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PHENOBARBITAL: THE CENTENARY

How phenobarbital revolutionized epilepsy therapy: The story of phenobarbital therapy in epilepsy in the last 100 years

Zeid Yasiry and Simon D. Shorvon

UCL Institute of Neurology, Queen Square, London, United Kingdom

Summary

Phenobarbital (phenobarbitone) was first used as an antiepileptic drug 100 years ago, in 1912. This article tells the story of the discovery of its antiepileptic action, its early development, and the subsequent course of its clinical use over the 100-year period. The side effects, pharmacokinetics, and misuse of barbiturates are considered, along with the more recent clinical trials and the drug's current clinical utilization. The introduction of controlled drug regulations, the comparative cost of phenobarbital, and its inclusion on the World Health Organization (WHO) essential drug list are discussed. It is one of the few drugs on the formulary in 1912 that is still listed today, and remarkably its efficacy in epilepsy has not been significantly bettered. The current recommendation by the WHO is that phenobarbital should be offered as the first option for therapy for convulsive epilepsy in adults and children if availability can be ensured. This is rated as a strong recommendation because of the proven efficacy and low cost of phenobarbital, and despite its perceived side-effect profile and the practical problems of access. Whether this recommendation puts "a hierarchy on the brain," as has been suggested, is arguable. Much still needs to be learned about the drug's effects, and the issues raised by phenobarbital have lessons for all antiepileptic drug therapy.

KEY WORDS: Phenobarbital, Antiepileptic drugs, History of antiepileptic drug therapy.

Phenobarbital (the International Nonproprietary Name; previously phenobarbitone—the British Approved Name) was identified as an antiepileptic drug in 1912. In the subsequent 100 years, it has remained on the formulary and is still a widely used medicament worldwide. There are only a handful of drugs in orthodox medicine with a longer pedigree—indeed we can find only 12 medicines available then and still on the current national formulary, many now hardly used or for different indications (British Pharmacopoeia, 1914). Phenobarbital ''revolutionized'' therapy, but this has been a slow-burning revolution, with the drug only gradually gaining recognition in the years after its introduction. Having done so, phenobarbital has maintained its prominent position ever since, despite a wide range of competitors. In this article, we review the course of phenobarbital therapy in epilepsy over the last century and draw some general conclusions from this history.

We consider only the clinical aspects. Phenobarbital has had a major effect on the medicinal chemistry of epilepsy, influencing drug discovery and the experimental aspects of epilepsy; these issues are covered in the accompanying articles in this supplement (Bialer, 2012; Löscher & Rogawski, 2012).

The Discovery of Phenobarbital

The story of phenobarbital started with the discovery of the benzene ring, which ushered in a new era of organic chemistry, and had a profound impact on all psychotropic therapy. The ring structure was first published in 1865 by the German chemist August Kekulé (Kekulé, 1865; Fig. 1). Kekulé told the amusing story of this discovery, possibly rather fancifully, at the 1890 meeting of the German Chemical Society. He claimed that at a time he was working on the concept of chemical structures, the idea of a ring came to him while he was dozing by the fire, in a reverie, when he saw ''atoms gamboling before

Address correspondence to Simon D. Shorvon, UCL Institute of Neurology, Queen Square, London WC1N 3BG, U.K. E-mail: s.shorvon@ucl.ac.uk

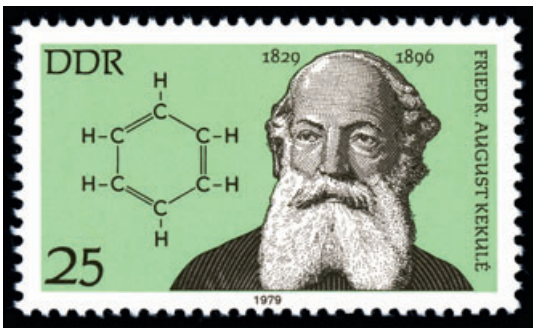

Figure 1.
East German stamp made in memory of August Kekulé.
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my eyes…. Long rows [like snakes], sometimes more closely fitted together…one of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightening, I awoke; and I spent the rest of the night working out the consequences of the hypotheses.'' Barbituric acid was first synthesized by the German chemist Adolf von Baeyer (Kekulé's student), formed by the condensation of urea and malonic acid (von Baeyer, 1864). How the substance was named is not known. One theory is that von Baeyer suggested the name because he synthesized the compound on December 4, 1864, the Feast of Saint Barbara; another is that he synthesized the substance from the urine of a friendly Munich waitress of his acquaintance named Barbara! von Baeyer also synthesized and described the plant dye indigo, and won the 1905 Nobel Prize for chemistry ''in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydro-aromatic compounds.'' Mulder elucidated the ring structure of barbituric acid in 1873, and this allowed derivative structures to be developed. By the end of the 19th century, many barbiturate variants had been made (for review, see López-Muñoz et al., 2005).

The first medicinal use of a barbiturate was in 1903, when Emil Fischer (a student of Kekulé and von Baeyer, and also a Nobel Laureate) and Joseph von Mering discovered that barbital (diethylbarbituric acid) was very effective in inducing sleep in dogs. The commercial opportunity was recognized, and the drug began to be manufactured by Bayer (a pharmaceutical company with no connection to Adolf von Baeyer) under the trade name Veronal, named, it has been said, by von Mering after Verona, the most peaceful town he knew. Veronal rapidly became widely used in the early 20th century as a hypnotic, displacing bromide for this indication. Phenobarbital was synthesized first in 1911 by Hörlein and marketed by Bayer in 1912 under the trade name Luminal, also for its hypnotic properties: note the rapid introduction of a drug into practice that was possible in those days. So successful were the barbiturates that, by 1960, >2,500 barbiturate derivatives had been synthesized, of which 50 had been used in clinical practice (Lennox & Lennox, 1960) as hypnotics, anxiolytics, antiepileptics, anesthetics, and sedatives.

1912–1940: The Early Years of Phenobarbital as an Antiepileptic Drug

The discovery of the antiepileptic action of phenobarbital is another famous story, possibly also elaborated on over time. In February 1912, Alfred Hauptmann, then a young clinical assistant in Freiburg, slept above the ward of patients with epilepsy. Annoyed by being kept awake by the noise of seizures at night, he gave them phenobarbital as a hypnotic and then observed that their seizures were also suppressed. Luminal had only just been licensed at this time, as an hypnotic, but of course there was a long history of the use of hypnotics as antiepileptics (chloral and bromides are examples), and it seems possible that Hauptmann was intending to try the drug as an antiepileptic. Whatever the truth of the story, his monumental article (Hauptmann, 1912) is an example of excellent clinical observation. Hauptmann records that following his first serendipitous observation, he began systematically to examine the potential for phenobarbital. He selected patients with epilepsy who had been at the clinic for many years because of the severity of their illness, who had been unsuccessfully treated with high-dose bromides and for whom there were good records of seizure frequency. He conducted his observations over many months to avoid the random fluctuation of seizures. He prescribed up to 300 mg/day (100 mg a.m. and 200 mg p.m.), a lower dose than that used for night sedation (apparently often up to 600 mg in Hauptmann's clinic). He presented one case of a patient where Luminal was substituted for bromide, and the patient's seizures lessened in frequency and severity, mental agility was enhanced, and the patient's ''state of nutrition and strength improved to a quite extraordinary degree.'' Hauptmann concluded that Luminal was effective in the severest cases of epilepsy that were beyond the influence of even the heaviest doses of bromide. Cases of medium severity could rendered seizure-free with doses between 150 and 200 mg daily; more severe cases never required more than 300 mg daily. He noted that there were no harmful side effects and that Luminal could replace bromide in less severe cases. In 1919, he extended his observations and then recommended phenobarbital for treatment of ''genuine'' epilepsy and also status epilepticus (Hauptmann, 1919).

Unlike the rapid adoption of bromide before, or of phenytoin later, phenobarbital was not quickly taken up internationally. This may have been partly because

Hauptmann's publication was in a relatively obscure German journal, or (more likely) because the 1914–1918 war disrupted international medical communication (and, for instance, resulted in the cessation of all International League Against Epilepsy [ILAE] activity; Shorvon et al., 2009). It was only in the early 1920s that the drug began to be used more widely as an antiepileptic.

