Longitudinal cohort studies of the prognosis of epilepsy: contribution of the National General Practice Study of Epilepsy and other studies

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Longitudinal cohort studies of prognosis in epilepsy have been carried out since the late 1970s and these have transformed our understanding of prognosis in epilepsy. This paper reviews the contribution of such studies and focuses particularly on the National General Practice Study of Epilepsy, a prospective population-based cohort study of 1195 patients that was initiated in 1983. The National General Practice Study of Epilepsy and other studies have shown that: (i) epilepsy has an often good prognosis with 65–85% of cases eventually entering long-term remission, and an even higher proportion of cases entering a short-term remission; (ii) the likelihood of long-term remission of seizures is much better in newly diagnosed cases than in patients with chronic epilepsy; (iii) the early response to treatment is a good guide to longer term prognosis (although not inevitably so, as in a minority of cases seizure remission can develop after prolonged activity); (iv) the longer is the remission (and follow-up), the less likely is subsequent recurrence; (v) the longer an epilepsy is active, the poorer is the longer term outlook; (vi) that delaying treatment, even for many years, does not worsen long-term prognosis; (vii) the ‘continuous’ and ‘burst’ patterns are more common than the ‘intermittent’ seizure pattern; (viii) epilepsy has a mortality that is highest in the early years after diagnosis, and in the early years is largely due to the underlying cause, however, higher mortality rates than expected are observed throughout the course of an epilepsy; (ix) the prognosis of febrile seizures is generally good, with ~6–7% developing later epilepsy; and (x) clinical factors associated with outcome have been well studied, and those consistently found to predict a worse outcome include: the presence of neurodeficit, high frequency of seizures before therapy (seizure density), poor response to initial therapy, some epilepsy syndromes.

Keywords: epilepsy prognosis; NGPSE; epidemiology; cohort studies

Abbreviations: GP = General Practice; NGPSE = National General Practice Study of Epilepsy; SMR = standardized mortality rate; SUDEP = sudden unexpected death in epilepsy

Introduction

Longitudinal cohort studies of prognosis in epilepsy from the time of initial diagnosis were first carried out in the late 1970s and this methodology has radically changed long-held perceptions. Before this time, the traditional view of epilepsy was that it was ‘a chronic condition characterized by a continuing tendency to seizure relapse’ (Shorvon, 1984). This view was summarized in the publication of the landmark book The prognosis of patients with epilepsy (Rodin, 1968) and was widely accepted (Anon, 1975).
Rodin’s book (1968), which reported a large cross-sectional clinic-based study and review of the literature, concluded that although prognosis had improved during the first half of the 20th century, less than one-third of patients would achieve a remission of 2 years or more, that the condition had a continuing tendency to relapse and that the longer was the follow-up the higher the likelihood of relapse. The studies underpinning this perception of epilepsy were all hospital or asylum-based, and none were cohort studies from the time of diagnosis. The selection bias caused by the over-representation of clinic-based chronic epilepsy was not recognized.

This paper reviews the contribution of the cohort studies from the time of initial diagnosis to the study of prognosis. It will focus particularly on the first and longest-running prospective population-based cohort study of adults and children, the National General Practice Study of Epilepsy (NGPSE), which was initiated in 1983, and provides a synoptical review of the life-cycle of this study and of other cohort studies, and a critical appraisal of what has been achieved and of what questions remain unanswered. As outlined below, the NGPSE has now been brought to a premature end, by bureaucratic obstruction, and we will reflect briefly on this also.

The Mayo Clinic Record Linkage Study, the Tonbridge Study and the Study from Turku

The first notable longitudinal community-based cohort study of prognosis in epilepsy was the landmark study from the Mayo Clinic (Annegers et al., 1979). This study used the card-based record linkage system, and looked in retrospect at all cases receiving their initial diagnosis of epilepsy between 1935–74 (excluding febrile seizures, single seizures and convulsions associated with acute illnesses). Four hundred and seventy-five patients were identified whose history stretched over at least 5 years and 141 patients with a history > 20 years. Terminal remission rates (defined as a current remission that had lasted at least 5 years) were calculated. At 5 years after diagnosis, 42% of cases were in remission and this rose to 65% at 10 years and 70% at 20 years (with another 6% of patients who had been in 5-year remission but then relapsed). Eventually therefore, over three-quarters of patients were in terminal remission and about half had discontinued antiepileptic drugs. This study suffered from being retrospective, and stretching back to the period when even EEG was not freely available and diagnostic criteria and classification were different, and the fact that the study population, although approximating to a population base, was still in fact ascertained from a single institution. Furthermore, fewer cases were included from the earlier years, suggesting ascertainment bias, and the overall figures varied somewhat from a previous paper describing the same study (Hauser and Kurland, 1975) perhaps reflecting diagnostic issues. Nevertheless, this was a detailed and comprehensive study, and the first published study to suggest that the overall prognosis was much more favourable than was the then orthodox opinion.

In 1981, the first study of prognosis in a population-based cohort was undertaken in Britain (the Tonbridge study). In this study, the records of 6000 persons in a single general practice (GP) were scrutinized in detail, and patients with a history of epilepsy or epileptic seizures identified and the course of their epilepsy followed. The organization of health care in Britain at GP level provided a unique opportunity to study prognosis, because each GP covered a specific geographical population, and the entire medical record from 1948 (the date of inception of the National Health Service; NHS) of each patient in that population was centralized in the patient notes in the practice. The GP patient notes included records of all post-1948 hospital visits as well as all visits to the GP made by that patient during their lifetime, and a record of all medication given to that patient. The GP is the ‘gatekeeper’ for referrals to hospitals and thus details of all hospital consultations are returned to the patient notes. All persons in the UK have a GP in their residential location, and when a person moves location, the record is transferred to the new GP. This system thus allows the lifetime medical record, of both primary and secondary care, of all persons in a population to be studied.

The Tonbridge study was initiated in 1981 and two papers were published (Goodridge and Shorvon, 1983a, b), the first on demography, diagnosis and classification and the role of the hospital service, and the second on treatment and prognosis. In the study, 122 patients with a history of epilepsy or epileptic seizures were identified in the population of 6000; a lifetime prevalence of epilepsy of 20.3/1000 including single seizures and 17.7/1000 excluding single seizures. As in the Mayo Clinic study, the tool of ‘remission’ and ‘relapse’ was used to study prognosis. Remission was defined as a period of 2 years without a seizure and a relapse period as a period (in years) in which seizures had occurred. Terminal remission was defined as a remission period that was continuing up until the end of the study. The pattern of seizure occurrence over time was also analysed. The cumulative % chance of a patient being in remission, and in terminal remission, was calculated using actuarial methods. By 10 years after the onset of epilepsy, about two-thirds of patients, and by 20 years 80% of patients, were in terminal remission—overall figures similar to those obtained in the Mayo Clinic study. Eighteen per cent of patients had had a single seizure only, 49% of patients had active seizures for a period, then entered terminal remission (the ‘burst pattern’), 21% had no remission at all after the onset of their seizures (the ‘continuous pattern’) and in 12% remission periods were followed by relapses (the ‘intermittent pattern’). This was the first time that the patterns of seizures over time had been reported.

