conditions. Ascertainment utilised GP records, death certificates, hospital records, and a random household survey of 11% of the town. No adequate definition of epilepsy was forthcoming. Single seizures, febrile seizures, and provoked seizures were not included. The incidence of epilepsy was 30/100,00 and the prevalence was 6/1000.

(De Graaf, 1974)

This was an incidence and prevalence study of patients ascertained in northern Norway, and based at Tromsø. Population was 213,116 persons and 749 patients were identified using a review of medical records. Epilepsy as diagnosed by a neurologist but not well defined and it was not clear if the study included single seizures. Incidence rates were calculated retrospectively and were 33/100,000, with a prevalence of 3.5/1000.

(Zielinski, 1974a)

A much quoted study as a thorough system of ascertainment was adopted by doing a house to house survey of 0.5% of Warsaw residents. This sample was compared to 3,983 patients with known epilepsy identified from their medical records. Interesting study because a number of known patients denied having epilepsy on the house to house survey, and a large number of patients were never treated (probably due to the deprivations during and following WW2). Patients identified in the population were then interviewed. Incidence rates were 20/100,000 and prevalence of active epilepsy was 8/1000.

(Blom, Heijbel & Begfors, 1978)

This study was carried out in Northern Sweden and all patients with a history suggestive of epilepsy were referred to the regional neurological centre.

Doctors in the region were contacted and encouraged to keep up referral rates. Only children were identified up to 15 years of age. In the 12 month incidence period 74 children were identified out of a population of over 52,000. Incidence rate of epilepsy (presence of seizures in prior 3 years) was 82/100,000.

(Chiofalo, Kirschbaum, Fuentes, Cordero & Madsen, 1979)

This study utilised a questionnaire to ascertain children with epilepsy in the town of Melpilla, in Chile. 44 cases were identified out of 2,085 children giving a prevalence of 31/1000. This low figure probably reflects the poor case ascertainment methodology used.

(Cavazutti, 1980)

A widely quoted study as it examined the frequency of the different types of epilepsy that occurred in children. The study was based on a case not review over a five year period from an epilepsy clinic and so was not by any means population-based. 127 children were identified out of a school population of over 22,000. Incidence, which was calculated retrospectively, was 82/100,000 and the prevalence was 4.4/1000.

(Granieri et al, 1983)

This was one of the few studies which allowed some estimation of possible time trends in the incidence of epilepsy. A reasonable effective system of ascertainment was instituted in the town of Capparo in Italy and was based on review of medical records, and survey of pharmacists, and private doctors. Only active epilepsy was included, or patients taking AEDs. Incidence was 33/100,000 and there was no demonstrable secular trends. Prevalence was 6.2/1000.

(Juul-Jensen & Foldspang, 1983)

This study was based at Aarhus in Denmark where an admirable system of registering all patients with epilepsy had been in operation since 1963. The population was 244,800 and 1870 patients were ascertained using the register and a medical records review going back to 1940. In spite of this system asertainment was not that complete and an incidence of 34/100,000 was calculated retrospectively, with a prevalence of 13/1000.

(Hauser, Annegers & Kurland, 1993)

The incidence of epilepsy and of all unprovoked seizures was determined for residents of Rochester, Minnesota U.S.A. from 1935 through 1984. Age-adjusted incidence of epilepsy was 44 per 100,000 person-years. Incidence in males was significantly higher than in females and was high in the first year of life but highest in persons aged > or = 75 years. Sixty percent of new cases had epilepsy manifested by partial seizures, and two thirds had no clearly identified antecedent. Cerebrovascular disease was the most commonly identified antecedent, accounting for 11% of cases. Neurological deficits from birth, mental retardation and/or cerebral palsy, observed in 8% of cases, was the next most frequently identified pre-existing condition. The cumulative incidence of epilepsy through age 74 years was 3.1%. The age-adjusted incidence of all unprovoked seizures was 61 per 100,000 person-years. Age- and gender-specific incidence trends were similar to those of epilepsy, but a higher proportion of cases was of unknown aetiology and was characterised by generalised onset seizures. The cumulative incidence of all unprovoked seizures was 4.1% through age 74 years. Important secular trends were discerned and with time, the incidence of epilepsy and of unprovoked seizures decreased in children and increased in the elderly.

(Sidenvall, Forsgren, Blomquist & Heijbel, 1993)

In this study during a 20-month period, an attempt was made to find all children with unprovoked non-febrile seizures. The first attendance and

incidence rates were 95 and 89/100,000, respectively, in the age group 0-15 years. These figures were lower than those found 10 years earlier in the same area. The highest incidence was during the first year of life and there was a higher proportion of girls (male:female ratio 1:1.4). Generalised seizures dominated in the first year of life. The incidence of benign childhood epilepsy with centro-temporal spikes was 10.7/100,000 and was the most common epilepsy syndrome found. The incidence of partial seizures increased with age up to the age of 10 years. One in 10 children had a history of febrile convulsions.

APPENDIX 2

List of General Practitioners currentlly particpating in the NGPSE

Dr.KN.Addey,
Dr.S.Ahmad,
Dr.HW.Aitken,
Dr.M.Al-Saleem,
Dr.SM.Amin,
Dr.N.Amin,
Dr.JC.Anderson,
Dr.DI.Anderson,
Dr.Y.Anthony,
Dr.DP M.Archer,
Dr.N.Arnott,
Dr.SM.Ashby,
Dr.YC.Au,
Dr.S.Bailey,
Dr.JW.Baker,
Dr.R.Baker,
Dr.FC.Ballinger,
Dr.BR.Bannar-Martin,
Dr.PM.Barrie,
Dr.SK.Bassi,
Dr..Beazer,
Dr.DJ.Bell,
Dr.SJ.Bellamy,
Dr.RB.Bennet,
Dr.RB.Bennet,
Dr.EN.Benson,
Dr.R.Bertram,
Dr..Bhanja,
Dr.MA.Bielenky,
Dr.CE.Birchall,
Dr.K.Biswas,
Dr.FJ.Borchardt,
Dr.p.Bosworth,
Dr.GM P.Boyes,
Dr.BH.Boyle,
Dr.JG.Bradbrooke,
Dr.P.Bradley,
Dr.D.Brodie,
Dr.PG.Brown,
Dr..Bryant,
Dr.BS.Bryant,
Dr.RJ.Buckle,
Dr.R.Bull,
Dr.AJ.Burch,
Dr.K.Burch,
Dr.S.Burcombe,
Dr.S.Burgoyne,
Dr.RH.Burton,
Dr.RH.Burton,
Dr.DF S.Burwood,
Dr.S.Butcher,
Dr..Butcher,
Dr.JR.Bywater,
Dr.MF.A.Cahill,
Dr.GR.Caird,
Dr..Calder,
Dr.GE.Calvert,
Dr.PD.Campion,
Dr.C.Campion-Smith,
Dr.TJ.Cantor,
Dr.S.Carne,
Dr.TA.Carney,
Dr.J.Carrol,
Dr.BE.Carter,
Dr.PM.Carter,
Dr.RJ S.Cave,
Dr.GJ.Charlwood,
Dr.DA.Chidwick,
Dr.JD.Churcher,
Dr.D.Clare,
Dr.RC.Clare,
Dr.P.Claydon,
Dr.C.Clayton-Payne,
Dr.A.Coggan,
Dr.RW.Coles,
Dr.M.Collins,
Dr.PH.Cook,
Dr.A.Cook,
Dr.H.Corcoran,
Dr.DJ.Corlett,
Dr.H.Cotton,
Dr.P.Cottrell,
Dr.EJ.Coutinho,
Dr.HL.Coysh,
Dr.D.Craig,
Dr.PJ.Craven,
Dr.JA.Crcc,
Dr.NR.Crossley,
Dr.ID.Cruickshank,
Dr.M.Cunningham,
Dr.MT.Cwynarski,
Dr.J.Czauderna,
Dr.M.D'Souza,
Dr.SL.Davidson,
Dr.F.Davidson,
Dr.HC R.Davies,
Dr.AW.Davies,
DR.PH.Davison,
Dr.SC.Davoodbhoy,
Dr.FW D.Debney,
Dr.AR.Del Mar,
Dr.CI.Dellaportas,
Dr.PJ.Dennis,
Dr.A.Dhesi,
Dr.LH.Dhiya,
Dr.GA.Dinnis,
Dr.JB.Donald,
Dr.RR.Donmall,
Dr.S.Dove,
Dr.J.Dowell,
Dr.M.Doyle,
Dr.W.Drysdale,
Dr.AR.Duke,
Dr..Dunn,
Dr.RJ.Dunstan,
Dr.AJ.Dutton,
Dr..Dyer,
Dr.L.Dyson,
Dr.NE.Early,
Dr.MP.Eddington,
Dr.DA.Edmonds,
Dr..Elder,
Dr..Elsby,
Dr.AR.Emerson,
Dr.H.Enright,
Dr.PR.Evans,
Dr.KG.Evans,
Dr.DJ.Fairclough,
Dr.TM.Farley,
Dr.A.Farmer,
Dr.G.Fletcher,
Dr.BA.Flintan,
Dr.R.Fosket,
Dr.IL.Foster,
Dr.RD.Fouracre,
Dr.PM.Francis,
Dr.A.Frazer,
Dr.GK.Freeman,
Dr.A.French,
Dr.AR.Gall,
Dr.B.Geffin,
Dr.D.Gelipter,
Dr.RL.Gibbins,
Dr.JS.Gibson,
Dr.JR.Gilbert,
Dr.BV.Gill,
Dr.SC.Gillam,
Dr.JB.Glass,
Dr.JD.Goddard,
Dr.DM G.Goodridge,
Dr.D.Gordon,
Dr.J.Granger,
Dr.GR.Green,
Dr.RW.Green,
Dr.DJ.Green,
Dr.RM.Greenfield,
Dr.ED.Gregson,