In Britain, an early recorded use of phenobarbital was in 1920 in London by Golla (1921). In an excellent study, he compared bromide and phenobarbital in 125 patients and noted only 36 (29%) who were either not improved or their epilepsy worsened when phenobarbital was tried, and commented that it was very well tolerated, and that ''most patients found that they were far brighter and more cheerful after a change to Luminal from bromide treatment.'' He regretted that no English firm has been willing to manufacture ''this important drug,'' which was then obtainable only from Germany; in 1923, the Winthrop Chemical Company began its manufacture in Britain. Gordon Holmes and James Collier were also using the drug in Britain by then, as were others elsewhere (Johnson, 1922). The impact and adoption of phenobarbital in English asylum practice can be observed from the annual reports of the Medical Officer at the Chalfont Centre of the National Society for Epileptics (Shorvon & Sander, 1996). The first record of the use of barbiturates was in the report of 1922 in which it was stated ''During the past 12 months, I have used Luminal sodium 1.5–3 grs [grains; ≈100–200 g] daily usually at night in 50 adult cases, with varying success'' (Brook, 1922, 1923). It was reportedly more useful in major convulsions than in minor attacks, and ''especially valuable for clearing the mentality.'' It was noted to be often effective at low doses; increasing the dose when low doses had been ineffective often did not help. It had not, however, replaced bromide.

The 1926 report gave the first statistics on the effect of Luminal (Haward, 1926). One hundred twenty-four cases had been treated for >6 months, and 46 showed markedly fewer seizures, with some reduction in 58 and no reduction in 20. Haward noted that the mental condition was much improved and the effect was greatest on ''major attacks,'' with a relatively small effect on minor seizures. Two patients with status epilepticus were treated successfully with subcutaneous phenobarbital. The 1928 report issued the following treatment guidelines for newly admitted patients: ''potassium bromide would be given as the treatment of first choice. If after a time there was no diminution of seizures, Luminal would be substituted.'' The patient would be monitored for 3 months and ''if at the end of this time there was little improvement, potassium bromide would be combined with the Luminal.'' Luminal was given at a dose of one grain (65 g) night and morning for adults and half a grain for children. The dose could be titrated upward according to clinical response but should not exceed six grains (≈ 400 mg) a day in any case'' (Haward, 1928).

The drug was also introduced around the same time in the United States. Grinker (1920, 1922), who had emigrated from central Europe, reported his first impressions of the drug in 1920; in 1922 he described its use in 200 cases, showing impressive results in patients with severe epilepsy. Of interest, even by then the drug had a mixed reception, with many practitioners still preferring bromide. In the 1924 book by the Dutch neurologist Muskens, for instance, phenobarbital was mentioned only briefly and listed after bromide and borax, with emphasis more on risks to spinal cord function, its tendency to cause ''apathy,'' and the dangers of status epilepticus on withdrawal. It was listed with other drug-adjuncts such as zinc, nitroglycerin, belladonna, and *Cannabis indica* (Muskens, 1924).

Not much changed over the next 15 years. Lennox (1938, 1939, 1940) published annual reviews of the contemporary literature in *Epilepsia*. In ''Epilepsy in America'' (published in 1938, but actually a review of the literature in the year 1936; Lennox, 1938) he reported studies of bromides, phenobarbital, prominal, antirabies vaccine, ergotamine tartrate, subarachnoid air injections, nondehydrating doses of Epsom salt, x-irradiation, atropine, fluid restriction, and the ketogenic diet. In Lennox (1939) described contemporary treatment in the United States, reporting that phenobarbital, bromide, and borotartrate were the mainstays of treatment, and also listed other old and sometimes bizarre therapies.

The orthodox view of therapy in the pre-phenytoin days can be gauged from Wilson (1940)'s standard (and monumental) textbook, published posthumously in 1940. Wilson considered only bromide and phenobarbital to be first-line therapy. He wrote of phenobarbital that ''although it was at first thought likely to supplant bromide as a remedy of choice, it was not its equal in general applicability,'' and bromide remained his drug of first choice (the ''sheet-anchor on which everyone relies''). Wilson noted the advantage of phenobarbital in terms of an ''absence of mental depression and of a lowering of somatic function,'' but also noted it was susceptible to tolerance, had a narrow therapeutic window, and a risk of status epilepticus on withdrawal. The drug was thus ''best in mild or moderate epilepsies,'' given alone. For the more severe or semi-chronic cases, he recommended its combination with bromide or another sedative (for instance borax); it appears ''to have least value in serial types recurring at longish intervals.'' Other drugs that Wilson recommended were borax (and now its compounds sodium biborate and the double tartrate of borax and potassium) and belladonna, which he considered especially effective in petit mal and when mixed with bromide or Luminal. Bromide, belladonna, and caffeine could be very useful, as was dialacetin (Dial) alone or mixed with allylparacetaminophenol.

Nitroglycerin was also mentioned, sometimes mixed with strychnine and bromide.

So, by 1940, phenobarbital was widely considered—with bromide—a drug of first choice. Which drug took precedence seems to have been a matter of individual preference, but many (perhaps most) physicians used phenobarbital only after bromides have proved ineffective or in combination with bromide. The main characteristics of therapy had been established: a dose of up to 200 mg/day (but usually less), a tendency for it to ''clear the mentality,'' its use parenterally in status epilepticus, its main effect against generalized convulsions rather than complex partial seizures, the risk of severe seizures or status epilepticus on drug withdrawal, and its lower toxicity than bromide. There were no clinical trials with any sort of controlled design; there was little emphasis on side effects and no mention of idiosyncratic or teratogenic effects. Its introduction had reduced almost all other therapies—except borax—to the status of ''adjuncts'' of bromide or phenobarbital.

Phenobarbital in 1940–1975

The world of epilepsy therapeutics was to change radically in this period: the agent of change was, of course, phenytoin. The first eight patients treated with phenytoin were reported in August 1937, and this was then rapidly followed by other larger clinical series, reported in June 1938 at the annual meeting of the American Medical Association (Lennox, 1940; Shorvon, 2009). By 1940, phenytoin was established as one of the drugs of first choice in many countries. This introduction had an interesting effect on epilepsy therapeutics—effectively banishing bromide from anything but occasional use, but interestingly not phenobarbital, which had hitherto been often considered as second line to bromide. Perhaps this was because soon the view arose that the combination of phenobarbital and phenytoin was particularly effective. With bromide now consigned to the margins, phenobarbital was now in conventional textbooks often recommended ahead of phenytoin. For instance, even as late as 1977, the standard textbook of neurology (Walton, 1977) states ''It is usual to begin in an adult with phenobarbitone 20 mg twice daily.'' Walton noted that phenobarbital was used more commonly than phenytoin (or ''even carbamazepine'') but was contraindicated in mentally defective and hyperkinetic children. It was noted that at higher doses, drowsiness was a problem. If phenobarbital did not control seizures, then it was recommended that phenytoin be added. If this did not control seizures, then it was recommended to substitute phenobarbital with primidone. Other drugs still recommended at this time included sulthiame, methoin, ethotoin, and pheneturide. Other ''weaker'' drugs were chlordiazepoxide, diazepam, and beclamide.

This was the age of medicinal chemistry when drug structures could be manipulated. The chemical structure of phenobarbital spawned an entire range of related drugs (Bialer, 2012). Of these, the most important were perhaps primidone, methylphenobarbital, amylobarbital, the thiobarbiturates, the hydantoins, and the succinimides. Despite all this activity though, phenobarbital remained the most prescribed barbiturate, and the workhorse of epilepsy therapeutics.

Side Effects

By the 1920s, phenobarbital was recognized to cause sedation, but remarkably, it was better known, universally, for ''clearing the mentality.'' Of interest, this claim was also made strongly for primidone, thought for many years after its introduction to be less sedative than phenobarbital, until it was recognized that its main metabolite was phenobarbital! We suppose that the ''clearing of mentality'' universally claimed to be due to phenobarbital was due to a reduction in bromide dose when phenobarbital was added as concomitant therapy (as Golla in his 1922 series noted), but it remains an interesting and intriguing observation.