One other long-running cohort study, confined to children, was initiated in the 1970s (Sillanpää, 1973). This study followed 144 children (from a cohort of 245 children) with epilepsy starting in 1961–64 from Turku in Finland until 2006. Patients resident in the region were identified initially retrospectively by the examination, carried out in 1972/3, of case journals of the 144 patients, who had developed epilepsy around 10 years previously, seen in the Department of Paediatrics in the main regional hospital (including psychiatric and surgical units), in the three other paediatric hospital departments, one central institution for mentally retarded, one special hospital for cerebral palsied and paediatric psychiatric patients, of one central institution for epileptics and three more central institutions for mentally retarded situated outside the region,
and the medical certificates for obtaining anticonvulants free of charge (Sillanpää 1973). Epilepsy was originally defined as more than three seizures occurring over a period exceeding 1 week (later publications mention two or more seizures without the time limitation) and the study excluded patients with progressive disease, situational seizures only (including febrile seizures) and those who were not hospitalized. The seizure prognosis was recorded in 1973 and then at 5-yearly intervals until 2006, and has continued to be reported (Sillanpää et al., 1998, 2012; Sillanpää and Schmidt, 2006; Sillanpää and Shinnar, 2010). Although ascertainment was hospital-based, because of the nature of the health care system the authors considered that this study reflected a true population-base. The findings are described below.

The National General Practice Study of Epilepsy

The Mayo Clinic and Tonbridge studies were the first of their kind, but were both retrospective, and the Turku study ascertained patients who had developed epilepsy ∼10 years previously, by a case-record review and was confined to children. It was on the basis of these studies, and especially the Tonbridge study, that the NGPSE was then conceived as the first prospective population-based cohort study of children and adults from the time of diagnosis. The primary research data from the NPGSE findings have been published in 19 full papers (Hart et al., 1989, 1990; Sander et al., 1990; Chaplin et al., 1992, 1993; Manford et al., 1992a, b; Cockerell et al., 1994a, b, 1995, 1997; MacDonald et al., 1999, 2000; Lhatoo et al., 2001a, b; Bell et al., 2004; Gaitatzis et al., 2004; Neligan et al., 2011, 2012), with the final paper in preparation, which have been cited over 1000 times, and have led to a greater number of indirect publications, abstracts and reviews.

Initiation

The NGPSE was conceived in September 1983. Details of the design of the study were published in a paper in Neuroepidemiology (Hart et al., 1989). The organization of care through the British NHS, the advantages of which for research are listed above, provided an ideal structure from which to conduct the study. The principal aims were to describe: (i) the prognosis of newly diagnosed seizures, and the patterns of seizure recurrence and remission, with special emphasis on temporal aspects, and including mortality; (ii) the clinical phenomenology and context of newly diagnosed seizures and epilepsy; (iii) treatment patterns in this cohort; (iv) psychological and social aspects; and (v) referral patterns and provision of services. Of these (i) was considered the most important aim, and forms the focus of this paper.

A representative sample of 275 GPs were recruited from around the country. An active surveillance process was put in place with monthly reminders made to ensure as complete a cohort as possible and recruitment carried out between 1984–87. Criteria for inclusion were patients with a new diagnosis of epileptic seizures or possible epileptic seizures, including those with febrile convulsions, single seizures, and seizures associated with acute illness, including the GP’s patients whose first seizures were first diagnosed in accident and emergency departments or in hospital.

Patients with a previous diagnosis of epileptic seizures were excluded, as were those with seizures starting in the neonatal period and those who resided in institutions for epilepsy (as only a very small proportion of patients with epilepsy in Britain are institutionalized, this was not thought to be a major source of bias). Those with provoked seizures were included, as in many cases, seizures have both provoked and unprovoked elements making a distinction difficult. In other studies ‘provoked seizures’ are excluded (including the Rochester and Turku cohorts; Table 1), and so to aid comparability, those with febrile seizures (the biggest group of ‘provoked’ seizures) were analysed separately. Study instruments were designed that recorded: medical history, family history, seizure description, circumstances of seizure, likely aetiology, hospital referral and treatment, and service-usage data. Details of hospital referral and visits were also collected, with results of diagnostic investigations and specialist opinion. Follow-up details of recurrence of seizures, treatment, and any neurological, medical, or psychological development were collected regularly at first 6-monthly and then annually. Classification of the epilepsy (or epileptic seizures—the terms were used synonymously in this study) was carried out at a time 6 months after entry to the study by the study team, based on the information received, from the GP and the hospital doctors, and was decided by a panel comprising the two authors (a neurologist specializing in epilepsy and a GP), a neurological research fellow (J.W.A.S. Sander) and a paediatric neurologist (E. Ross). The patient information was anonymized and strict confidentiality maintained, although patient consent was not required at that time. A total of 1195 patients were notified. Of these, in 183 the attacks turned out not to be epileptic, in a further 220 the attack were classified as febrile seizures, in 228 as possible epileptic seizures and in 564 as definite epileptic seizures. Amongst the definite cases, the epilepsy was categorized as: idiopathic or cryptogenic in 346, remote symptomatic in 119, acute symptomatic in 83 and associated with neurological deficit in 16. The commonest symptomatic aetiologies were cerebrovascular disease in 15% and tumour in 6%. Fifty-two per cent of the patients had partial or secondarily generalized seizures, and only 39% had generalized seizures. The median age was 32 years for those with definite seizures, and 25% were between 1 month and 15 years of age, 24% were 60 years of age or older. The study was approved by the Institutional Ethics Committee of the National Hospital for Nervous Diseases, and was also recommended to its members by the research committee of the Royal College of General Practitioners.