Dr.DN H.Greig,
Dr.SK W.Griffith,
Dr.HG.Gunton,
Dr.PE.Hadden,
Dr.JL.Hadley,
Dr.SA.Hall,
Dr.W.Hall,
Dr.I.Hamilton,
Dr.RA.Hamlin,
Dr.CH.Hand,
Dr.MC.Hannan,
Dr.M.Harland,
Dr.DW.Harley,
Dr.A.Harris,
Dr.JJ.Harris,
Dr.RG.Harrison,
Dr.KR.Harrison,
Dr.EA.Harrison,
Dr.R.Harrod,
Dr..Hassan,
Dr.MF.Hassenfuss,
Dr..Hassey,
Dr.T.Hatch,
Dr..Hawkins,
Dr.JL.Haworth,
Dr.KA.Heatley,
Dr.GD.Heaton,
Dr.IN.Hempshall,
Dr.F.Hennessey,
Dr.C.Henry,
Dr.J.Hewlett,
Prof..Higgins,
Dr.F.Higgs,
Dr.S.Highton,
Dr.AP.Hill,
Dr.S.Hilton,
Dr.IM K.Hiscock,
Dr.SJ.Hogg,
Dr.RD.Hollands,
Dr.R.Holloway,
Dr.SGT.Holmes,
Dr.DH J.Hood,
Dr.P.Hopkins,
Dr.P.Horsfield,
Dr.B.Hourihane,
Dr.TR.Howard,
Dr.A.Howe,
Dr.IE.Hughes,
Dr.ME.Hughes,
Dr.D.Hughes,
Dr.CC.Hulbert,
Dr.MH.Husain,
Dr.WJ.Isherwood,
Dr.M.Jackson,
Dr.NR.Jackson,
Dr.PW.James,
Dr.I.Jamieson,
Dr.RJ T.Jarvis,
Dr.P.Jeavons,
Dr.JM.Jones,
Dr.KJ.Jones,
Dr.MR.Jones,
Dr.B.Jones,
Dr.WM.Jordan,
Dr.JF.Judge,
Dr.A.Jumaily,
Dr.J.Kane,
Dr.JF.Kedward,
Dr.MR.Kennedy,
Dr.IS.Kewley,
Dr.SJ L.King,
Dr.RH.King,
Dr.KN.Kini,
Dr.RN.Kirby,
Dr.P.Kirk-Smith,
Dr.S.Kitson,
Dr.J.Kloer,
Prof..JD F.Knox,
Dr..Koppel,
Dr.MG.Kremer,
Dr.JM.Lakeman,
Dr.DC.Langley,
Dr.MJ.Latham,
Dr.J.Launer,
Dr.D.Law,
Dr.D.Lawton,
Dr.C.Lay,
Dr..Lean,
Dr.CPB.Lennon,
Dr.PL.Lewis,
Dr.A.Lightfoot,
Dr.C.Littlejohn,
Dr.G.Livingstone,
Dr.R.Lloyd,
Dr.ND.Lloyd-Jones,
Dr.M.Logan,
Dr.JA.London,
Dr.J.Lorimer,
Dr.JR M.Lough,
Dr.PW.Love,
Dr.BM.Lower,
Dr..Lundy,
Dr.AJ.Macdonald-Brown,
Dr.RM.MacKenzie,
Dr.ID.Mackenzie,
Dr.N.MacLennan,
Dr.AG.Males,
Dr.S.Mallik,
Dr.P.Markus,
Dr.WS.Marsen,
Dr.AJ.Marshall,
Dr.DA.Martin,
Dr.JD.Martin,
Dr.DN.Masters,
Dr.A.Matthews,
Dr.M.McBride,
Dr.TJ D.McConnell,
Dr.JL.McCorrigan,
Dr..McCullagh,
Dr.B.McCullough,
Dr.HM.McDermott,
Dr..McIntosh,
Dr.M.McKendrick,
Dr..McKinstry,
Dr.JJ.McMullan,
Dr.VM.McVey,
Dr.PB.Medcalf,
Dr.R.Mee,
Dr.AJ.Membrey,
Dr.RJ.Meredith,
Dr.H.Merrilees,
Dr.A.Meynell,
Dr.CS H.Middleton,
Dr.JA.Mir,
Dr.KM.Mishra,
Dr.S.Mohammed,
Dr.M.Momen,
Dr.CG.Moore,
Dr.M.Morgan,
Dr.J.Morrell,
Dr.DC.Morrell,
Dr.E.Morris,
Dr.JR.Morton,
Dr.JP.Mounty,
Dr.AJ.Muir,
Dr.K.Muncey,
Dr.S.Murray,
Dr..Murthy,
Dr.J.Neary,
Dr.AS.Nijjar,
Dr.DR H.Norminton,
Dr.P.O'Neill,
Dr.JD.O'Neill,
Dr.AG.Oakanfull,
Dr.N.Padfield,
Dr.AN.Painter,
Dr.DA.Palmer,
Dr.A.Palmer,
Dr.V.Parker,
Dr.J.Parkes,
Dr.FM.Parrish,
Dr.CP.Patel,
Dr.J.Paton,
Dr.MG.Patten,
Dr.MM.Peddie,
Dr.SC.Pennell,
Dr.BA W.Perkins,
Dr.MCR.Phillis,
Dr.RA Y.Pietroni,
Dr.N.Pile,
Dr.RS.Pinches,
Dr.PV.Player,
Dr.SL.Pocklington,