The neurotoxic side effects of phenobarbital, particularly at high doses, were early recognized but were not emphasized much until more recently. This may be because they were less severe than those associated with bromide and because sedation was expected as an integral part of antiepileptic action. By the 1960s, however, it was reported that drowsiness was without doubt the most frequent complaint of patients taking phenobarbital (Livingstone, 1966). Tolerance to the drowsiness was also emphasized (Butler et al., 1954), but often amphetamines were coprescribed with phenobarbital to counteract the sedative effects (and still are). Paradoxical excitation in children was also widely recognized by the 1960s with irritability, belligerence, and hyperactivity (Millichap, 1965; Livingstone, 1966). Other neurotoxic effects such as nystagmus, ataxia, hypotonia, and diplopia were recognized early. The significant risk of severe seizure exacerbation and of status epilepticus on too rapid a withdrawal of phenobarbital were recognized in the 1920s.

One important and still unresolved issue is the extent, if any, of negative effects on learning. Early findings were that phenobarbital therapy improved learning and mental progress (Lennox, 1942), but Wapner et al. (1962) first reported slight negative effects on learning and mental performance. Since then, it has been commonly suggested that phenobarbital impairs learning, but whether this is the case and if so to what extent remains obscure, despite phenobarbital being widely used in children for >100 years.

Exfoliative dermatitis was reported with phenobarbital by Sexton et al. (1941) and Sneddon and Lishman (1952), in a review, found 14 fatal cases. The phenobarbital

hypersensitivity reaction was reported in 1953 (Mcgreachy & Bloomer, 1953). Agranulocytosis was reported in 1937 (Plum, 1937), but by then the risks of blood dyscrasias and marrow aplasia were known to be lower on barbiturate than on phenytoin; most authorities therefore considered the drug ''safe'' in this respect (De Vries, 1965). The first association with megaloblastic anemia was noted in 1956 (Hawkings & Meynell, 1958) and this was more fully elucidated by Chanarin et al. (1960), who also attributed this to folate deficiency. The effects on vitamin K and the risk of neonatal vitamin K deficiency were described in 1958 (Van Creveld, 1958), the ''shoulder-hand'' syndrome in 1966 (Van Der Korst et al., 1966), and osteomalacia in 1968 (Kruse, 1968).

Phenobarbital was recognized early on to be fatal in overdose, with much discussion in the early literature of the risks of high doses causing coma and respiratory depression. However, it was also clear early on that the therapeutic index of phenobarbital was superior to that both of bromide and, later, of phenytoin. Much of the prescribing of phenobarbital remained for its hypnotic and anxiolytic properties and not for epilepsy. By the 1940s, the potential for dependency, addiction, and tolerance were already well recognized in psychiatric practice, at a time when barbiturates were widely misused and casually used for sedation, insomnia, sleep-induction, crisis management, depression, anxiety, and psychopathic disorders. By 1960, the annual consumption of barbiturates in the United States was around 300 tons (Lennox & Lennox, 1960), one presumes mainly for its psychiatric indications, and it accounted for 5% of deaths by poison (1,500 cases).

Reynolds (Reynolds, 1975) pointed out how long it has taken for side effects due to antiepileptics generally to be recognized: this is an important message, as relevant today as previously.

Pharmacokinetics

In the 1950s and 1960s, the science of pharmacokinetics began to be applied to clinical practice, and the metabolic handling of antiepileptics, including phenobarbital, was studied. Methods for measuring serum levels became established in the late 1940s and early 1950s (Butler, 1952; Butler et al., 1954), and there were systematic studies of absorption, protein binding, and rates of metabolism and excretion. The pathways of metabolism were established and the half-life and drug–drug interactions and other pharmacokinetic variables were published. By the early 1960s, serum level monitoring had been adopted in advanced clinical practice. The first published clinical method for measuring phenobarbital was probably by Bush (1961), and gas chromatographic analysis was introduced in 1966 (Anders, 1966). Buchthal et al. (1968) published the first therapeutic range for phenobarbital in 1968, in 11 patients starting phenobarbital monotherapy—and a range of 10–30 μg/ml was postulated in adults with a lower limit of 15 μg/ml suggested for children with febrile seizures (Faerø et al., 1972). A relationship between blood levels and effectiveness and also toxicity was established in various clinical situations over the next decade (Feely et al., 1980; Schmidt et al., 1986). Its drug–drug interactions have been intensively studied, from the late 1960s and early 1970s, for example between phenytoin and phenobarbital (Morselli et al., 1971; Fig. 2).

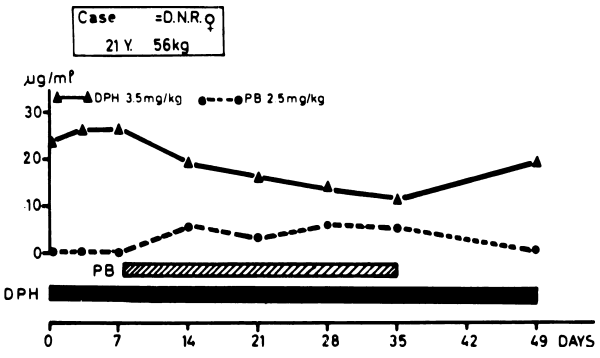

Figure 2.
An early study of the interaction of phenobarbital and phenytoin (from Morselli et al., 1971).
Epilepsia © ILAE

A landmark in this field was the publication of the first edition of *Antiepileptic Drugs* in 1972 (Woodbury et al., 1972; Fig. 3). By then, the essentials of phenobarbital pharmacokinetics were well established. The book included seven chapters on phenobarbital, and covered its chemistry and methods for determination (of blood levels), absorption distribution and excretion, biotransformation, interactions, relation of plasma levels to clinical control and control of seizures, and toxicity. The book thus established the pattern for conveying information about antiepileptics, which remains unchanged to this day.

The next important discovery was the identification of the mechanism of action of phenobarbital at the γ-aminobutyric acid A ($GABA_A$) receptor. This was recognized in the late 1970s, some 60 years after its introduction into clinical practice, and studies continue (Löscher & Rogawski, 2012). The barbiturates as a group also have hypnotic, sedative, and anesthetic actions, and effort has been expended at trying to develop a drug with strong antiepileptic effects but without sedative side effects. These were properties initially claimed for primidone, and then subsequently for other barbiturate derivatives, but nothing to date has bettered phenobarbital in this regard. The introduction of safer hypnotics and anesthetics had lessened the use of barbiturate for these indications, but its use in epilepsy remained.

Figure 3.
Antiepileptic Drugs (First Edition).
Epilepsia © ILAE

Phenobarbital after 1975

Clinical use

Walton, in the 1977 textbook, also mentioned in passing two new drugs: carbamazepine and valproate. In the next few years, these two knocked phenobarbital from its top place, with increasing recognition of their advantages over phenobarbital (and phenytoin). From then on, phenobarbital was recommended as second line in specialist practice, at least in most western countries. Over the last 20 years, there has been a further rush of new antiepileptics, and there are now at least 20 drugs licensed for current use for epilepsy. Despite this abundance of new compounds, phenobarbital—by far the oldest drug in the antiepileptic formulary—continues to be prescribed, although with a rather remarkable geographic variation, and especially in pediatric, old age, and nonspecialist practice. Drug-utilization studies have repeatedly demonstrated relatively high use in a number of countries, notably in Italy and in Scandinavia. In Denmark, phenobarbital was still the third most commonly prescribed antiepileptic in 2001 and had the highest amount prescribed as monotherapy (Rochat et al., 2001), and in 2006 it was the second most commonly used antiepileptic, after carbamazepine, based on the total number of users and on the quantity as prescribed daily doses; phenobarbital had the highest quantity dispensed as monotherapy and the fourth highest quantity as polytherapy (Tsiropoulos et al., 2006). Another study, from Norway (Johannessen Landmark et al., 2011) in 2011 showed phenobarbital to be the fifth most commonly prescribed antiepileptic after lamotrigine, carbamazepine, valproate, and levetiracetam, and the second most commonly combined antiepileptic in men (with phenytoin), accounting for 20% of all combinations. Phenobarbital was, with carbamazepine, the most commonly used drug in the elderly age group. In the landmark monotherapy study by the FIRST group, phenobarbital was started in 47% of patients who experienced first unprovoked seizure and were randomized to receive antiepileptic therapy, reflecting the preference for phenobarbital in Italy by that time (Musicco et al., 1997). In a study of prescribing practice from Italy, phenobarbital was shown to be the second most commonly used antiepileptic (behind carbamazepine) at least until 2003 (Savica et al., 2007). In another study from Southern Italy, phenobarbital was between 2003 and 2005 the fourth most commonly prescribed antiepileptic, after lamotrigine, pregabalin, and valproate (Alacqua et al., 2009). Even in tertiary centers in Italy, where newer drugs are more likely to be prescribed, phenobarbital remained the fourth most commonly prescribed drug in children, accounting for 20% of total antiepileptic prescriptions, and the sixth most commonly prescribed drug in adults, accounting for 17% of antiepileptic prescriptions; it remained the most commonly prescribed for generalized and unclassified epilepsy (24% of total) (Malerba et al., 2010). The most recent study of its use is from Germany, where a total of 17,526 patients are currently using phenobarbital (2.8% of the total antiepileptic usage) (Hamer et al., 2012). There are other interesting regional differences, with primidone still used in Britain and metharbital still being commonly prescribed in Australia.