Findings in relation to prognosis of epilepsy and patterns of seizures

The primary goal of the study, from its onset, was to elucidate the prognosis of epilepsy and epileptic seizures. A series of papers were published presenting the results as follow-up lengthened, with a final paper in preparation (Hart et al., 1990; Sander et al., 1990; Cockerell et al., 1995, 1997; Macdonald et al., 2000). The first prognostic question examined was the rate of recurrence after the first attack (Hart et al., 1990). By then the 564 patients classified as having definite seizures had been followed for
### Table 1 Cohort studies of epilepsy with patients followed from the time of diagnosis

<table>
<thead>
<tr>
<th>Description of cohort</th>
<th>Number of cases</th>
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<tr>
<td><strong>Population-based cohort studies</strong></td>
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<tr>
<td>NGPSE (Hart et al., 1990; Sander et al., 1990; Cockerell et al., 1995, 1997; Macdonald et al., 2000; Neligan et al., 2013)</td>
<td>1008</td>
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<tr>
<td>Patients identified through 275 GPs over a 3-year period from 1984, and followed prospectively. At 6 months of follow-up, the patients were categorized into febrile convulsions (220 patients), definite and possible epileptic seizures (564 and 228 patients, respectively), and were followed for a median of 22 years.</td>
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<tr>
<td>Shorvon and Goodridge, 1983</td>
<td>122</td>
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<tr>
<td>Those with a history of at least one epileptic seizure (any type), in a retrospective survey of general population of 6000 persons</td>
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<td>Britten et al., 1986</td>
<td>42</td>
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<tr>
<td>Those with a history of epilepsy reaching the age of 26 years, from a selected prospective cohort study of 5362 patients born in one week in UK in 1946.</td>
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<td>Ross et al., 1980</td>
<td>59</td>
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<td>Those with epilepsy reaching the age of 16 years, from a prospective cohort study of all persons born in one week in 1958 in UK.</td>
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<td>Verity et al., 1992</td>
<td>63</td>
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<tr>
<td>Those with epilepsy reaching their 10th birthday, from a prospective cohort study of 16 004 neonatal survivors.</td>
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<tr>
<td>Forsgren, 1990; Lindsten et al., 2001</td>
<td>107</td>
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<tr>
<td>Those with newly diagnosed unprovoked seizures, at the age 17 years or more, identified prospectively from a variety of sources, over a 31-month period between 1985–1987, in a single district of Sweden. Follow-up was between 1–13 years.</td>
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<td><strong>Cohort studies with cases ascertained through hospital records from a defined population base</strong></td>
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<td>Annergers et al., 1979</td>
<td>475</td>
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<tr>
<td>Patients with unprovoked seizures, ascertained retrospectively between 1935–74 through the Mayo Clinic Record Linkage system and reported in 1979, with all patients having at least 5 years follow-up and 141 patients with 20 years of more.</td>
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<td>Bronson and Wranne, 1987</td>
<td>194</td>
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<tr>
<td>Retrospective study of children between the age of 0–19 years, in a county of Sweden, with an existing diagnosis of ‘active epilepsy’ in 1964, and then contacted 12–13 years later.</td>
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<tr>
<td>Wakamoto et al., 2000</td>
<td>148</td>
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<tr>
<td>Retrospective study of childhood-onset epilepsy with mean history of 18.9 years since onset of epilepsy.</td>
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<td>Sillanpää et al., 1998, 2012; Sillanpää and Schmidt, 2006, 2012; Sillanpää and Shinnar, 2010</td>
<td>144</td>
</tr>
<tr>
<td>Children (under the age of 16 years) with epilepsy developing in 1961–64, identified in a review of case-journals carried out in 1972/3 from hospitals in a region of Finland (Turku), and then followed prospectively every 5 years up to 2002. Epilepsy was defined as more than three seizures occurring over a period exceeding 1 week. Children were excluded who had progressive disease, situational seizures only (including febrile seizures) and who were hospitalized.</td>
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<tr>
<td><strong>Hospital-based cohort studies</strong></td>
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<tr>
<td>Okuma and Kumashiro, 1981 (the group for the study of prognosis of epilepsy in Japan)</td>
<td>794</td>
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<tr>
<td>Retrospective multi-institutional study of childhood-onset epilepsy, 10 years after onset of epilepsy (42% case-ascertainment rate).</td>
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<tr>
<td>Beghi and Tognoni, 1988; Collaborative Group for the Study of Epilepsy, 1992</td>
<td>280</td>
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<tr>
<td>Prospective multicentre hospital clinic cohort study of patients with newly diagnosed seizures aged 2–81 years, with median follow-up of 48 months.</td>
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<td>de Silva et al., 1996</td>
<td>167</td>
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<tr>
<td>Patients with newly diagnosed epilepsy, aged 3–15 years, identified between 1981 and 1987, and followed for a median of 44 months.</td>
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<tr>
<td>Oka et al., 1989</td>
<td>730</td>
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<tr>
<td>Retrospective study of patients with childhood onset epilepsy 10–15 years after the initial diagnosis (56% case ascertainment rate).</td>
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<td>Musicco et al., 1997</td>
<td>419</td>
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<tr>
<td>Patients aged 2 years or more, seen in 35 hospitals within 7 days of first unprovoked tonic-clonic seizure, and followed prospectively for a median of 3 years.</td>
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<tr>
<td>Heller et al., 1995</td>
<td>243</td>
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<tr>
<td>Patients with newly diagnosed epilepsy, aged 16 years or over, identified between 1981 and 1987, and followed prospectively for a median of 30 months.</td>
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<tr>
<td>Kwan and Brodie, 2000; Mohanraj and Brodie, 2006; Brodie et al., 2012</td>
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<tr>
<td>Patients with newly diagnosed epilepsy, aged 9–93, recruited between 1982–2006, and followed prospectively for a median of 7.5 years.</td>
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(continued)
2–4 years. Sixty-seven per cent [confidence interval (CI) 63–71%] had a recurrence within 12 months of the first seizure, and 78% (74–81%) had a recurrence within 36 months (figures similar to those in the Tonbridge study). Seizures associated with a neurological deficit presumed present at birth had a high rate of recurrence (100% by 12 months), whereas seizures that occurred within 3 months of an acute insult to the brain, such as head injury or stroke, or in the context of an acute precipitant such as alcohol, carried a much lower risk of recurrence (40%, CI 29–51%) by 12 months. The other factors affecting the risk of recurrence were age with the highest risk being for patients under the age of 16 (83%, CI 77–89%) or over the age of 59 (83%, CI 76–90%), and type of first seizure, with the risk of recurrence of simple partial or complex partial seizures (94%, CI 90–99% by 36 months) being higher than that for generalized tonic-clonic seizures (72%, CI 67–77%). The risk of recurrence after a first seizure had been variously reported and the overall figure here (78%) was higher than any other previous estimate, and this was taken to reflect the completeness of the information received.

The paper also made, for the first time, the important point that the reported rates of relapse depend on the time after the first seizure (Fig. 1). Most relapses occur soon after the first seizures, and the longer the patient remains seizure-free the less likely is a relapse. Thus, the hazard rate (HR) for seizure recurrence (i.e. the percentage risk of having a recurrence) was 0.033 (95% CI 0.030–0.036) per week in the 6 months after the first seizure, 0.007 (95% CI 0.005–0.010) per week in 6–12 months, and 0.004 (95% CI 0.003–0.005) per week in the next 24 months. The overall relapse rate at 3 years after the first seizure was 78%, but this fell to 44% (95% CI 33–55%) if a patient had no relapse in the first 6 months, to 32% (95% CI 18–46%) if the patient had no relapse after 12 months, and to 17% if there was no relapse in the first 18 months. It was largely on the basis of this study that the UK driving laws changed to allow licensing after an elapsed 12-month period after a single attack.