Dr.LG.Posser,
Dr.DJ.Poulton,
Dr.P.Preston,
Dr.L.Price,
Dr.JF.Primavesi,
Dr.MA.Pringle,
Dr.R.Proudlove,
Dr.G.Pye,
Dr.A.Raban-Williams,
Dr.K.Radia,
Dr.SE.Ramsbottom,
Dr.HE G.Rees,
Dr.GD.Reilly,
Dr.C.Renwick,
Dr.K.Richards,
Dr.MI.Richardson,
Dr.ME.Riddoch,
Dr.RM.Ridsdill-Smith,
Dr.CH.Rigby,
Dr.MS.Rigler,
Dr.DJ.Riley,
Dr.GW.Roberts,
Dr.RC.Robinson,
Dr.JC.Robinson,
Dr.HJ.Rodgers,
Dr.LV.Ross,
Dr..Rowland,
Dr.JV.Rubner,
Dr.CS K.Ruck,
Dr.AO.Russell,
Dr..Russell,
Dr.P.Ryba,
Dr.S.Rye,
Dr.W.Sagar,
Dr..Sagar,
Dr.JS.Samill,
Dr.H.Sapper,
Dr.D.Sapsford,
Dr.J.Saunders,
Dr.JS.Savage,
Dr.D.Savage,
Dr.JN.Savory,
Dr.CL.Scott,
Dr.SK.Sehmi,
Dr.ST.Selvan,
Dr.P.Sengupta,
Dr.SC.Shah,
Dr.EH.Shaw,
Dr.C.Shearer,
Dr.AN.Sherwood,
Dr.C.Short,
Dr.C.Side,
Dr.JD.Silverman,
Dr..Singh,
Dr.G.Singh,
Dr.CM.Skott,
Dr.AP.Smaling,
Dr.DW.Smith,
Dr.PK.Smith,
Dr.PR.Soper,
Dr.MA.Spencer,
Dr.PD.Sprackling,
Dr.SM.Stanton,
Dr.WM.Steele,
Dr.D.Stewart,
Dr.FI.Stewart,
Dr.SH.Street,
Dr.CA.Stubbings,
Dr.RA.Suchett-Kaye,
Dr.S.Sudlow,
Dr.J.Suffield,
Dr.DJ.Sumner,
Dr.MV.Sutherland,
Dr.KM E.Sykes,
Dr.DR.Tant,
Dr.PR W.Tasker,
Dr.NH.Taylor,
Dr.MP.Taylor,
Dr..Taylor,
Dr.MB.Taylor,
Dr.JP.Taylor,
Dr.JD.Temple,
Dr.HA.Thomas,
Dr.RS.Thomas,
Dr.JM.Thompson,
Dr..Thompson,
Dr.OA.Thurtle,
Dr.GJ.Titmas,
Dr.VA.Todd,
Dr.DA.Toorawa,
Dr.CH.Tseung,
Dr.BC.Tulloch,
Dr.R.Turner,
Dr.AM.Valori,
Dr.R.Vibhuti,
Dr.M.Walter,
Dr.TO.Ward,
Dr.E.Ward,
Dr.CE J.Warren,
Dr.J.Watkings,
Dr..Watson,
Dr.GM.Watson,
Dr.JV.Weinkove,
Dr.RP.Whitbread,
Dr.DM.Whitcher,
Dr.PT.White,
Dr.W.Whitlow,
Dr.MM.Wicks,
Dr.IH.Widdrington,
Dr.CJ.Wilcox,
Dr..Willcox-Jones,
Dr.PG.Williams,
Dr.JB.Williamson,
Dr.P.Willis,
Dr.DA.Wood,
Dr.MJ.Wright,
Dr.DS.Wright,
Dr.RH.Yearsley,
Dr.A.Zahorski,

APPENDIX 3 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 FORM TO: Dr.S.D.Shorvon
FREEPOST
Chalfont Centre for Epilepsy
Chalfont St.Peter Bucks, SL9 7BR

1. General Practitioner 2.Patient

(label)

If patient has changed address or general practice, please insert new address/general practice. (If not known please give as much information 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 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 & 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:

4. We have the following information regarding

Aetiology

Circumstances/precipitating factors

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

5 Have there been ANY NEUROLOGICAL, MEDICAL AND PSYCHOLOGICAL DEVELOPMENTS? If so, please give further details:

6. 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:

7. 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

8. 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:

REFERENCES

Abiodun, O.A. (1988). Mortality in a psychiatric population: a Nigerian psychiatric hospital experience. Acta Psychiatrica Scandinavica, 77, 654-657.

Aicardi, J. (1986). Consequences and prognosis of convulsive status epilepticus in infants and children. Japanese Journal of Psychiatry and Neurology, 40, 283-290.

Alstrom, C.H. (1950). A study of epilepsy in its clinical, social and genetic aspects. Acta Psychiatria Neurologica Scandanavia (Supplement), 53, 1-285.

Annegers, J.F., Elveback, L.R., Labarthe, D.R. & Hauser, W.A. (1976). Ischemic heart disease in patients with epilepsy. Epilepsia, 17, 11-14.

Annegers, J.F., Grabow, J.D., Groover, R.V., Laws, E.R., Elveback, L.R. & Kurland, L.T. (1980). Seizures after head trauma: a population study. Neurology, 30, 683-689.

Annegers, J.F., Hauser, W.A. & Elveback, L.R. (1979). Remission of seizures and relapse in patients with epilepsy. Epilepsia, 20, 729-737.

Annegers, J.F., Hauser, W.A. & Shirts, S.B. (1984). Heart disease mortality and morbidity in patients with epilepsy. Epilepsia, 25, 699-704.

Annegers, J.F., Shirts, S.B., Hauser, W.A. & Kurland, L.T. (1986). Risk of recurrence after an initial unprovoked seizure. Epilepsia, 27, 43-50.

Anonymous. (1980). Prognosis of temporal lobe epilepsy in childhood [editorial]. British Medical Journal, 280, 812-813.

Anonymous. (1985). Prognosis in childhood epilepsy [editorial]. Lancet, 1, 963-964.

Anonymous. (1993). Neurological disease and cost in the European decade of the Brain. World Neurology, 2, 2-3.

Anthony, V. (1970). Malignant lymphoma associated with hydantoin drugs. Archives of Neurology, 22, 450-454.

Arief, A.J. (1942). Detioration of patients with organic epilepsy. Journal of Nervous and Mental Disease, 96, 49.

Arts, W.F., Visser, L.H., Loonen, M.C., Tjiam, A.T., Stroink, H., Stuurman, P.M. & PoortvlietDC. (1988). Follow-up of 146 children with epilepsy after withdrawal of antiepileptic therapy. Epilepsia, 29, 244-250.

Barraclough, B.M. (1987). The suicide rate of epilepsy. Acta Psychiatrica Scandinavica, 76, 339-345.

Beghi, E. & Tognoni, G. (1988). Prognosis of epilepsy in newly referred patients: a multicenter prospective study. Collaborative Group for the Study of Epilepsy. Epilepsia, 29, 236-243.

Begley, C.E., Annegers, J.F., Lairson, D., Reynolds, T. & Hauser, W.A. (1993). The cost of epilepsy: a model based on incidence and prognosis. Epilepsia, 34 Suppl 2, 146-146.