Phenobarbital remains a particularly prominent drug in pediatric practice and especially in persons younger than 2 years of age. Dutch databases show phenobarbital as the fourth most commonly prescribed antiepileptic in the pediatric age group, with almost stable figures throughout the last decade (Van De Vrie-Hoekstra et al., 2008). In Hong Kong, phenobarbital was the second most commonly used antiepileptic in children 4 years old and younger, constituting one third of total antiepileptic use; however, this rate rapidly declines to as low as 3% in the 5–19 year age group (Kwong et al., 2012). Phenobarbital is the drug of choice for treatment of neonatal seizures

(Painter et al., 1999). In Germany, phenobarbital is the most commonly used conventional antiepileptic in children aged <2 years, accounting for 40.1% of antiepileptic drug use, falling to 2.6% (4th place) in the 12–17 year age group (Dörks et al., 2012). A study from Taiwan showed a similar trend, with 42% utilization in children 4 years or younger, dropping to 12% (third rank) in 5–9 year-olds, and to 1% in middle-aged people (Hsieh & Huang, 2009). That study showed that, for an Asian population of all ages, phenobarbital was the fifth most commonly used antiepileptic, accounting for around 4.2% of total use.

Clinical trials

Despite phenobarbital being used as an antiepileptic for >100 years, its efficacy has been evaluated in only a very small number of controlled studies. Several authors have suggested that the main reason is the lack of commercial interest in funding further research (Kwan & Brodie, 2004). In total, there are 14 randomized controlled trials that have addressed the efficacy of phenobarbital efficacy directly or indirectly (Gruber et al., 1962; Bird et al., 1966; Cereghino et al., 1974; Mattson et al., 1985; Mitchell & Chavez, 1987; Feksi et al., 1991; Placencia et al., 1993; Heller et al., 1995; Meador et al., 1995; Chen et al., 1996; De Silva et al., 1996; Thilothammal et al., 1996; Czapinski et al., 1997; Pal et al., 1998), the most recent of which ceased recruiting patients in 1996 (Pal et al., 1998). Most of these have compared phenobarbital with another antiepileptic. Two systematic and meta-analytic reviews summarized the findings of trials comparing phenobarbital to carbamazepine and to phenytoin (Taylor et al., 2001; Tudur Smith et al., 2003). There are no reviews comparing phenobarbital with valproate or any of the other more recent antiepileptic drugs. The two reviews both conclude that phenobarbital is as effective as either carbamazepine or phenytoin, both in treating first seizures and established epilepsy, but it is less likely to be continued due to higher incidence of side effects, especially when taken long term. These reviews were the foundations upon which the World Health Organization (WHO, 2008) derived its recommendation for phenobarbital usage and its listing as an essential medication.

Cohort studies have also served to provide evidence for the efficacy of phenobarbital in epilepsy. Most observational studies come from developing countries (Kwan & Brodie, 2004) where phenobarbital is still widely used. Notable papers came from Tanzania (Jilek-Aall & Rwiza, 1992), Nigeria (Sykes, 2002), India (Mani et al., 2001), Mali (Nimaga et al., 2002) and China (Wang et al., 2006). These studies all show relatively similar efficacy rates of around 50–55% seizure control. Another interesting point is that, compared to the randomized trials from developed countries, side effects are less common or less reported. It has been suggested that this is attributable to patients or carers knowing that phenobarbital is the only effective medication available, which deters complaining (Kwan & Brodie, 2004). These studies also showed acceptable efficacy despite poor syndromic classification, inadequate neurophysiologic testing, drug level monitoring, and long previous periods of active untreated epilepsy.

Essential drug list of the WHO

In WHO (1977) adopted the concept of the Essential Drug List in response to the request submitted by the World Health Assembly (1975) for a plan to help member countries to select and procure essential, effective, and inexpensive medications to meet the needs of their populations (WHO, 2001; Laing et al., 2003). Phenobarbital made its way into that part of the list, which is of ''drugs that are of utmost importance, basic, indispensable and necessary for the health of population.'' The only other antiepileptics included were diazepam, ethosuximide, phenytoin and, if seizures remained uncontrolled on these therapies, carbamazepine (WHO, 1977). Phenobarbital has remained on the list right through its various modifications from 1977 to 2012. In 1979, details of formulations were included, with the recommendation to have 50 and 100 mg tablets and elixir 15 mg/5 ml (WHO, 1979). In 1988, the recommendation was changed to tablets 15–100 mg (WHO, 1987), and in 2007, elixir was changed to oral liquid phenobarbital 15 mg/5 ml and 5 ml phenobarbital sodium. In addition, injectable 200 mg/ml phenobarbital sodium was added as second-line therapy in status epilepticus in 2007 (WHO, 2007).

The choice of medications is based on their efficacy, cost, availability, current and future public-health relevance, and potential for safety and cost effectiveness. In 2002, stricter evidence-based criteria were introduced (Laing et al., 2003). Phenobarbital remained designated as a core drug, with the evidence base from two Cochrane systematic reviews that analyzed data from 13 trials: nine trials examining carbamazepine versus phenobarbital (684 patients) (Tudur Smith et al., 2003) and four trials examining phenobarbital versus phenytoin (599 patients) (Taylor et al., 2001). The stated WHO rationale for advocating phenobarbital was that it is effective and inexpensive (WHO, 2008). Phenobarbital has been included on the national essential drug lists of >90% of responding countries in all regions except Southeast Asia, where it is included in 80% of responding countries (WHO, 2005).

The current recommendation of the WHO for the treatment of epilepsy is that: ''Monotherapy with any of the standard antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy. Given the acquisition costs, phenobarbital should be offered as a first option if availability can be assured. If available,

carbamazepine should be offered to children and adults with partial-onset seizures.'' The strength of this recommendation is categorised as ''strong,'' that is, a recommendation that the guideline development group is confident will result in most patients receiving the recommended course of action, and that policy makers can easily adapt as policy in most situations (WHO, 2010a).

Phenobarbital as a controlled drug

The tendency to produce dependency, at least in the psychiatric population, has been well recognized since the early 1950s. The drug was also widely used in a variety of situations where ''stress'' was thought contributory (e.g., migraine, hypertension, asthma, and panic attacks), often with what seems now a rather shocking casualness. There was also considerable prescription and nonprescription misuse of the drug in the 1950s and 1960s in the United States and in Europe, with problems of addiction, dependency, and fatal overdose. Recreational use of phenobarbital was then widespread, with the tablets sometimes called goofballs or purple hearts. This led to efforts to control manufacture, distribution, and prescription through a number of international treaties (UN, 1971). Controlled medications were defined by United Nations convention on psychotropic substances in Vienna in 1971 as ''those that have the potential to produce physical and/or psychological dependence and CNS stimulation or depression, causing abnormal sensory experience or altered motor, behavioral, cognitive, perceptive or affective function.'' At that conference, sedative, hypnotic, stimulant, and psychedelic drugs were organized into schedules according to the WHO recommendation, based on the likelihood of being abused/misused, the drug's influence on society and public health, the extent of the drug's use for medicinal purposes and whether the international control procedures would be practical and effective (UN, 1971). Phenobarbital was designated as a schedule IV drug; a category that included other sedative, anxiolytic, and hypnotic drugs, and the shorter-acting barbiturates were designated as schedule III medicines, which have stricter control measures. It was recommended thus that phenobarbital should be controlled by specific licensing of manufacture, trade, and distribution, but without a strict record of its manufacture, distribution, or acquisition. It should be supplied or dispensed only by licensed individuals for medical prescription; however, in the same article of the treaty, phenobarbital and other drugs in schedules III and IV are permitted to be dispensed without prescription by licensed pharmacists and retailers for medical purposes in small quantities at their own discretion. The WHO review of psychotropic substances in 1978 suggested that phenobarbital should be removed from the list of controlled drugs in view of its low potential for dependence when appropriately used—compared with shorter acting barbiturates, narcotics, or benzodiazepines—and its widespread medical use as an anticonvulsant and low cost. However, this suggestion was rejected. Of interest, primidone, in effect a prodrug of phenobarbital, was subject to no restrictions.