The first major studies of longer-term of prognosis and mortality were published in 1995 (Cockerell et al., 1995, 1997). At this stage, only 33 patients of the total 792 patients with definite or possible epilepsy were completely lost to follow-up—a reflection of the effectiveness of the methodology of the study, and the efficiency of the system for tracking patients as they moved locations and GPs. Eighty-six per cent (95% CI 81–90) of patients with definite epilepsy had achieved a remission of 3 years, and 68% (95% CI 61–75), had achieved a remission of 5 years (and slightly higher figures if patients with possible/probable epilepsy were included). The rate increased to 87% (95% CI 83–91) for 3-year remission and 71% (95% CI 65–77) for 5-year remission. The proportion of patients with definite epilepsy who were still in remission at 9-year follow-up (terminal remission) was 68% (95% CI 62–74) for 3-year remission and 54% (95% CI 48–60) for 5-year remission. Remission rates were greatest for those with idiopathic epilepsy (69%: 95% CI 60–77). Age and seizure type had small effects on the chances of achieving remission, with children experiencing slightly lower rates than older patients, and partial seizures having lower remission rates than generalized seizures. The latest follow-up data from the study are in the process of publication, and at a median follow-up of 22 years, 84% of surviving patients with definite epilepsy were in terminal remission (Neligan et al., 2013).
NGPSE: the influence of seizure density on long-term remission. The percentage of patients achieving remission in those who had experienced one (dashed line), two (solid line), five (dotted line), or 10 (dashed and dotted line) seizures in the period from the index seizure to 6 months.

MacDonald et al. (2000) analysed the factors predicting outcome (remission versus relapse) using the Cox proportional hazards regression model. The dominant clinical feature predicting remission was found to be the number of seizures in the first 6 months after notification to the study (the seizure density) and this important finding has been replicated in other studies carried out since. Thus for a patient who had two seizures during this initial 6 months, the chance of entering 1 year of remission by 6 years was 95% and 47% for a 5-year remission, in contrast with 75% for 1 year of remission and 24% for 5 years of remission if there had been 10 or more seizures during this period (Fig. 2).

The findings from these studies, which have been influential, are: (i) the prognosis of newly diagnosed epilepsy is better than often thought; (ii) that the early course of epilepsy is important in determining prognosis; (iii) the number of seizures (the seizure density) in the early phase of epilepsy is the single most important predictive factor for both early and long-term remission of seizures; and (iv) the longer seizures continue, the worse is the long-term prognosis. These findings have become part of the orthodoxy of epilepsy.

Findings in relation to mortality

In 1994, the mortality rates of the NGPSE were published for the first time (Cockrell et al., 1994a). This was a time when interest in mortality had been ignited by the focus on sudden unexpected death in epilepsy (SUDEP) and the opinion that epilepsy was perhaps, in mortality terms, not as benign as once thought. At this stage, the median follow-up of the cohort was 6.9 years. The standardized mortality rate (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 definite epilepsy. The SMR was highest during the first year after diagnosis 5.1 (95% CI 3.8–6.5), declined to 2.5 (95% CI 1.5–3.9) at 3 years, and 1.3 (95% CI 0.7–2.0) at 5 years. The SMR for patients with idiopathic epilepsy was 1.6 (95% CI 1.0–2.4), remote symptomatic epilepsy 4.3 (95% CI 3.3–5.5), and acute symptomatic epilepsy 2.9 (95% CI 1.7–4.5). It was recognized therefore that rates of mortality were indeed higher in patients with newly-diagnosed epilepsy, but that this was largely due to the underlying cause.

In 2001, at a median follow-up of 11.8 years, a total of 11400 person-years, data were considered sufficient for a detailed analysis of mortality in early epilepsy (Lhatoo et al., 2001a). The SMR was 2.1 (95% CI 1.8–2.4). Patients with acute symptomatic epilepsy (SMR 3.0; 95% CI 2.0–4.3), remote symptomatic epilepsy (SMR 3.7; 95% CI 2.9–4.6), and epilepsy due to congenital neurological deficits (SMR 25; 95% CI 5.1–73.1) had significantly increased long-term mortality rates, whereas patients with idiopathic epilepsy did not (SMR 1.3; 95% CI 0.9–1.9). This increase in mortality rate was again noted particularly in the first few years after diagnosis and it is likely that this is because the contribution of the underlying cause of the epilepsy to the mortality rates is greater than that of the epilepsy itself. Multivariate Cox regression and time-dependent covariate analyses were used for the first time in a prospective study of mortality in epilepsy, and showed those with generalized tonic-clonic seizures to have a higher risk of mortality, and highest risks in those with cerebrovascular disease (HR 2.4; CI 1.7–3.4; P < 0.0001), CNS tumour (HR 12.0; 95% CI 7.9–18.2; P < 0.0001), alcohol (HR 2.9; 95% CI 1.5–5.7; P = 0.004), and congenital neurological deficits (HR 10.9; 95% CI 3.2–36.1; P = 0.003) as causes for epilepsy and an older age at index seizure (HR 1.9; 95% CI 1.7–2.0; P < 0.0001). Seizure recurrence (HR 1.30; 95% CI 0.84–2.01) and antiepileptic drug treatment (HR 0.97; 95% CI 0.67–1.38) did not influence mortality rate. There were only five epilepsy-related deaths (one each of SUDEP, status epilepticus, burns, drowning and cervical fracture), suggesting that death directly due to epileptic seizures is uncommon in a population-based cohort with epilepsy.

In 2004, a parametric survival model based on the Weibull distribution was devised by the statistician of the study, Dr A.J. Johnson, to look at life expectancy in epilepsy and used this to study the NGPSE cohort (Gaitatzis et al., 2004). This was the first time that life expectancy had been reported in any epilepsy cohort and the information is useful for predicting prognosis in clinical and legal settings. By then the mean follow-up of the cohort was ~15 years. Life expectancy was estimated as a function of age at, and time from, diagnosis according to two broad aetiological groups. These estimates were then compared with life expectancy in people of the same age and sex in the general population. Reduction in life expectancy was found to be up to 2 years for people with a diagnosis of idiopathic/cryptogenic epilepsy, and up to 10 years in people with symptomatic epilepsy. Reductions in life expectancy were found to be highest at the time of diagnosis and diminish with time. A second paper (Neligan et al., 2011) analysed mortality when the median follow-up was 22.8 years. By then there had been 300 deaths in those with definite or possible seizures. Death certificates were obtained for all but three of those who died. The overall SMR for those with definite epilepsy was 2.55 (95% CI 2.24–2.91). Pneumonia and cerebrovascular disease were the causes of death with the most consistently elevated SMRs throughout follow-up. It was noteworthy to see again that few people died from epilepsy-related causes. The SMR remained elevated even in those alive at
20 years, despite the fact that most of the cohort was in terminal remission (defined as 5 years or more seizure-free, on or off antiepileptic medication). This is an unexpected finding that requires further exploration.