Beran, R.G. & Regan, K.J. (1993). The prevalence and cost of epilepsy in Australia. Epilepsia, 34 Suppl 2, 146.

Beran, R.G., Hall, L. & Michelazzi, J. (1985). An accurate assessment of the prevalence ratio of epilepsy adjusted for influencing factors. Neuroepidemiology, 4, 71-81.

Berlit, P., Krause, K.H. & Schellenberg, B. (1982). Serum lipids and anticonvulsants. Acta Neurologica Scandinavica, 66, 328-334.

Betts, T.A. (1983). Psychiatry in epilepsy. In: J. Laidlaw. & A. Richens (Eds.), A textbook of epilepsy. (pp. 145-184). Edinburgh: Churchill-Livingstone.

Bharucha, N.E. & Bharucha, E. (1988). Prevalence of epilepsy in the Parsi community of Bombay. Epilepsia, 29, 111-115.

Birnbach, C.D., Wilensky, A.J. & Dodrill, C. (1991). Predictors of early mortality and sudden death in epilepsy: a multidisciplinary approach. J Epilepsy, 4, 11-17.

Blom, J. (1990). The cost of epilepsy for society. Epilepsy Bulletin, 18, 19-26.

Blom, S., Heijbel, J. & Begfors, P.J. (1978). Incidence of epilepsy in children. Epilepsia, 19, 343-350.

Blom, S., Heijbel, J. & Bergfors, P.G. (1978). The incidence of epilepsy in children: a follow up study three years after the first seizure. Epilepsia, 19, 343-350.

Bouma, P.A.D., Peters, A.C.B., Arts, R.J.H.M., Stijnen, T. & Rossum, J.V. (1987). Discontinuation of antiepileptic therapy: a prospective study. Journal of Neurology, Neurosurgery and Psychiatry, 50, 1579-1583.

Bowerman, D.L., Levisky, J.A., Urich, R.W. & Wittenberg, P.H. (1978). Premature deaths in persons with seizure disorders--subtherapeutic levels of anticonvulsant drugs in postmortem blood specimens. Journal of Forensic Sciences, 23, 522-526.

Bradford-Hill, A. (1984). Collection statistics: forms of record and enquiry. A short textbook of medical statistics. (pp 31-39). London: Hodder& Stoughton.

Bradford-Hill, A. (1984). Fallacies and difficulties: the incidence and causes of mortality. A short textbook of medical statistics. (pp 259-264). London: Hodder& Stoughton.

Brain, W.R. (1951). Diseases of the nervous system. London: OUP.

Brewis, M., Poskanzer, C.R. & Miller, H. (1966). Neurological disease in an English city. Acta Neurologica Scandinavica, 42 (Suppl.), 1-89.

Brorson, L.O. & Wranne, L. (1987). Long-term prognosis in childhood epilepsy: survival and seizure prognosis. Epilepsia, 28, 324-330.

Callaghan, N., Garrett, A. & Goggin, T. (1988). Withdrawal of anticonvulsant drugs in patients free of seizures for three years. New England Journal of Medicine, 318, 942-946.

Callaghan, N., O'Callaghan, M.O., Dugan, B. & Feely, M. (1978). Carbamazepine as a single drug in the treatment of epilepsy. Journal of Neurology, Neurosurgery and Psychiatry, 41, 907-912.

Camfield, P.R., Camfield, C.S., Dooley, J.M., Tibbles, J.A.R., Fung, T. & Garner, B. (1985). Epilepsy after a first unprovoked seizure in childhood. Neurology, 35, 1657-1660.

Camfield, P.R., Camfield, C.S., Smith, E.C. & Tibbles, J.A.R. (1985). Newly treated childhood epilepsy: a prospective study of recurrence and side effects. Neurology, 35, 722-725.

Cavazutti, G.B., Ferrari, P. & Lalla, M. (1984). Follow up study of 482 cases with convulsive disorders in the first year of life. Dev Ment Child Neurol, 24, 425-437.

Chadwick, D. (1991). Epilepsy after first seizures: risks and implications [editorial]. Journal of Neurology, Neurosurgery and Psychiatry, 54, 385-387.

Chadwick, D. (1994). Multicentre study of early epilepsy and single seizures. Epilepsia, 35 (Suppl. 7), 15-15.

Chevrie, J.J. & Aicardi, J. (1978). Convulsive disorders in the first year of life: neurological and mental outcome and mortality. Epilepsia, 19, 67-74.

Chiofalo, N., Kirschbaum, A., Fuentes, A., Cordero, M. & Madsen, J. (1979). Prevalence of epilepsy in Melipilla, Chile. Epilepsia, 20, p 261-266.

Cleland, P.G., Mosquera, I., Steward, W.P. & Foster, J.B. (1981). Prognosis of isolated seizures in adult life. BMJ, 283, 1364.

Clemmensen, J. (1974). Are anticonvulsants oncogenic? Lancet, 1, 705-707.

Cockerell, O.C., Sander, J.W.A.S. & Shorvon, S.D. (1993). Neuroepidemiology in the UK. Journal of Neurology, Neurosurgery and Psychiatry, 56, 735-738.

Coleman, M.P., Herman, C, &. Douglar, A. (1989). Person-years (PYRS): a further program for cohort study analysis. September, WHO.

Collaborative Group for the Study of Epilepsy. (1992). Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of

monotherapy on the long-term course of epilepsy. Collaborative Group for the Study of Epilepsy. Epilepsia, 33, 45-51.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989). Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia, 30, 389-399.

Cooper, J.E. (1965). Epilepsy in a longitudinal study of 5,000 children. BMJ, 1, 1020-1022.

Costeff, H. (1965). Convulsions in childhood: their natural history and indications for treatment. New England Journal of Medicine, 273, 1410-1413.

Covanis, A., Gupta, A.K. & Jeavons, P.M. (1983). Sodium valproate monotherapy and polytherapy. Epilepsia, 23, 693-720.

Crombie, D.L., Cross, K.W., Fry, J., Pinsent, R.J. & Watts, C.A. (1960). A survey of the epilepsies in general practice: a report of the Research Committee of the Royal College of General Practiitioners. BMJ, 2, 416-422.

Dalby, M.A. (1969). Epilepsy and 3 per second spike and wave rhythms. A clinical, electroencephalographic and prognostic analysis of 346 patients. Acta Neurologica Scandinavica, Suppl.

Dasheiff, R.M. (1991). Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. Journal of Clinical Neurophysiology, 8, 216-222.

Davalos, A., Cendra, E., Genis, D. & Lopez-Pousa, S. (1988). The frequency, characteristics and prognosis of epileptic seizures at the onset of stroke [letter]. Journal of Neurology, Neurosurgery and Psychiatry, 51, 1464.

Davidson, D.L.W., Swingler, R.J. & Moulding, F. (1992). The cost of epilepsy in patients attending an out- patient clinic. Seizure, 1 Suppl A, 12-13.

De Graaf, A.S. (1974). Epidemiological aspects of epilepsy in Northern Norway. Epilepsia, 15, 291-299.

Dodge, P.R., Richardson, E.P. & Victor, M. (1954). Recurrent convulsive seizures as a sequel to cerebral infarction; a clinical and pathological study. Brain, 77, 610.

Dorn, H.F. (1950). Untitled. Human Biology, 22, 238.

Dreifus, F.E., Langer, D.H., Moline, K.A. & Maxwell, J.E. (1989). Valpoic acid hepatic fatalities. US experience since 1984. Neurology, 39, 201-207.

Duncan, J. & Hart, Y.M. (1993). Medical Services. In: J. Laildaw, A. Richens. & D. Chadwick (Eds.), A Textbook of Epilepsy. (pp. 705-721). London: Churchill-Livingstone.