Although >175 countries are parties to that treaty, the exact measures of control and the criteria for scheduling differed between countries. For example, in the United States, phenobarbital was designated a Schedule IV drug 1 year before the UN Convention in the Controlled Substances Act (1970a,b), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. It was not allowed to be dispensed without a prescription, and that prescription could not be refilled more than five times, or after 6 months of the date of writing that prescription. The penalty of illegal distribution of phenobarbital then was 5 years imprisonment, whereas a second felony led to a 10-year penalty (Controlled Substances Act, 1970a,b). In the United Kingdom, in 1984, phenobarbital was added with other 5,5-disubstituted barbituric acids to the United Kingdom 1971 Drug Misuse Act and was scheduled as a Class B medication (The Misuse of Drugs Act 1971 (Modification) (1984). In 2001, and to comply with the 1971 Convention on Psychotropic Substances, phenobarbital was designated as a Schedule III medication (The Misuse of Drugs Regulations, 2001) to be dispensed only by prescription that clearly documents the form, strength, and quantity, with the prescriber responsible for ensuring that the indication, quantity, and dosage are suitable for the underlying medical condition (The Misuse of Drugs Regulations, 2001). This regulation, however, does not require safe custody for storage or a separate register for documentation; yet, the invoices were to be kept for at least 2 years (The Misuse of Drugs Regulations, 2001). In addition, an emergency supply on patient's request was permitted only in cases of epilepsy (RPS, 2010). In the United Kingdom, the legal consequence of possession of phenobarbital is up to 5 years in prison and/or an unlimited fine, whereas illicit drug dealing results in up to 14 years in prison and/or an unlimited fine (The Home Office, 2009).

The fact that some drugs are classed as both essential and also controlled has caused difficulty of access in some countries. For example, approximately 90% of people with epilepsy in Africa have been denied their treatment, and this is partly because the most widely recommended medication is phenobarbital, to which access is often poor. Access is limited by inefficient manufacturing, marketing, and central distribution policies more than by restricted prescription; and in many resource-poor countries, in practice, the drug can easily be acquired without prescription. Recognizing this, the WHO (2010b) initiated an Access to Controlled Medication Program that aims, while raising awareness to the potentials of abuse, to modify the local policies.

The cost of phenobarbital

The low cost of production, and therefore affordability, by the resource-poor countries, is a major reason to recommend phenobarbital as the mainstay of therapy for established epilepsy. According to the latest update of the International Drug Price Indicator Guide, a 1,000-tab/cap package of 100 mg strength phenobarbital can be supplied for $4.82–$9.58; a 100 tab/cap of 500 mg valproate is bought for $23.68–$26.38; and a pack of 1,000 tablet/capsule of 200 mg carbamazepine costs $9.25–$15.03 (MSH, 2010). In the United Kingdom, phenobarbital costs £0.71 ($1.13) for a 60-mg 28-tab pack (BNF, 2012c), whereas a valproate 500-mg 100-tab pack costs £19.25 ($30.91) (BNF, 2012e) and an 84-tab pack of 200 mg carbamazepine costs £3.83 ($6.14) (BNF, 2012a). Newer generation antiepileptics cost far more; for example a 56-tab pack of 100 mg lamotrigine (Lamictal) costs £57.53 ($92.21) (BNF, 2012b). The third-generation antiepileptics are even more expensive, for example, retigabine costs £116.78 ($187.17) for a 300-mg, 84-tab pack (BNF, 2012d).

Other epilepsy indications for phenobarbital

Phenobarbital, despite its low efficacy of around 43%, is the antiepileptic of choice in neonatal seizures (Painter et al., 1999), even when evidence shows that its efficacy for seizure control is similar to that of phenytoin. It also remains one of the few agents widely used for its neuroprotective action, especially in pediatrics and neonatology. It has been given for many decades prenatally to mothers or perinatally to premature neonates, although evidence of value is poor (Barnes & Thompson, 1993; Tholl et al., 1994; Crowther & Henderson-Smart, 2003; Whitelaw & Odd, 2007; Crowther et al., 2010). It is used widely to reduce oxidative stress in neonates with birth asphyxia and hypoxic ischemic encephalopathy, although again with uncertain results (Ruth et al., 1988; Hall et al., 1998; Singh et al., 2004, 2005; Vargas-Origel et al., 2004; Gathwala et al., 2011).

In addition, it has been used widely prophylactically to prevent recurrence of febrile seizures. Some studies have found that long-term phenobarbital therapy reduces recurrence after simple or atypical febrile convulsions (Wolf et al., 1977; Camfield et al., 1980; Bacon et al., 1981; Mamelle et al., 1984; Thilothammal et al., 1993), whereas others have found no significant difference when compared to placebo or intermittent diazepam (Knudsen & Vestermark, 1978; Mckinlay & Newton, 1989). Two meta-analytic reviews concluded that, despite a statistically significant benefit in seizure rate reduction, the heterogeneity of participating studies and side effects did not allow any recommendation for using phenobarbital as long-term prophylaxis (Rantala et al., 1997; Masuko et al., 2003).

Phenobarbital is still considered a first-line treatment in idiopathic (genetic) generalized epilepsy in many areas of the world due to its cost and ease of use (Lerman-Sagie & Lerman, 1999). It is also the most commonly prescribed antiepileptic in West syndrome in many developing countries because of its cost and the unavailability of first-line treatments, such as adrenocorticotropic hormone (ACTH) or vigabatrin (Kalra et al., 2001; Salonga et al., 2001). Nevertheless, in 2007 it was considered inappropriate for West syndrome by most European experts (Wheless et al., 2007). Similarly, in other childhood epilepsy syndromes, such as juvenile myoclonic epilepsy, childhood absence epilepsy, benign childhood epilepsy with centrotemporal spikes, and Lennox-Gastaut syndromes, phenobarbital is considered ''inappropriate or equivocal'' (Wheless et al., 2007). Phenobarbital was one of four antiepileptics used as first-line treatment of neuronal ceroid lipofuscinosis in children, yet it is associated with the highest rates of side effects (Åberg et al., 2000).

Phenobarbital is a second-line treatment of partial-onset and generalized seizures, in refractory idiopathic (genetic) generalized epilepsy, and intractable secondarily generalized epilepsy syndromes (Shorvon, 2010).

It remains a major first-line therapy in status epilepticus. The first studies were reported in the 1920s, usually from epilepsy colonies, for instance at Chalfont, United Kingdom, in 1924 (Haward, 1924), and intravenous phenobarbital was considered the therapy of choice in the Sonyea colony in 1926 (Patterson et al., 1926). However, there have been few controlled trials. An influential study was from the Veterans Hospitals showing that phenobarbital, as an initial treatment, was as effective as lorazepam or diazepam and phenytoin but superior to phenytoin when the latter is used alone (Treiman et al., 1998), confirming the results of an earlier important study by Shaner et al. (1988). A systematic review of benzodiazepine-resistant status epilepticus showed that phenobarbital was effective in 73.6% of treated patients (more effective than phenytoin) and may be neuroprotective, but less well tolerated than valproate or levetiracetam (Yasiry Z, Shorvon SD, unpublished work). Other studies have shown varying rates of success of high doses in patients with refractory status epilepticus (Crawford et al., 1988; Lee et al., 2006; Tiamkao et al., 2007; Wilmshurst et al., 2010). Intravenous phenobarbital remains today as a first-line therapy in benzodiazepine-resistant status epilepticus, nearly 100 years after the first reports of its use in this the most severe form of epilepsy.

Reflections on a Century of Phenobarbital in Epilepsy

It is worth reflecting on several final points from this history of phenobarbital therapy in epilepsy. First, the treatment was discovered by an astute clinical observation

of a chance finding. The potential for deriving discovery from clinical observation in our contemporary over-bureaucratized and protocol-driven medical practice is increasingly less likely. Bureaucracy is the enemy of innovation and this is nowhere more apparent than in medical therapeutics. Furthermore, although we are in currently an era in which drug design is based on our current molecular scientific knowledge, many of even recent drug introductions have depended on chance observation as much as on rational design. It is important to maintain vigilance for the unexpected or unexplained.