**Findings in relation to treatment patterns**

In 2001, the patterns of treatment in the cohort were first analysed and published in detail at a time when the follow-up of all patients was between 11–14 years (Lhatoo et al., 2001b). Treatment had been started in 433 (77%) patients who had developed seizures. Only 15% of single seizure patients had medication prescribed initially, although due to high seizure recurrence, >70% ultimately received antiepileptic medication. At the time of follow-up 37% of the patients were still on drug therapy for epilepsy (30% had been continuously on medication and another 7% had restarted drug therapy having previously withdrawn medication). Forty-seven per cent of those on treatment were in 5-year terminal remission. Nine of 31 (29%) patients with one or more seizure a week at last follow-up had never tried a second drug and only seven (23%) had tried four or more drugs. It was concluded that there was considerable room for improvement in prescribing practice in the UK, that therapy was often not appropriately or consistently applied and that there were too few drug changes made in patients with ongoing and sometimes frequent seizures. It was also noted that the chances of remission fell with each treatment change, an observation often repeated since.

**Long-term prognosis of febrile seizures**

Macdonald et al. (1999) published the prognosis of the 220 children in the NGPSE cohort who were registered with febrile convulsions (median follow-up of 11.2 years, minimum of 8.4 years). In this cohort, 6% of the children developed subsequent epilepsy, which compares with a population risk of 1.4%. Ten per cent had neurological sequelae. Eleven per cent of the children had received medication to prevent recurrence of febrile convulsions, and in one-third of these cases, this was for simple febrile convulsions. The more febrile convulsions that occurred, the more likely was subsequent epilepsy in this cohort, but there was no association found between complex febrile convulsions and subsequent epilepsy. It was noted at the time of the first febrile convulsion (1984–87), about one-third of patients were treated with prophylactic antiepileptic drugs, a practice now not encouraged. By 2012, with a mean follow-up of 21.6 years, information was available in 83% of the original cohort, the rate of those developing epilepsy was still 6% (by then a 10-fold increase over that of the general population (SMR 9.7, 95% CI 5.7–16.4) (Nelligan et al., 2012).

**Other findings**

Apart from the findings in relation to prognosis, a number of other investigations were carried out in this cohort. The social and psychological effects of newly diagnosed epilepsy in this cohort were published in 1992 (Chaplin et al., 1992, 1993). Pilot work was carried out to devise a questionnaire through a series of structured interviews, based partly on the Washington psychosocial inventory, but subjects were also encouraged to talk freely about psychosocial problems. This pilot lead to the identification of 21 areas specifically relevant to psychosocial adjustment in epilepsy, and on the basis of these interviews a new attitude questionnaire was constructed for use in a postal survey. The questionnaire was then sent to 216 patients in the study, of whom 192 (89%) responded. Problems in at least one area were experienced by 175 (91%) of the 192 subjects, but these were generally rated as mild. It was in only four areas that >10% of subjects found severe problems. These four areas were: fear of seizures, fear of stigma in employment, adverse effects on leisure, and lack of energy. It was noted that the generally slight impact of newly diagnosed epilepsy strongly contrasted with that commonly reported in chronic cases. A highly significant relation was also found between psychosocial effects and both the frequency and recency of seizures. It was concluded that in the early stages of epilepsy, the stigmatizing effect of the diagnosis is less important than previously thought. Furthermore, the diagnosis by itself did not seem to lead to high levels of maladjustment (i.e. stigma). The psychosocial impact was related to the severity of the medical condition, and it was also concluded that the psychosocial problems of epilepsy evolve as the condition becomes chronic.

Manford et al. (1992a) published an analysis of type and anatomical location of partial seizures in the cohort. Manford et al. (1992b) also looked at whether the International League Against Epilepsy classification of Epilepsies and Epilepsy Syndromes was useful at a population level. An analysis of the direct health costs of epilepsy in the cohort was also calculated, amounting then to £611 per annum (US$917) (Cockerell et al., 1994b).

Finally, one other noteworthy achievement of the NGPSE has been its research training and its role in advancing the career of a number of junior research fellows recruited into the study. Research degrees from the study were completed by six junior fellows, all of whom have had a continuing involvement in epilepsy and epilepsy research. One is now professor of clinical epilepsy (J.W.A.S. Sander) and another a professor of neurology in Cleveland USA (Sam Lhatoo), one a consultant neurologist and Hospital Trust clinical director (Mark Manford), and three are British-based consultant neurologists (Yvonne Hart, Charles Cockerell and Bridget MacDonald). Such a training role is vitally important in any medical research programme.

**The end of the National General Practice Study of Epilepsy**

The NGPSE has now run into bureaucratic hurdles due to the changing governance arrangements for research. Ethics Committee (IRB) approval had been obtained at the beginning of the study, which did not require patient consent for the anonymized prognostic data to be collected (from the GPs). On the basis of the Health and Social Care Act of 2001, however, we were advised in 2007 that the study no longer had authorization to collect clinical data on patients from their GPs without patient consent, and that we needed to apply to the Patients Information Advisory Group (PIAG; a government appointed committee), to gain exemption from this provision. After 8 months of debate, the PIAG did agree to provide exemption, but: (i) only on people who were in long remission and who were not taking antiepileptic drugs, and for all other patients, consent was needed to complete the questionnaire; (ii) only data on seizure frequency and
antiepileptic drugs taken, and not any of the other routine data on co-morbidities and other medical details; and (iii) that all records should be destroyed after a final round of data collection is completed.

Restrictions (i) and (ii) seemed arbitrary and to lack logic and yet they have reduced the data collection to a rump of what had previously been collected. Restriction (iii) has resulted in the premature termination of the study. Furthermore, in Scotland, additional logistical requirements were requested, rendering the issues of data collection too great to be feasible, so patients based in Scotland had to be excluded. We can not see any advantage to these restrictions, as all patient data were anonymized and the risk to confidentiality was minimal. Yet, they have resulted in a loss of data on the course of epilepsy and the long-term co-morbidities in people with epilepsy (particularly unfortunate as the latter may have shed some light on the persistently high mortality rate). An unthinking approach to medical governance by appointed bodies such as the PIAG, lead to a defensive view of research that has greatly harmed large-scale epidemiological studies in Britain, a country that previously led in this area. A prospective 30-year follow-up of a large cohort of people with epilepsy has never been reported in the past; and because of this approach, the opportunity for us to report this has been lost.