Earnest, M.P., Thomas, G.E., Eden, R.A. & Hossack, K.F. (1992). The sudden unexplained death syndrome in epilepsy: demographic, clinical, and postmortem features. Epilepsia, 33, 310-316.

Elwes, R.D., Chesterman, P. & Reynolds, E.H. (1985). Prognosis after a first untreated tonic-clonic seizure. Lancet, 2, 752-753.

Elwes, R.D., Johnson, A.L. & Reynolds, E.H. (1988). The course of untreated epilepsy. BMJ, 297, 948-950.

Elwes, R.D., Johnson, A.L., Shorvon, S.D. & Reynolds, E.H. (1984). The prognosis for seizure control in newly diagnosed epilepsy. New England Journal of Medicine, 311, 944-947.

Emerson, R., D'Souza, B.J., Vining, E.P., Holden, K.R., Mellitis, E.D. & Freeman, J.M. (1981). Stopping medication in children with epilepsy. New England Journal of Medicine, 304, 1125-1129.

Feely, M., O'Callaghan, M.O., Dugan, B. & Callaghan, N. (1980). Phenobarbitone in previously untreated epilepsy. Journal of Neurology, Neurosurgery and Psychiatry, 43, 365-368.

Fetski, A.T., Kaamugisha, J., Jander, J.W.A.S., Gatti, S. & Shorvon, S.D. (1991). Comprehensive primary health care antiepileptic drug treatment programme in rural and semi urban Kenya. Lancet, 337, 406-409.

First Seizure Trial Group. (1993). Randomised clinical trial of antiepileptic drugs in reucing the risk of relapse after a first unprovoked tonic-clonic seizure. Neurology, 43, 478-483.

Fish, D.R., Miller, D.H., Roberts, R.C., Blackie, J.D. & Gilliatt, R.W. (1989). The natural history of late-onset epilepsy secondary to vascular disease. Acta Neurologica Scandinavica, 80, 524-526.

Forssman, H. & Akesson, H.O. (1970). Mortality of the mentally deficient: a study of 12,903 institutionalised subjects. Journal of Mental Deficiency Research, 14, 276-294.

Fredberg, U., Botker, H.E. & Romer, F.K. (1988). Acute neurogenic pulmonary oedema following generalized tonic clonic seizure. A case report and a review of the literature. European Heart Journal, 9, 933-936.

Friedman, G.D. (1981). Barbiturates and lung cancer in humans. J Nat Cancer Inst, 67, 291-295.

Friedmann, M. (1915). Zur Auffasung der gehauften kleinen Anfalle. Monatschr f Psychiat u Neurol, 38, 131.

Fukishima, Y. (1969). Prognosis and EEG of epilepsy with special reference to the focal spike abnormality. Clin EEG (Japan), 11, 287-290.

Gessner, U., Sagmeister, M. & Horisberger, B. (1993). The cost of epilepsy in Switzerland. International Journal of Health Sciences, 4, 121-128.

Gold, E., Gordis, L., Tonascai, J. & Szklo, M. (1978). Increased risk of brain tumours in children exposed o barbiturates. J Nat Cancer Inst, 61, 1031-1034.

Goodridge, D.M. & Shorvon, S.D. (1983). Epileptic seizures in a population of 6000. II: Treatment and prognosis. British Medical Journal [Clinical Research Ed], 287, 645-647.

Gowers, W.R. (1885). Epilepsy and other chronic disorders: their causes, symptoms, and treatment. London: Willaim Wood & Co.

Gram, L. (1990). Epileptic seizures and syndromes. Lancet, 336, 161-163.

Granieri, E., Rosati, G., Tola, R., Pavoni, M., Paolino, E., Pinna, L. & Monetti, V.C. (1983). A descriptive study of epilepsy in the district of Copparo, Italy, 1964-1978. Epilepsia, 24, 502-514.

Gray, A. & Fenn, P. (1993). Alzheimer's disease: the burden of the illness in England. Health Trends, 25, 31-37.

Griffin, J. & Wiles, M. (1991). Epilepsy. London: Office of Health Economics.

Gudmundsson, G. (1966). Epilepsy in Iceland. A clinical and epidemiological investigation. Acta Neurologica Scandinavica, 43 (Suppl.), 1-25.

Gumnit, R.J. (1991). Cost, Accessibility, and Quality of Life Issues in Surgery. In: H. Luders (Ed.), Epilepsy Surgery. (pp. 601-612). New York: Raven Press Ltd.

Habermas, S. (1901). Uber Die Prognose Der Epilepsie. Allg ZF Psychiat, 58, 243-253.

Haerer, A.F., Anderson, D.W. & Schoenberg, B.S. (1986). Prevalence and clinical features in a biracial United Stated population. Epilepsia, 27, 66-75.

Hart, Y.M. (1992). MD thesis. UK: University of London.

Hart, Y.M., Sander, J.W. & Shorvon, S.D. (1989). National General Practice Study of Epilepsy and Epileptic Seizures: objectives and study methodology of the largest reported prospective cohort study of epilepsy. National General Practice Study of Epilepsy and Epileptic Seizures (NGPSE). Neuroepidemiology, 8, 221-227.

Hart, Y.M., Sander, J.W., Johnson, A.L. & Shorvon, S.D. (1990). National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet, 336, 1271-1274.

Hashimoto, K., Fukushima, Y., Saito, F. & Wada, K. (1989). Mortality and cause of death in patients with epilepsy over 16 years of age. Japanese Journal of Psychiatry and Neurology, 43, 546-547.

Hauser, W.A. & Kurland, L.T. (1975). The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia, 16, 1-66.

Hauser, W.A. (1992). Seizure disorders: The changes with age. Epilepsia, 33, 6-14.

Hauser, W.A., Anderson, V.E., Loewenson, R.B. & McRoberts, S.M. (1982). Seizure recurrence after a first unprovoked seizure. New England Journal of Medicine, 307, 522-528.

Hauser, W.A., Annegers, J.F. & Elveback, L.R. (1980). Mortality in patients with epilepsy. Epilepsia, 21, 399-412.

Hauser, W.A., Rich, S.S., Annegers, J.F. & Anderson, V.E. (1990). Seizure recurrence after 1st unprovoked seizure: an extended follow up. Neurology, 40, 1163-1170.

Hauser, W.A., Annegers, J.F. & Kurland, L. (1991). Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. Epilepsia, 32, 429-445.

Hauser, W.A., Annegers, J.F. & Kurland, L.T. (1993). Incidence of epilepsy and unprovoked siezures in Rochester, Minnesota: 1935-1984. Epilepsia, 34, 453-468.

Hawton, K., Fagg, J. & Marsack, P. (1980). Association between epilepsy and attempted suicide. Journal of Neurology, Neurosurgery and Psychiatry, 43, 168-170.

Heijbel, J., Blom, S. & Bergfors, P.G. (1975). Benign epilepsy of children with centro temporal foci. Epilepsia, 16, 657-664.

Henriksen, P.B., Juul-Jensen, P. & Lund, M. (1967). The mortality of epileptics. Acta Neurologica Scandinavica Supplementum, 43, pp.

Hirsch, C.S. & Martin, D.L. (1971). Unexpected death in young epileptics. Neurology, 21, 682-690.

Hirtz, D.G., Ellenberg, J.H. & Nelson, K.B. (1984). The risk of recurrence of nonfebrile seizures in children. Neurology, 34, 637-641.