Second is the marked and intriguing contrast between the rapid international dissemination of bromides or phenytoin, following the discovery of their antiepileptic effect, and the much slower uptake of phenobarbital. It is interesting to speculate on the reasons for this. This was probably largely the disruption in medical communication by World War I, and possibly also because the article was published in a rather obscure German language journal. Possibly too, phenobarbital, unlike bromide (Locock) and phenytoin (Lennox) had no prominent medical champion. For whatever reason, phenobarbital became widely used only in the early 1920s, 10 or so years after its discovery. Phenytoin, by contrast, was tried first in 1937, but by 1940 was used around the world, such was the efficiency of the medical journals and meetings in disseminating information and the promotion by Lennox and by the pharmaceutical manufacturers. Similarly, carbamazepine and valproate were rapidly introduced after the first studies, when it became obvious that they had clinical value. Nowadays, because of regulatory constraints, it usually takes >10 years from the time of the first experimentation for a new drug to be tried in the clinic, largely to avoid unrecognized toxicity and to ensure efficacy. However, ''unrecognized toxicity'' has occurred despite this caution in recent times (visual field defects with vigabatrin, hepatic failure with felbamate), and the current testing regimen seems insensitive—not least because the rigidity and red tape of clinical trials obscures the unexpected. The delay incurred in the current system of regulation results in hugely inflated costs, and also a lost opportunity for uncontrolled patients excluded from benefiting from a drug during the prolonged prelicensing phase. Whether the current system is significantly safer seems at least arguable.

Another most intriguing point is that the efficacy of phenobarbital has not been demonstrably bettered by any other drug, despite its age and the large number of alternatives. There have been no large-scale clinical trials but, but on the basis of existing evidence (see the Cochrane reviews), phenobarbital seems as effective as other therapies. In view of this, one wonders why phenobarbital has not maintained its place as first-line therapy in the so-called evidence-based guidelines of organizations in the Western world (National Institute of Clinical Excellence, American Academy of Neurology, and ILAE guidelines, for instance). Phenobarbital has no marketing backing and no manufacturer providing any marketing support, and is not backed up by the huge marketing budgets of other pharmaceutical products, and perhaps this explains why it does not have a larger proportion of market share. Its extreme low cost, due to the simplicity of its manufacture, would, one might have imagined, been a major advantage, but this has not been fully realized in the marketing-driven environment of modern therapeutics.

The first-line prescription of phenobarbital does, however, have the backing of the WHO, but with the rather confusing assignation as both an essential and also a controlled drug. This can have a dire effect on availability in resource-poor regions, where the central facilities for administrating the regulations for controlling medication are not well developed. In many resource-poor countries, medicines can be obtained without prescription, and this in practice applies also to phenobarbital, but the main problems of access are linked to problems of supply and it is here that the controlled-drug regulations cause their impact. The extreme low cost of phenobarbital also results in a lack of manufacturing interest. These factors conspire in many rural situations to an intermittency of supply, which carries real dangers as the sudden withdrawal of the drug due to sudden nonavailability carries the significant risk of withdrawal-induced status epilepticus. It is not clear to what extent this problem would be alleviated by removing the categorization of phenobarbital as a ''controlled drug'' or by a more sustained effort in ensuring regular manufacturing, but these issues should both be addressed.

The severity of the side-effect profile of phenobarbital has remained controversial. There is no doubt that it has sedative effects, but these are in most adults slight at lower doses. There is also no doubt that it has paradoxical behavioral effects in children, and for instance these were the reason for the premature withdrawal of the phenobarbital arm in the pediatric studies from King's College Hospital in the 1990s (De Silva et al., 1996). In addition, despite its 100-year pedigree, it is still not known exactly to what extent phenobarbital causes learning or cognitive difficulties, especially in children. The lack of systematic study of side effects, and indeed the prolonged time required to recognize some of the side effects of phenobarbital, are an indictment of clinical surveillance—and a warning to those prescribing modern or newly licensed drugs. The same applies to teratogenicity, and despite a century of widespread prescribing among women, it is still not known precisely to what extent phenobarbital carries a teratogenic risk.

The advantages of high efficacy and low cost are the major reasons for the WHO recommendation for its first-line use in resource-poor countries. Phenobarbital is widely used in these situations, but now much less so in Western practice for the following reasons: the perception

that the side-effect profile is unacceptable, but this is probably in most cases, at low doses, only slightly worse than other drugs; the lack of any marketing support (in the face of huge marketing budgets for other compounds); the controlled drug regulations; and anxiety about dependency and addiction, despite the evidence that the risks are also slight. Opinion is divided about whether the benefit of cost and efficacy are overridden by the risks of side effects, the lack of support, and the regulatory framework. We remember the reaction to the WHO recommendations by the then ILAE president, Fritz Dreifuss, a pediatric neurologist, that to use phenobarbital in resource-poor settings puts ''a hierarchy on the brain'' meaning that people in resource-poor countries but not the Western countries are consigned to second-class medication. The equation is not as simple as this, though, where cost, availability, safety, and efficacy all enter the mix.

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References

Åberg LE, Backman M, Kirveskari E, Santavuori P. (2000) Epilepsy and antiepileptic drug therapy in juvenile neuronal ceroid lipofuscinosis. *Epilepsia* 41:1296–1302.

Alacqua M, Trifirò G, Spina E, Moretti S, Tari DU, Bramanti P, Caputi AP, Arcoraci V. (2009) Newer and older antiepileptic drug use in southern Italy: a population-based study during the years 2003–2005. *Epilepsy Res* 85:107–113.

Anders M. (1966) Rapid micromethod for gas chromatographic determination of blood barbiturates. *Anal Chem* 38:1945–1947.

Bacon CJ, Hierons AM, Mucklow JC, Webb JK, Rawlins MD, Weightman D. (1981) Placebo-controlled study of phenobarbitone and phenytoin in the prophylaxis of febrile convulsions. *Lancet* 2:600–604.

Barnes ER, Thompson DF. (1993) Antenatal phenobarbital to prevent or minimize intraventricular hemorrhage in the low-birthweight neonate. *Ann Pharmacother* 27:49–52.

Bialer M. (2012) How did phenobarbital's chemical structure affect the development of subsequent antiepileptic drugs (AEDs)? *Epilepsia* 53(Suppl. 8):3–11.

Bird CAK, Griffin BP, Miklasewska MJ, Galbraith AW. (1966) Tegretol (carbamazepine): a controlled trial of a new anticonvulsant. *Br J Psychiatry* 112:737–742.

BNF. (2012a) *Carbamazepine (tegretol) [online]*. BMJ Group and Pharmaceutical Press, London. Available at: http://www.medicinescomplete.com/mc/bnf/current/3577.htm?q=carbamazepine&t=search&ss=text&p = 1#_hit [Accessed August 26, 2012].

BNF. (2012b) *Lamotrigine (lamictal) [online]*. BMJ Group and Pharmaceutical Press, London. Available at: http://www.medicinescomplete.com/mc/bnf/current/9833.htm#_9833 [Accessed August 26, 2012].

BNF. (2012c) *Phenobarbital [online]*. BMJ Group and Pharmaceutical Press, London. Available at: http://www.medicinescomplete.com/mc/bnf/current/search.htm?q=phenobarbital [Accessed August 26, 2012].

BNF. (2012d) *Retigabine (trobalt) [online]*. BMJ Group and Pharmaceutical Press, London. Available at: http://www.medicinescomplete.com/mc/bnf/current/215509.htm#_215509 [Accessed August 26, 2012].

BNF. (2012e) *Valproate (epilim) [online]*. BMJ Group and Pharmaceutical Press, London. Available at: http://www.medicinescomplete.com/mc/bnf/current/3601.htm#_3601 [Accessed August 26, 2012].

British Pharmacopoeia. (1914) *British Pharmacopoeia Commission*. Constable & co. ltd, London.

Brook C. (1922) Report of the medical officer. The National Society of Epilepsy: 30th Annual Report: 19.

Brook C. (1923) Report of the medical officer. The National Society of Epilepsy: 30th Annual Report: 28.