Other cohort studies of prognosis in epilepsy from the time of diagnosis

Other cohort studies from the time of diagnosis have been reported in the past three decades, which provide data on the prognosis of newly-diagnosed epilepsy. These can be broadly divided into those that are: population-based, clinic-based but from a defined population, and clinic-based without a defined population (Table 1). The early population-based studies were based on registries that were established to study health and development more broadly, and from which epilepsy data were extracted retrospectively (Ross et al., 1980; Britten et al., 1986; Verity et al., 1992). These have epidemiologically-valid population-based methodology, but because epilepsy was not the main focus of the studies, the number of epilepsy cases in each study is small. Some valuable prognostic data have been obtained but not in the same detail as the studies primarily concerned with epilepsy. The first such study, the National Survey of Health and Development study, was a survey initiated in Britain of a cohort of 5362 selected individuals born in the first week of March 1946, and followed by at least 2-yearly enquiry. Fifty-five persons who had had two or more non-febrile epileptic seizures by the age of 26 years were identified (84% of those patients living in Britain were contacted) and data were available on 42 of whom 12 had died and 24 were still on anticonvulsant therapy, which was taken as a surrogate measure of prognosis (Britten et al. 1986). The National Child Development study was a prospective cohort study of all persons born in one week in March 1958, followed at the ages of 7 and 11 years of age. At the age of 11 years, of 15,496 children studied, 1,043 reported a history of seizures or other episodes of loss of consciousness (Ross et al., 1980). A clear-cut diagnosis of epilepsy, defined as two or more spontaneous non-febrile seizures, was established in 64 children (a prevalence rate of 4.1/1000) of whom 59 took part in a follow-up study in their 16th year. Of these, 29 of 59 (49%) had had at least one further seizure in the previous 5 years (and 21 in the previous 12 months). The Child Health and Education Study was another long-term British cohort study of 16,004 neonatal survivors born in one week in April 1970. Eighty-four children were identified who had had one or more afebrile seizures (incidence 5.7/1000). Sixty-three children had more than one afebrile seizures (therefore categorized as a having a diagnosis of epilepsy; incidence 4.3/1000) (Verity et al., 1992), and at the age of 10 years, 22 of 59 (37%) of the children alive with a diagnosis of epilepsy were in an at least 2-year remission. Forsgren et al. (1990) and Lindsten et al. (2001) carried out a population-based study in 107 adult patients with unprovoked seizures, from one location (Västerbottens county) in Sweden. The prognosis of these cases was ascertained in 1996 by medical file review and telephone or postal interview. Follow-up varied from 1–12 years, exceeding 5 years in 80% of the cohort and 10 years in 35% of the cohort, and cumulative 1-, 3- and 5-year remission rates of 68%, 64% and 58%, respectively were found (Lindsten et al., 2001).

Hospital clinic-based studies in a defined population can be considered as an approximation to an epidemiologically-valid population-based study when all patients in a region developing seizures are referred to the hospital clinics engaged in the study, with the advantage of larger recruitment than the registry-based cohort population studies. This situation usually applies in small towns in rural locations in which there is a well-developed health service, and two such studies from Scandinavia have been carried out. In Sweden, Bronson and Wranne (1987) reported long-standing remission in 124 (64%) of 194 children after 12–13 years follow-up with neurodeficit, frequent seizures, and multiple seizure types as features associated with poor prognosis. Wakamoto et al. (2000) reported the prognosis of 148 patients from their institution (Uwajima City Hospital), which was said to cover 97% of the population and thus be close to a population base, identified over a 30-year period, and found a 62.8% 5-year remission rate after a mean 18.9 years after the onset of epilepsy. In the study from Turku referred to above, 144 children were followed for a median of 37 years from the initiation of therapy (19–47 years; by 5-yearly enquiry) (Sillanpää et al., 1998; Sillanpää and Schmidt, 2006). The patterns of seizure recurrence were studied (as in the Tonbridge studies; Shorvon and Goodridge, 1983). The authors reported that 82% entered a 5-year remission in 60% of whom no relapse occurred and in total 67% were in terminal remission of at least 5-years. Early 5-year remission, defined as that starting within the first year of treatment, occurred in 31% and in 16% the first remission continued, uninterrupted by relapse, to terminal remission. Late remission with a mean delay of 9 years was achieved by a further 50% of patients including 32% who achieved terminal remission without any subsequent relapse. Following a relapse after early or late remission, 19% of patients achieved terminal remission, suggesting a remitting-relapsing pattern. Fourteen per cent of patients did not re-enter remission indicating a worsening course of epilepsy, and 19% of patients never achieved a remission. A subsequent analysis of the initially drug-resistant cases (110 of the cohort of 245 cases) showed that
eventually 51% were in a 5-year or more terminal remission (Sillanpää and Schmidt, 2012). Brodie et al. (2012) have subsequently used a similar method to analyse seizure patterns in his hospital-based cohort. The results from these studies are broadly confirmatory of those from the Tonbridge study.

Other hospital-based studies focusing on prognosis include the Dutch Study of Epilepsy in Childhood (Callenbach et al., 2001; Geerts et al., 2010), which found a 5-year terminal remission rate of 71% at mean follow-up of 14.8 years, a retrospective multi-institutional study from Japan that found a remission rate of 56% after 10 years after the onset of epilepsy in the 42% of the cohort whose data could be found (total at 10 years of 794 patients; Okuma and Kumashiro, 1981), and in a study from Okayama (Oka et al., 1989) a 79.1% 5-year remission rate 10–15 years after the onset of epilepsy in 56% of the cohort whose data could be found (730 children).

A further type of prospective cohort studies from hospital-based clinics have been reported that are focused on response to treatment (usually initial monotherapy). These have the disadvantages of being relatively short-term and also not being primarily concerned with ‘prognosis’, but nevertheless are included in this review as they are cohort studies and do provide some synoptical prognostic information. They have the advantage of specialist assessment of all patients and regular more intensive follow-up, and thus with a potentially higher quality of follow-up data than in some of the population-based studies mentioned above. The first such study was the Collaborative Group for the Study of Epilepsy, a prospective multicentre hospital-based study from Italy (Beghi and Tognoni, 1988; Collaborative Group for the Study of Epilepsy, 1992). In this investigation, a cohort of 280 patients with previously untreated epilepsy were followed for a median period of 48 months. One-year remission rates were reported in 62% of patients by 1 year, 81% by 2 years, 92% by 3 years, and 98% by 5 years. In a variant of this design, the FIRST study (First Seizure Trial: Musicco et al., 1997) was conducted primarily to determine whether long-term prognosis differed if first tonic-clonic seizures were treated or not. The study reported 83–87% rates of 1-year remission and 60–68% rates of 2-year remission following a first unprovoked seizure in patients followed for 3 years. A series of hospital studies of antiepileptic drug treatment in newly diagnosed patients with epilepsy have been conducted, led by Dr E.H. Reynolds (Reynolds et al., 1976; Shorvon et al., 1978; Shorvon and Reynolds, 1982; Elwes et al., 1984; Reynolds, 1987, 1990; Heller et al., 1995; de Silva et al., 1996). These were designed primarily to investigate the response to monotherapy with specific drugs, but in doing so have also provided some prognostic information on the early course of epilepsy, with 60–90% of patients entering terminal remission after initiation of monotherapy treatment, and followed for various time periods. Heller et al. (1995) reported that 75% of patients had entered an at least 1-year remission by 3 years of follow-up and de Silva et al. (1989) a 73% 1-year remission in children by 3 years. Other hospital-based studies reported similar findings (Callaghan et al., 1978, 1985). In the longest running cohort studies of this nature, led by Brodie in Glasgow, patients with newly diagnosed epilepsy were recruited into a variety of new drug and other trials. At the time of the latest publication (Brodie et al., 2012), 68% of 1098 patients, with a median follow-up of 7.5 years, were in terminal remission. In this study, the frequency or methods for follow-up are not stated. The MESS study (MRC Multicentre trial for Early Epilepsy and Single Seizures; Marson et al., 2005) followed a cohort of patients, allocated to a strategy of immediate or deferred antiepileptic drug treatment, with the primary purpose of examining whether the choice of treatment strategy influenced median-term prognosis (cases reported by >250 doctors from 13 countries). Patients with newly diagnosed and early epilepsy (n = 1142) were followed for a median of 4.4 years, and 94–98% were found to have experienced at least one 2-year remission period at 8 years of follow-up, and 76–77% were free of seizures for at least 3–5 years, 5 years after randomization. The SANAD study (Standard and New Antiepileptic Drugs) was a similar large multicentre study looking at the median term response to monotherapy with one of six drugs. Among 2430 patients, 2040 were newly diagnosed. At a follow-up of 5 years (albeit, a follow-up that only ~10% of the patients reached) 12-month remission rates of ~75–87% were recorded.