Hollowach, J., Thurston, D.L. & O' Leary, J. (1972). Prognosis in childhood epilepsy. Follow up study in 148 cases in which therapy had been suspended after prolonged anticonvulsant control. New England Journal of Medicine, 286, 169-174.

Holowach, J., Thurston, D.L. & O'Leary, J.L. (1062). Petit Mal epilepsy. Paediatrics, 30, 893-899.

Hopkins, A., Garman, A. & Clarke, C. (1988). The first seizure in adult life: value of clinical features, electroencephalogram, and computerised tomography scanning in prediction of recurrence. Lancet, 1, 721-726.

Huttenlocher, P.R. & Hapke, R.J. (1990). A follow up study of intractable seizues in childhood. Annals of Neurology, 28, 699-705.

Iivanainen, M. & Lehtinen, J. (1979). Causes of death in institutionalized epileptics. Epilepsia, 20, 485-491.

International Agency for Research on Cancer. (1974). Monographs on the evaluation of carcinogenic risk of chemicals to man. 13, (pp 157-182). Lyon: IARC.

Jancar, J. (1980). Anticonvulsant drugs and cancer. Lancet, 1, 484.

Jancar, J. (1990). Cancer and mental handicap. A further study (1976-85). British Journal of Psychiatry, 156, 531-533.

Janz, D. (1955). Die klinische Stellung der Pyknolepsie. Dtsch Z Neverenheilk, 1392, 22-32.

Janz, D. (1990). Juvenile myoclonic epilepsy. In: M. Dam. & L. Gram (Eds.), Comprehensive epileptology. (pp. 171-185). New York: Raven Press.

Jay, G.W. & Leestma, J.E. (1981). Sudden death in epilepsy. A comprehensive review of the literature and proposed mechanisms. Acta Neurologica Scandinavica Supplementum, 82, 1-66.

Jennett, B. (1974). Early traumatic epilepsy. Incidence and significance after nonmissile injuries. Archives of Neurology, 30, 394-398.

Jilek-Aal, L. (1965). Epilepsy in the Wapogoro tribe in Tanganyka. Acta Neurologica Scandinavica, 41, 57-86.

Johnson, L.C., DeBolt, W.L., Long, M.T., Ross., J, L., Sassin, J.F., Arthur, R.J. & Walter, R.D. (1972). Diagnostic factors in adult males following initial siezures. Archives of Neurology, 27, 193-197.

Juul-Jensen, P. & Foldspang, A. (1983). Natural history of epileptic seizures. Epilepsia, 24, 297-312.

Juul-Jensen, P. (1964). Frequency of recurrence after discontinuation of anti-convulsant therapy in patients with epileptic seizures. Epilepsia, 5, 352-364.

Kahn, H.A. & Sempos, C.T. (1989). Statistical methods in epidemiology. (pp 100-101). Oxford: Oxford University Press.

Karalus, N.C., Cursons, R.T., Leng, R.A., Mahood, C.B., Rothwell, R.P., Hancock, B., Cepulis, Z., Cepulis, S., Wawatai, M. & Coleman, L. (1991). Community acquired pneumonia: aetiology and prognostic index evaluation. Thorax, 46, 413-418.

Keeling, J.W. & Knowles, S.A. (1989). Sudden death in childhood and adolescence. Journal of Pathology, 159, 221-224.

Keranen, T. & Riekkinen, P.J. (1993). Remission of seizures in untreated epilepsy. BMJ, 307, 483.

Kilpatrick, C.J., Davis, S.M., Tress, B.M., Rossiter, S.C., Hopper, J.L. & Vandendriesen, M.L. (1990). Epileptic seizures in acute stroke [see comments]. Archives of Neurology, 47, 157-160.

Klenerman, P., Sander, J.W.A.S. & Shorvon, S.D. (1993). Mortality in patients with epilepsy: a study of patients in long term residential care. Journal of Neurology, Neurosurgery and Psychiatry, 56, 149-152.

Krohn, W. (1963). Causes of death among epileptics. Epilepsia, 4, 315-321.

Krohn, W.A. (1961). A study of epilepsy in Northern Norway, its frequency and character. Acta Psychiatrica Scandinavica, 36, 215-225.

Kuhl, V., Kiorboe, E. & Lund, M. (1967). The prognosis of epilepsy with special reference to traffic security. Epilepsia, 8, 195-209.

Kurland, L.T. & Molgaard, C.A. (1981). The patient record in epidemiology. Scientific American, 245, 46-55.

Kurokawa, T., Fung, K.C., Hanai, T. & Goya, N. (1982). Mortality and clinical features in cases of death among epileptic children. Brain Dev, 4, 321-325.

Leestma, J.E., Walczak, T., Hughes, J.R., Kalelkar, M.B. & Teas, S.S. (1989). A prospective study on sudden unexpected death in epilepsy. Annals of Neurology, 26, 195-203.

Lewis, J.A. (1978). Death and epilepsy. Proceedings, Annual Meeting of the Medical Section of the American Council of Life Insurance, 121-131.

Li, S.C., Schoenberg, B.S. & Bolis, C.L. (1985). Epidemiology of epilepsy in urban regions of the Peoples Republic of China. Epilepsia, 26, 391-394.

Linden, V. (1975). Myocardial infarction in epileptics. BMJ, 2, 87.

Lindholm, L. & Sifvenius, H. (1993). Costs of epilepsy and savings from treatment. Epilepsia, 34 Suppl 2, 139.

Lindsay, J., Ounsted, C. & Richards, P. (1979). Long-term outcome in children with temporal lobe seizures. I: Social outcome and childhood factors. Developmental Medicine and Child Neurology, 21, 285-298.

Lindsay, J., Ounsted, C. & Richards, P. (1980). Long-term outcome in children with temporal lobe seizures. IV: Genetic factors, febrile convulsions and the remission of seizures. Developmental Medicine and Child Neurology, 22, 429-439.

Livingston, S. (1963). Living with epileptic seizures. Springfield: Charles C Thomas.

Logan, W.R. & Hart, R.G. (1983). Seizure recurrence after a siezure. New England Journal of Medicine, 308, 158.

Loiseau, P., Dartigues, J.F. & Pestre, M. (1983a). Prognosis of partial epileptic seizures in the adolescent. Epilepsia, 24, 472-481.

Loiseau, P., Pestre, M., Dartigues, J.F., Commenges, D., Barberger-Gateau, C. & Cohadon, S. (1983b). Long-term prognosis in two forms of childhood epilepsy: typical absence seizures and epilepsy with rolandic (centrotemporal) EEG foci. Annals of Neurology, 13, 642-648.

Loiseau, P., Duche, B., Cordova, S., Dartigues, J.F. & Cohadon, S. (1988). Prognosis of benign childhood epilepsy with centrotemporal spikes: a follow-up study of 168 patients. Epilepsia, 29, 229-235.

Lorenzo, R.J. (1990). The epilespies. In: Bradley, Darrioff. & C.D. Marsden (Eds.), Neurology in clincical practice. (pp. 1443-1477). Boston: Butterworth-Heinemann.

Luce, B.R. & Elixhauser, A. (1990). Standards for the socioeconomic evaluation of health. London: Springer-Verlag.

Luhdorf, K., Jensen, L.K. & Plesner, A.M. (1987). Epilepsy in the elderly: life expectancy and causes of death. Acta Neurologica Scandinavica, 76, 183-190.

Lund, A. & Gormsen, H. (1985). The role of antiepileptics in sudden death in epilepsy. Acta Neurologica Scandinavica, 72, 444-446.

Massey, E.W. & Schoenberg, B.S. (1985). Mortality from epilepsy. International patterns and changes over time. Neuroepidemiology, 4, 65-70.