Buchthal F, Svensmark O, Simonsen H. (1968) Relation of EEG and seizures to phenobarbital in serum. *Arch Neurol* 19:567–572.

Bush M. (1961) Sedatives and hypnotics: absorption fate and excretion. In Root WS, Hoffmann FG (Eds) *Physiological pharmacology*. Vol. 561. Academic Press, New York, pp. 185–218.

Butler TC. (1952) Quantitative studies of the metabolic fate of mephobarbital (N-methylphenobarbital). *J Pharmacol Exp Ther* 106:235–245.

Butler TC, Mahaffee C, Waddell WJ. (1954) Phenobarbital: studies of elimination, accumulation, tolerance, and dosage schedules. *J Pharmacol Exp Ther* 111:425–435.

Camfield PR, Camfield CS, Shapiro SH, Cummings C. (1980) The first febrile seizure – antipyretic instruction plus either phenobarbital or placebo to prevent recurrence. *J Pediatr* 97:16–21.

Cereghino JJ, Brock JT, Van Meter JC, Penry JK, Smith LD, White BG. (1974) Carbamazepine for epilepsy. A controlled prospective evaluation. *Neurology* 24:401–410.

Chanarin I, Laidlaw J, Loughridge LW, Mollin DL. (1960) Megaloblastic anaemia due to phenobarbitone. *BMJ* 1:1099–1102.

Chen YJ, Kang WM, So WC. (1996) Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: a psychometric and neurophysiological study. *Epilepsia* 37:81–86.

Controlled Substances Act. (1970a) 21 USC § 801 – Congressional findings and declarations: controlled substances [online]. USA. Available at: http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm [Accessed September 4, 2012].

Controlled Substances Act. (1970b) 21 USC § 801 – Congressional findings and declarations: controlled substances, part D: offenses and penalties [online]. USA. Available at: http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm#cntlsbd [Accessed September 4, 2012].

Crawford TO, Mitchell WG, Fishman IS, Snodgrass SR. (1988) Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology* 38:1035–1040.

Crowther CA, Henderson-Smart DJ. (2003) Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. *Cochrane Database Syst Rev* 3:CD000164.

Crowther CA, Crosby DD, Henderson-Smart DJ. (2010) Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. *Cochrane Database Syst Rev* 1:CD000164.

Czapinski P, Terczynski A, Czapinska E. (1997) Randomised 36-month comparative study of valproic acid, phenytoin, phenobarbital and carbamazepine efficacy in patients with newly diagnosed epilepsy with partial complex seizures. 22nd International Epilepsy Congress 1997 Dublin, Ireland. *Epilepsia*, 38(Suppl. 3):1–288.

De Silva M, Macardle B, Mcgowan M, Hughes E, Stewart J, Neville BG, Johnson AL, Reynolds EH. (1996) Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 347:709–713.

De Vries SI. (1965) Haematological aspects during treatment with anticonvulsant drugs. *Epilepsia* 6:1–15.

Dörks M, Langner I, Timmer A, Garbe E. (2012) Treatment of paediatric epilepsy in Germany: antiepileptic drug utilisation in children and adolescents with a focus on new antiepileptic drugs. *Epilepsy Res* July 11 [Epub ahead of print].

Faerø O, Kastrup KW, Lykkegaard Nielsen E, Melchior JC, Thorn I. (1972) Successful prophylaxis of febrile convulsions with phenobarbital. *Epilepsia* 13:279–285.

Feely M, O'Callagan M, Duggan B, Callaghan N. (1980) Phenobarbitone in previously untreated epilepsy. *J Neurol Neurosurg Psychiatry* 43:365–368.

Feksi AT, Kaamugisha J, Sander JWAS, Gatiti S, Shorvon SD. (1991) Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. ICEBERG (International Community-Based Epilepsy Research Group). *Lancet* 337:406–409.

Gathwala G, Marwah A, Gahlaut V, Marwah P. (2011) Effect of high-dose phenobarbital on oxidative stress in perinatal asphyxia: an open label randomized controlled trial. *Indian Pediatr* 48:613–617.

Golla F. (1921) Luminal contrasted with bromide in epilepsy. *BMJ* 27:320–321.

Grinker J. (1920) Experiences with luminal in epilepsy. *JAMA* 75:588–592.

Grinker J. (1922) Further experiences with phenobarbital (luminal) in epilepsy. *JAMA* 79:788–793.

Gruber CM Jr, Brocket JT, Dyken M. (1962) Comparison of the effectiveness of phenobarital, mephobarbital, primidone, diphenylhydantoin, ethotoin, metharbital, and methylphenylethylhydantoin in motor seizures. *Clin Pharmacol Ther* 3:23–28.

Hall RT, Hall FK, Daily DK. (1998) High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 132:345–348.

Hamer H, Dodel R, Strzelczyk A, Balzer-Geldsetzer M, Reese JP, Schöffski O, Graf W, Schwab S, Knake S, Oertel W, Rosenow F, Kostev K. (2012) Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany – a nationwide population-based study in children and adults. *J Neurol* Apr 28 [Epub ahead of print].

Hauptmann A. (1912) Luminal bei epilepsie. *Munch Med Wochenschr* 59:1907–1909.

Hauptmann A. (1919) Erfahrungen aus der behandlung der epilepsie mit luminal. *Munch Med Wochenschr* 46:1319–1321.

Haward F. (1924) Report of the medical officer. The National Society of Epilepsy.

Haward F. (1926) Report of the medical officer. The National Society of Epilepsy.

Haward F. (1928) Report of the medical officer. The National Society of Epilepsy.

Hawkings CF, Meynell MJ. (1958) Macrocytosis and macrocytic anaemia caused by anticonvulsant drugs. *Q J Med* 27:45–63.

Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AI, Reynolds EH. (1995) Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *J Neurol Neurosurg Psychiatry* 58:44–50.

Hsieh IP, Huang CY. (2009) Antiepileptic drug utilization in Taiwan: analysis of prescription using national health insurance database. *Epilepsy Res* 84:21–27.

Jilek-Aall l, Rwiza HT. (1992) Prognosis of epilepsy in a rural African community: a 30-year follow-up of 164 patients in an outpatient clinic in rural Tanzania. *Epilepsia* 33:645–650.

Johannessen Landmark C, Fossmark H, Larsson PG, Rytter E, Johannessen SI. (2011) Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. *Epilepsy Res* 95:51–59.

Johnson W. (1922) A note on luminal. *Lancet* 200:275–276.

Kalra V, Gulati S, Pandey RM, Menon S. (2001) West syndrome and other infantile epileptic encephalopathies – Iindian hospital experience. *Brain Dev* 23:593–602.

Kekulé A. (1865) Sur la constitution des substances aromatiques. *Bull Soc Chim Paris* 3:98–110.

Knudsen FU, Vestermark S. (1978) Prophylactic diazepam or phenobarbitone in febrile convulsions: a prospective, controlled study. *Arch Dis Child* 53:660–663.

Kruse R. (1968) Osteopathies in antiepileptic long-term therapy (preliminary report). *Monatsschr Kinderheilkd* 116:378–381.

Kwan P, Brodie MJ. (2004) Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia* 45:1141–1149.

Kwong KI, Tsui KW, Wu SP, Yung A, Yau E, Eva F, Ma CK, Cherk S, Liu KT, Cheng WW, Yau MM. (2012) Utilization of antiepileptic drugs in Hong Kong children. *Pediatr Neurol* 46:281–286.

Laing R, Waning B, Gray A, Ford N, 't Hoen E. (2003) 25 years of the WHO essential medicines lists: progress and challenges. *Lancet* 361:1723–1729.

Lee WK, Liu KT, Young BWY. (2006) Very-high-dose phenobarbital for childhood refractory status epilepticus. *Pediatr Neurol* 34:63–65.

Lennox WG. (1938) The literature on epilepsy in 1936. *Epilepsia* 2nd Series; 1:128–164.

Lennox WG. (1939) Progress in the study of epilepsy in America in 1937. *Epilepsia* 2nd series; 1:196–208.

Lennox WG. (1940) Study of epilepsy in America in 1938. *Epilepsia* 2nd series; 1:279–291.

Lennox WG. (1942) Brain injury, drugs and environment as causes of mental decay in epilepsy. *Am J Psychiatry* 99:174–180.

Lennox WG, Lennox M. (1960) *Epilepsy and related disorders*. Little Brown, Boston, MA.