Problems with evaluating or comparing such studies include the large variations in methodology and in recruitment and the fact that inclusion criteria vary, notably whether those with provoked or acute symptomatic seizures, febrile seizures or single seizures are included, different age ranges and whether epilepsy due to progressive disorders are included. Variation in all these factors will influence prognosis, with remission rates amongst those with acute symptomatic and febrile seizures, for instance, significantly higher. Those with neurodeficit or learning disabilities also have lower remission rates, and if a study is biased towards these groups, then the reported rates of seizure remissions will be lower. In childhood-onset epilepsy too, different remission rates will be found in different syndromes. All these factors reflect the heterogeneity of ‘epilepsy’. Nevertheless, a clear picture emerges from all these published investigations, which is largely concordant with that found in the NGPSE and the Rochester and Tonbridge studies, and the summary findings from these studies are discussed in the next section.

One postulate, proposed on the basis of the much better prognosis in newly diagnosed cases, was that early control of seizures resulted in better long-term seizure control (Shorvon, 1984; Reynolds, 1990). This was addressed by a multicentre clinic-based study in Italy of first tonic-clonic seizures (Musico et al., 1997) and then a large randomized multicentre study from Britain (the MESS study; Kim et al., 2006; Marson et al., 2006), both finding that the timing of treatment at the onset of epilepsy had no effect on long-term prognosis. No population-based study has addressed this issue, although some information can be gathered from studies of prognosis and of response to treatment in developing countries, where many patients are identified who have been untreated for years. In these studies from a variety of developing countries, rates of remission on treatment have been found to be as high as in the studies from Western populations even in patients who had been previously left untreated for many years (Feksi et al., 1991; Placencia et al., 1993; Kwan et al., 2013).

The risk of mortality in epilepsy has also been the subject of study. In the Mayo Clinic study, an overall SMR of 2.3 was reported (Hauser et al., 1980). The NGPSE reported an overall SMR...
of 2.6 (95% CI 2.1–3.0) with a median prospective follow-up of 22.8 years (Neligan et al., 2011). Standardized epilepsy mortality ratios were found to be elevated to the greatest extent in the early years after diagnosis, reflecting the deaths caused by the underlying causes (tumour and cerebrovascular disease for instance) but remained persistently elevated in later years, even though many patients were in long remission. The mortality rate in the cohort of 245 children followed by Sillanpää et al. (2010) mentioned above has also been reported. A rate of death of over three times that expected was found, with 18 deaths assumed to have been due to SUDEP. There have been three other prospective population-based cohort studies of mortality in epilepsy (Loiseau et al., 2000; Lindsten et al., 2000; Ding et al., 2013) and three based on case-record cohorts (Hauser et al., 1980; Olafsson et al., 1998; Camfield et al., 2002) reporting similar overall SMRs (between 1.6 (95% CI 1.2–2.2) and 4.1 (95% CI 2.5–6.2)). A study of changes in mortality over recent decades did not find any differences (Neligan et al., 2011). Interestingly, although much of the focus in the field of epilepsy mortality has been on SUDEP (see Shorvon and Tomson, 2011 for a review) only one of the 300 deaths in the NGPSE was due to SUDEP (Lhatoo et al., 1999), an annual rate of death due to SUDEP of 0.09 per 1000 (after 11 400 years of patient follow-up; Lhatoo et al., 2001a). Other population-based samples have found rates of SUDEP between 0.94–2.3 per 1000 persons (Terrence et al., 1975; Leestma et al., 1984, 1989; Jick et al., 1992; Tennis et al., 1995; Ficker et al., 1998; Langan et al., 1998; Opeskin et al. 2003; Ding et al., 2013). There have been two notable clinic-based prospective cohort studies of new-onset epilepsy in children (613 children, Berg et al., 2004; 472 children, Callenbach et al., 2001) both of which found a higher death rate than expected (SMR of 7.54 and 7, respectively), but this was almost entirely due to the underlying cause of the epilepsy. In the Dutch study for instance, there were no deaths in the non-symptomatic cases and a 20-fold increase in the rate of death in the symptomatic cases. The NGPSE is also the only study that has also provided life-expectancy figures on epilepsy (Gaitatzis et al., 2004) and these are useful in clinical and medico-legal practice as the only data on this topic.