Mattson, R.H., Cramer, J.A. & Collins, J.F. (1992). A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. New England Journal of Medicine, 327, 765-771.

Maytal, J., Shinnar, S., Moshe, S.L. & Alvarez, L.A. (1989). Low morbidity and mortality of status epilepticus in children. Pediatrics, 83, 323-331.

McLoughlin, I.J. (1988). A study of mortality experiences in a mental-handicap hospital. British Journal of Psychiatry, 153, 645-649.

Medical Research Council Antiepileptic Drug Withdrawal Study Group. (1991). Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet, 337, 1175-1180.

Miller, J.D. & Jennett, W.B. (1968). Complications of depressed skull fracture. Lancet, 2, 991-995.

Miyake, S., Tanaka, M., Matsui, K., Miyagawa, T., Yamashita, S., Yamada, M. & Iwamoto, H. (1991). Mortality patterns of children with epilepsies in a children's medical center. No To Hattatsu, 23, 329-335.

Moore, M.T. (1959). Pulmonary changes in hydantoin therapy. JAMA, 171, 1328-1333.

Munson, J.F. (1910). Death in epilepsy. Medical Record, 77, 58-62.

Muuronen, A., Kaste, M., Nikkila, E.A. & Tolppanen, E.M. (1985). Mortality from ischaemic heart disease among patients using anticonvulsive drugs: a case-control study. BMJ, 291, 1481-1483.

Neuspiel, D.R. & Kuller, L.H. (1985). Sudden and unexpected natural death in childhood and adolescence. JAMA, 254, 1321-1325.

Norman, M.G., Taylor, G.P. & Clarke, L.A. (1990). Sudden, unexpected, natural death in childhood. Pediatric Pathology, 10, 769-784.

Office of Population Census and Surveys. (1991). Mortality statistics. London: HMSO.

Okuma, T. & Kumashiro, H. (1978). Prognosis of epilepsy: the second interim report of a multi-institutional study in Japan. Folia Psychiatrica et Neurologica Japonica, 32, 421-431.

Okuma, T. & Kamashiro, H. (1981). Natural history and prognosis of epilepsy: report of a multi institutional study in Japan. Epilepsia, 22, 35-53.

Okuno, T., Ito, M., Nakano, S., Hattori, H., Fujii, T., Go, T. & Mikawa, H. (1989). Carbamazepine in the therapy and long-term prognosis in epilepsy in childhood. Epilepsia, 30, 57-61.

Osuntokun, B.O., Adeuja, A.O.G. & Nottidge, V.A. (1987). Prevalence of the epilepsies in Nigerian African: a community based study. Epilepsia, 28, 272-283.

Overweg, J., Binnie, C.D., Oosting, J. & Rowan, A.J. (1987). Clinical and EEG prediction of seizure recurrence following antiepileptic drug withdrawal. Epilpsy Res, 1, 272-283.

Oxbury, J.M. & Whitty, C.W. (1971). Causes and consequences of status epilepticus in adults. A study of 86 cases. Brain, 94, 733-744.

Paal, G. (1957). Katamnestische Untersuchungen und EEG bei Pyknolepsie. Z ges Neurol Psychiat, 196, 132-143.

Pachlatko, C. (1993). The economic cost of epilepsy. Epilepsia, 34 Suppl 2, 137.

Panayiotopoulos, C.P. (1989). Benign childhood epilepsy with occipital paroxysms: a 15-year prospective study. Annals of Neurology, 26, 51-56.

Pendergrass, J.W. & Nanson, J.W. (1976). Fetal hydantoin syndrome and neuroblastoma. Lancet, 2, 150.

Penning, R., Muller, C. & Ciompi, L. (1969). Mortality and causes of death of epileptics. Psychiatria Clinica, 2, 85-94.

Placencia, M., Paredes, V., Cascante, S., Sander, J.W.A.S. & Shorvon, S.D. (1992). Epileptic seizures in an Andean region of Ecuador: prevalence and incidence and regional variation. Brain, 115, 783-794.

Pond, D., Bidwell, B. & Stein, L. (1960). A survey of 14 general practices. Part 1 medical and demographic data. Psychiatria, Neurologia, Neurochirurgia, 63, 217-236.

Quan, L., Gore, E.J., Wentz, K., Allen, J. & Novack, A.H. (1989). Ten-year study of pediatric drownings and near-drownings in King County, Washington: lessons in injury prevention. Pediatrics, 83, 1035-1040.

Ramsay, R.E., Wilder, B.J., Berger, J.R. & Bruni, J. (1983). A double blind study comparing carbamazepine with phenytoin as initial therapy seizure therapy in adults. Neurology, 33, 904-910.

Reynolds, E.H. (1987). Early treatment and prognosis of epilepsy. Epilepsia, 28, 97-106.

Reynolds, E.H. (1988). The prevention of chronic epilepsy. Epilepsia, 29, S25-S28.

Richens, A., Davidson, D.L.W., Cartlidge, N.E.F. & Easter, D.J. (1994). A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Journal of Neurology, Neurosurgery and Psychiatry, 57, 682-687.

Robinson, R. (1993). Economic evaluation and health care: what does it mean? BMJ, 307, 670-673.

Rodin, E.A. (1968). The prognosis of patients with epilepsy. (pp 326-329). Illinois: Charles C Thomas.

Rodin, E.A. (1972). Medical and social prognosis in epilepsy. Epilepsia, 13, 121-131.

Rodin, E.A. (1978). Various prognostic aspects in patients with epilepsy. Folia Psychiatrica et Neurologica Japonica, 32, 407-418.

Ross, E.M., Peckham, C.S., West, P.B. & Butler, N.R. (1980). Epilepsy in childhood: findings from the National Child Development Study. British Medical Journal, 280, 207-210.

Sander, J.W.A.S. & Shorvon, S.D. (1987). Incidence and prevalence studies in epilepsy and their methodological problems: a review. Journal of Neurology, Neurosurgery and Psychiatry, 50, 829-839.

Sander, J.W., Hart, Y.M., Johnson, A.L. & Shorvon, S.D. (1990). National General Practice Study of Epilepsy: newly diagnosed epileptic seizures in a general population. Lancet, 336, 1267-1271.

Sander, J.W.A.S. (1993). Some aspects of the prognosis of the epilepsies; a review. Epilepsia, 34, 1007-1016.

Sander, J.W.A.S., Cockerell, O.C., Hart, Y.M. & Shorvon, S.D. (1993). Is the incidence of epilepsy falling in the UK? Lancet, 342, 874.

Sarkioja, T. & Hirvonen, J. (1984). Causes of sudden unexpected deaths in young and middle-aged persons. Forensic Science International, 24, 247-261.

Satishchandra, P., Chandra, V. & Schoenberg, B.S. (1988). Case-control study of associated conditions at the time of death in patients with epilepsy. Neuroepidemiology, 7, 109-114.

Sato, S. (1964). The epidemiological and clinico-statisical study of epilepsy in Nigata City. Clin Neurol (Tokyo), 4, 313-424.

Sato, S., Dreifuss, F.E. & Penry, J.K. (1976). Prognostic factors in absence seizures. Neurology, 26, 788-796.

Saunders, M. & Marshall, C. (1975). Isolated seizures: an EEG and clinical assessment. Epilepsia, 16, 731-733.

Scambler, G. & Hopkins, A. (1980). Social class, epileptic activity, and disadvantage at work. Journal of Epidemiology and Community Health, 34, 129-133.

Schoenberg, B.S. (1983). Calculating confidence intervals for rates and ratios. Neuroepidemiology, 2, 257-256.

Schmidt, D. (1982). Adverse effects of antiepileptic drugs. New York: Raven Press.

Schraeder, P.L. & Lathers, C.M. (1989). Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death. Epilepsy Research, 3, 55-62.

Schwade, E. & Cwen, O. (1954). Mortality in epilepsy. JAMA, 156, 1526-1527.

Schwender, L.A. & Troncoso, J.C. (1986). Evaluation of sudden death in epilepsy. American Journal of Forensic Medicine and Pathology, 7, 283-287.

Scott, G.M. & Gibberd, F.B. (1980). Epilepsy and other factors in the prognosis of gliomas. Acta Neurologica Scandinavica, 61, 227-239.

Shafer, S.Q., Hauser, W.A., Annegers, J.F. & Klass, D.W. (1988). EEG and other predictors of epilepsy remissiom: a community study. Epilepsia, 29, 590-600.

Shinnar, S., Vining, E.P., Mellits, E.D., D'Souza, B.J., Holden, K., Baumgardner, R.A. & Freeman, J.M. (1985). Discontinuing antiepileptic medication in children with epilepsy after two years without seizures. A prospective study. New England Journal of Medicine, 313, 976-980.

Shinton, R.A., Gill, J.S., Melnick, S.C., Gupta, A.K. & Beevers, D.G. (1988). The frequency, characteristics and prognosis of epileptic seizures at the onset of stroke. Journal of Neurology, Neurosurgery and Psychiatry, 51, 273-276.

Shorvon, S.D. & Reynolds, E.H. (1982). Early prognosis of epilepsy. British Medical Journal [Clinical Research Ed], 285, 1699-1701.

Shorvon, S.D. & Sander, J.W.A.S. (1986). Temporal patterns of remission and relapse of seizures in patients with epilepsy. In: D. Schmidt. & P. Morrelli (Eds.), Intractable epilepsy. (pp. 13-23). New York: Raven Press.

Shorvon, S.D. (1984). The temporal aspects of prognosis in epilepsy. Journal of Neurology, Neurosurgery and Psychiatry, 47, 1157-1165.

Sidenvall, R., Forsgren, L., Blomquist, H.K. & Heijbel, J. (1993). A community-based prospective incidence study of epileptic seizures in children. Acta Paediatrica, 82, 60-65.

Silfvenius, H. & Olivecrona, M. (1988). Epilepsy in Sweden as revealed by mortality, disability pensions, and drug consumption, 1971-1984. Acta Neurologica Scandinavica Supplementum, 117, 15-23.

Sofijanov, N.G. (1982). Clinical evolution and prognosis of childhood epilepsies. Epilepsia, 23, 61-69.

Spratling, W.P. (1902). The causes and manner of death in epilepsy. Medical News, 80, 1225-1227.

Stone, S. & Lange, L.S. (1986). Syncope and unexpected sudden death attributed to carbamazepine in a 20 year old epileptic. Journal of Neurology, Neurosurgery and Psychiatry, 49, 1460-1461.

Strobos, R.J. (1959). Prognosis of convulsive disorders. Archives of Neurology, 1, 216-225.

Suchy, F.J., Balistreri, W.F., Buchino, J.J., Sondheimer, J.M., Bates, S.R., Kearns, G.L., Stull, J.D. & Bove, K.E. (1979). Acute hepatic failure associated with the use of sodium valproate. New England Journal of Medicine, 300, 962-966.

Swinyard, E.A. (1980). History of antiepileptic drugs. Advances in Neurology, 27, 1-10.

Taylor, D.C. & Marsh, S.M. (1977). Implications of long term follow up studies in epilepsy: with a note on the cause of death. In: J.K. Penry (Ed.), Epilepsy: the 8th international symposium. (pp. 27-34). New York: Raven Press.

Taylor, J. (1931). Selected writings of John Hughlings Jackson. Vol 1: On epilepsy and epileptiform convulsions. London: Hodder & Staughton.

Tekle-Haimanot, R., Forsgren, L. & Adebe, M. (1990). Clinical and electroencephalographic characteristics of epilepsy in rural Ethiopa. Epilepsy Research, 7, 230-239.

Terrence Jr, C.F., Wisotzkey, H.M. & Perper, J.A. (1975). Unexpected, unexplained death in epileptic patients. Neurology, 25, 594-598.

Thomas, M.H. (1959). The single seizure: its study and management. JAMA, 169, 457-459.

Thurston, J.H., Thurston, D.L., Hixon, B.B. & Keller, A.J. (1982). Prognosis in childhood epilepsy: additional follow-up of 148 children 15 to 23 years after withdrawal of anticonvulsant therapy. New England Journal of Medicine, 306, 831-836.

Todt, H. (1984). The late prognosis of epilepsy in childhood: results of a prospective follow-up study. Epilepsia, 25, 137-144.

Tsuboi, T. (1984). Epidemiology of febrile and afebrile convulsions in children in Japan. Neurology, 34, 175-181.

Turnbull, D.M., Rawlins, M.D., Weightman, D. & Chadwick, D.W. (1982). A comparison of phenytoin and valproate in previously untreated adult epileptic patients. Journal of Neurology, Neurosurgery and Psychiatry, 45, 55-59.

Turner, W.A. (1907). Epilepsy: a study of the idiopathic disease. London: MacMillan.

US Commission for the control of Epilepsy, and its consequences. (1978). Plan for nation-wide action on Epilepsy. (pp 78-279). USA: NIH.

Van Donselaar, C.A., Geerts, A.T. & Schimsheimer, R.J. (1991). Idiopathic first seizure in adult life: who should be treated? BMJ, 302, 620-623.

Wada, T. (1963). Present state of anti-epileptic drug treatment in Japan. Rinsho-to-Kenkyu (Japan), 40, 914.

Wagner, A.L. (1983). A clinical and epidemiological study of adult patients with epilepsy. Acta Neurologica Scandinavica Supplementum, 94, 63-72.

Watts, A.E. (1992). The natural history of untreated epilepsy in a rural community in Africa. Epilepsia, 33, 464-468.

Weiss, G.H. & Caveness, W.F. (1972). Prognostic factors in the persistence of posttraumatic epilepsy. Journal of Neurosurgery, 37, 164-169.

White, S.J., McLean, A.E. & Howland, C. (1979). Anticonvulsant drugs and cancer. A cohort study in patients with severe epilepsy. Lancet, 2, 458-461.

Wise, P.H., Kotelchuck, M., Wilson, M. & Mills, M. (1985). Racial and socioeconomic disparities in childhood mortality in Boston. New England Journal of Medicine, 313, 360-366.

Wolfersdorf, M. & Froscher, W. (1987). Suicide in epileptic patients. Fortschritte der Neurologie-Psychiatrie, 55, 294-298.

Yahr, M.D., Sciarra, D., Carter, S. & Merritt, H. (1952). Evaluation of standard anticonvulsant therapy in three hundred nineteen patients. JAMA, 150, 663-667.

Ziegler, H.T. & Kamecke, A. (1967). Uber unerwarteten Tod von Epileptikern. Epileptikern Nervartz, 38, 343-348.

Zielinski, J.J. (1974). Epidemiology and medical and social problems of epilepsy in Warsaw. Final report on research program No. 19-P-58325-F-01. Washington: US:DHEW, Social and rehabilitation service.

Zielinski, J.J. (1974). Epilepsy and mortality rate and cause of death. Epilepsia, 15, 191-201.

Zielinski, J.J. (1974). Epileptics not in treatment. Epilepsia, 15, 203-210.