The NGPSE also looked at the long-term prognosis of febrile seizures. Six per cent of the 220 children in the NGPSE cohort developed subsequent afebrile seizures compared with an expected rate in a similar population of ~1.4% (Macdonald et al., 1999). A figure of 2.3% was found in the Mayo Clinic study (Hauser and Kurland, 1975). In an early population-based study of 1706 children with febrile seizures, including those with neurodeficit before the febrile seizure, epilepsy had developed by 7 years of age in 2%, and another 1% had had at least one afebrile seizure (Nelson and Ellenberg, 1976). Since then, 33 other studies (Pavone et al., 1993; Rosman et al., 1993; Verity et al., 1993; Laditan, 1994; Neo et al., 1995; Tsai and Hung, 1995; Berg and Shinnar 1996; Miyake et al., 1996; van Esch et al., 1996; Forsgren et al., 1997; Hackett et al., 1997; El-Radhi, 1998; Tarkka et al., 1998; Macdonald et al., 1999; Pavlovic et al., 1999; Chang et al., 2000; Sapir et al., 2000; Kjeldsen et al., 2002; Mauceri and Pavone, 2002; Piperidou et al., 2002; Borusia and Herbold, 2003; Tarkka et al., 2003; Lee and Ong, 2004; Metsärinta et al., 2004; Okumara et al., 2004; Vestergaard et al., 2004, 2007; Yücel et al., 2004; Birca et al., 2005; Yu et al., 2007; Hussain et al., 2008), both community and hospital-based, have reported rates of seizures and epilepsy after febrile seizures, and these and the NGPSE findings were reviewed by Chungath and Shorvon (2008). Among the 4160 patients who had febrile seizures in these studies, 241 (5.8%) later developed afebrile seizures. Twenty-three studies described the risk of epilepsy in patients who had one or more febrile seizures. An interesting comparison can be made between the hospital-based studies that reported risks of epilepsy ranging from 0.1–32%, and the population-based studies that reported risks of 2–7%, showing the importance of selection bias. The largest and most impressive study has been a Danish, population-based, prospective study of a cohort of 1.54 million individuals born in Denmark during 1978–2002 (Vestergaard et al., 2007). Only 13% of patients with epilepsy in this study had a previous history of febrile seizures. After 23 years of follow-up, the overall cumulative incidence of epilepsy was 6.9% for patients with febrile seizures, compared with only 1.8% for those without a history of such seizures. The rate of epilepsy was higher in those developing febrile seizures before the age of 1 year or after the age of 3 years and in those with complex febrile seizures.

A major transformation in the epidemiological studies over the course of the three decades of the study has been the establishment of large computer data sets—an advance made possible only by increasing computing power, the computerization of GP or other community-based record systems, and the availability of searchable databases. In Britain, the General Practice Research Database (GPRD) for instance is the largest database of anonymized longitudinal primary care medical records (this has been recently renamed the Clinical Practice Research Datalink). It is managed by the Secretary of State for Health and contains over 3 million active patient records drawn from ~400 primary care practices in the UK. It provides an automated alternative to such studies as the Tonbridge study (which had to be conducted by a manual search of the GP records) or the Mayo Clinic Record Linkage System (which was based on a card index). Similar large databases of public hospital admissions data are available in many countries. These large databases have largely replaced the type of manual follow-up of the NGPSE and other older studies, and have the advantages of much larger numbers and much wider scope. The GPRD has been used in epilepsy, for instance, to look at incidence and prevalence, mortality, fracture risk, teratogenicity, medication and the co-prescription of pro-convulsant drugs and anti-convulsant drugs, and of enzyme-inducing antiepileptic drugs and the contraceptive pill (Derby et al., 1996; Wallace et al., 1998; Shorvon et al., 2002; Cleary et al., 2004; Souverein et al., 2005, 2006; Charlton et al., 2010, 2011; Ridsdale et al., 2011; Nicholas et al., 2013). However, no large-scale cohort study of prognosis has yet been reported, and this would be an important and interesting investigation.

Summary of conclusions from cohort studies

The conclusions relating to the prognosis of course of epilepsy, deriving from the cohort studies and which are now fully accepted, can be summarized as follows: (i) epilepsy has an often

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good prognosis with 65–85% of cases eventually entering long-term remission, and an even higher proportion of cases entering a short-term remission; (ii) the likelihood of long-term remission of seizures is much better in newly diagnosed cases than in patients with chronic epilepsy; (iii) the early response to treatment is a good guide to longer term prognosis (although not inevitably so, as in a minority of cases seizure remission can develop after prolonged activity) (Shorvon and Luciano, 2007; Sillanpää and Schmidt, 2012); (iv) the longer is the remission (and follow-up), the less likely is subsequent recurrence; (v) the longer an epilepsy is active, the poorer is the longer term outlook; (vi) delaying treatment, even for many years, does not worsen long-term prognosis; (vii) the ‘continuous’ and ‘burst’ patterns are more common than the ‘intermittent’ seizure pattern; (viii) epilepsy has a mortality that is highest in the early years after diagnosis, and in the early years is largely due to the underlying cause, however, higher mortality rates than expected are observed throughout the course of an epilepsy; (ix) the prognosis of febrile seizures is generally good, with ~6–7% developing later epilepsy; and (x) clinical factors associated with outcome have been well studied, and those consistently found to predict a worse outcome include: the presence of neurodeficit, high frequency of seizures before therapy (seizure density), poor response to initial therapy, some epilepsy syndromes.

Unresolved questions

Several aspects of prognosis in epilepsy have not been fully resolved by any of these studies. One outstanding issue concerns the natural history of untreated epilepsy—and the proportion of patients in whom epilepsy remits without treatment (Shorvon, 1984; Shorvon and Luciano, 2007; Sillanpää and Schmidt, 2012). The extent of ‘natural’ remission is unknown, yet this figure is obviously important when assessing the role and true effectiveness of therapy. The definitive method to determine this would be to compare prospectively the outcome in a randomized treated and untreated group, but this is equally obviously unethical. Observations in populations where health care availability is limited (usually rural areas in under-developed countries) have suggested that a significant number of individuals in a community do develop epilepsy, which then remits without treatment, but complete information on this point is limited (Watts et al., 1992; Keranen and Reikkinen, 1993; Placencia et al., 1994; Nicoletti et al., 2009). It is equally unclear to what extent findings from cohort studies in Western populations will differ from those in other settings.

Another and most important question is that of whether the prognosis of epilepsy is improving due perhaps to the large expansion in the number of antiepileptic drugs now available to treat epilepsy (as suggested by Luciano and Shorvon, 2007). We feel it is likely that prognosis has improved, but there are no definitive data on this point, and this would be an important study to carry out but will require a sophisticated epidemiological approach. In this respect, it is interesting to note that Rodin (1968) noted that studies of prognosis in the 1950s (the period of the introduction of new drugs including phenytoin) showed consistently better results than the earlier investigations. Furthermore, epilepsy is heterogeneous, and some childhood syndromes are self-limiting and others intractable with modern therapy, the prognosis of some syndromes and epilepsy types is not known.

The genetic influences on prognosis have been the subject of much recent interest. Large funding has recently become available particularly to identify the genetic influences on drug response. Clearly there are genetic influences on drug metabolism (especially in relation to hepatic enzyme systems), drug transport and handling and the target receptors of drugs. However, response to drugs is also highly dependent on the site of the epileptogenic lesion, its size and its inherent severity, on age, on medication, on dose, on provoking factors, and other environmental effects, and it seems unlikely to the authors that polymorphisms in single genes will contribute any major insight to the prognosis in any individual patient with non-syndromic epilepsy.

Finally epidemiologically-valid cohort studies have an important role in contributing to an understanding of the development over the life cycle of an epilepsy of the co-morbidities of epilepsy, epilepsy-related disability, and the psychosocial and economic consequences of epilepsy. A better understanding of this would allow focused interventions to prevent these secondary handicaps of epilepsy.

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