Lerman-Sagie T, Lerman P. (1999) Phenobarbital still has a role in epilepsy treatment. *J Child Neurol* 14:820–821.

Livingstone S. (1966) *Drug therapy for epilepsy*. Charles C Thomas, Springfield.

López-Muñoz F, Ucha-Udabe R, Alamo C. (2005) The history of barbiturates a century after their clinical introduction. *Neuropsychiatr Dis Treat* 1:329–343.

Löscher W, Rogawski M. (2012) How theories evolved concerning the mechanism of action of barbiturates. *Epilepsia* 53(Suppl. 8):12–25.

Malerba A, Ciampa C, De Fazio S, Fattore C, Frassine B, La Neve A, Pellacani S, Specchio LM, Tiberti A, Tinuper P, Perucca E. (2010) Patterns of prescription of antiepileptic drugs in patients with refractory epilepsy at tertiary referral centres in Italy. *Epilepsy Res* 91: 273–282.

Mamelle N, Mamelle JC, Plasse JC, Revol M, Gilly R. (1984) Prevention of recurrent febrile convulsions – a randomized therapeutic assay: sodium valproate, phenobarbital and placebo. *Neuropediatrics* 15:37–42.

Mani KS, Rangan G, Srinivas HV, Srindharan VS, Subbakrishna DK. (2001) Epilepsy control with phenobarbital or phenytoin in rural south India: the Yelandur Study. *Lancet* 357:1316–1320.

Masuko AH, Castro AA, Santos GR, Atallah AN, Do Prado LB, De Carvalho LB, Do Prado GF. (2003) Intermittent diazepam and continuous phenobarbital to treat ecurrence of febrile seizures: a systematic review with meta-analysis. *Arq Neuropsiquiatr* 61:897–901.

Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, Mcnamara JO, Mccutchen CB, Homan RW, Crill WE, Lubozynski MF, Rosenthal NP, Mayersdorf A. (1985) Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. *N Engl J Med* 313:145–151.

Mcgreachy TE, Bloomer WE. (1953) The phenobarbital sensitivity syndrome. *Am J Med* 14:600–604.

Mckinlay I, Newton R. (1989) Intention to treat febrile convulsions with rectal diazepam, valproate or phenobarbitone. *Dev Med Child Neurol* 31:617–625.

Meador KJ, Loring DW, Moore EE, Thompson WO, Nichols ME, Oberzan RE, Durkin MW, Gallagher BB, King DW. (1995) Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. *Neurology* 45:1494–1499.

Millichap J. (1965) Aticonvulsant drugs: clinical and electrocencephalographic indications, efficacy and toxicity. *Postgrad Med* 37:22–34.

Mitchell WG, Chavez JM. (1987) Carbamazepine versus phenobarbital for partial onset seizures in children. *Epilepsia* 28:56–60.

Morselli PA, Rizzo M, Garattini S. (1971) Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 6:88–107.

MSH. (2010) *Phenobarbital-international drug price indicator guide [online]*. Management Science for Health, Cambridge, MA. Available at: http://erc.msh.org/dmpguide/resultsdetail.cfm?language=english&code=phe100t&s_year=2010&year=2010&str=100%20mg&desc=phenobarbital&pack=new&frm=tab-cap&rte=po&class_code2=05%

2e&supplement=&class_name=%2805%2e%29anticonvulsants%2fantiepileptics%3cbr%3e [Accessed August 24, 2012].

Musicco M, Beghi E, Solari A, Viani F. (1997) Treatment of first tonic–clonic seizure does not improve the prognosis of epilepsy. FIRst Seizure Trial Group (FIRST Group). *Neurology* 49:991–998.

Muskens L. (1924) *Epilepsie: vergelijkende pathogenese, verschijnselen, behandeling*. Van Rossen, Amsterdam.

Nimaga K, Desplats D, Doumbo O, Farnarier G. (2002) Treatment with phenobarbital and monitoring of epileptic patients in rural Mali. *Bull World Health Organ* 80:532–537.

Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, Paneth N, Minnigh B, Alvin J. (1999) Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 341:485–489.

Pal DK, Das T, Chaudhury G, Johnson AL, Neville BG. (1998) Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet* 351:19–23.

Patterson H, Damon LG, Levi P. (1926) A comparative study of various methods of the administration of luminal in epilepsy. *J Nerv Ment Dis* 63:275.

Placencia M, Sander JW, Shorvon SD, Roman M, Alarcon F, Bimos C, Cascante S. (1993) Antiepileptic drug treatment in a community health care setting in northern Ecuador: a prospective 12-month assessment. *Epilepsy Res* 14:237–244.

Plum P. (1937) *Clinical and experimental investigation in agranulocytosis*. H. K. Lewis Co, London.

Rantala H, Tarkka R, Uhari M. (1997) A meta-analytic review of the preventive treatment of recurrences of febrile seizures. *J Pediatr* 131:922–925.

Reynolds EH. (1975) Chronic antiepileptic toxicity: a review. *Epilepsia* 16:319–352.

Rochat P, Hallas J, Gaist D, Friis ML. (2001) Antiepileptic drug utilization: a Danish prescription database analysis. *Acta Neurol Scand* 104:6–11.

RPS. (2010) *A-Z list of human medicines [online]*. Royal Pharmacist Society, London. Available at: http://www.rpharms.com/support-pdfs/az-list-of-human-medicines-July-2010.pdf [Accessed August 16, 2012].

Ruth V, Virkola K, Paetau R, Raivio KO. (1988) Early high-dose phenobarbital treatment for prevention of hypoxic-ischemic brain damage in very low birth weight infants. *J Pediatr* 112:81–86.

Salonga AM, Lukban MB, Ortiz MH, Balatero-Terencio B, Lagman AM. (2001) West syndrome: the Philippine experience. *Brain Dev* 23:616–623.

Savica R, Beghi E, Mazzaglia G, Innocenti F, Brignoli O, Cricelli C, Caputi AP, Musolino R, Spina E, Trifirò G. (2007) Prescribing patterns of antiepileptic drugs in Italy: a nationwide population-based study in the years 2000–2005. *Eur J Neurol* 14:1317–1321.

Schmidt D, Einicke I, Haenel F. (1986) The influence of seizure type on the efficacy of plasma concentrations of phenytoin, phenobarbital, and carbamazepine. *Arch Neurol* 43:263–265.

Sexton DL, Pike GM, Nielson A. (1941) Exfoliative dermatitis and death due to Phenobarbital. *JAMA* 1116:700–701.

Shaner DM, Mccurdy SA, Herring MO, Gabor AJ. (1988) Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 38:202–207.

Shorvon SD. (2009) Drug treatment of epilepsy in the century of the ILAE: the first 50 years 1909–1959. *Epilepsia* 50(Suppl. 3):1–25.

Shorvon SD. (2010) The antiepileptic drugs – phenobarbital. In Shorvon SD (Ed.) *Handbook of epilepsy treatment*. 3rd ed. Wiley-Blackwell, Chichester, pp. 210–218.

Shorvon SD, Sander JWAS. (1996) The treatment of epilepsy at the National Hospital Queen Square, 1857–1939: a mirror of the first phase of the modern history of medical and surgical therapy. In Shorvon SD, Dreifuss F, Fish D, Thomas D (Eds) *The treatment of epilepsy*. Blackwell Science, Oxford, pp. xvii–xliv.

Shorvon SD, Weiss G, Avanzini G, Engel J, Meinardi H, Moshe S, Reynolds E, Wolf P. (2009) *The International League Against Epilepsy 1909–2009*: *A centenary history*. Oxford, Wiley Blackwell.

Singh D, Kumar P, Majumdar S, Narang A. (2004) Effect of phenobarbital on free radicals in neonates with hypoxic ischemic encephalopathy – a randomized controlled trial. *J Perinat Med* 32:278–281.

Singh D, Kumar P, Narang A. (2005) A randomized controlled trial of phenobarbital in neonates with hypoxic ischemic encephalopathy. *J Matern Fetal Neonatal Med* 18:391–395.

Sneddon IB, Lishman AWD. (1952) Severe and fatal phenobarbitone eruprtions. *BMJ* 1:1276–1278.

Sykes RM. (2002) Epilepsy in children in Benin City, Nigeria. *Ann Trop Paediatr* 22:287–296.

Taylor S, Tudur Smith C, Williamson PR, Marson AG. (2001) Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic–clonic seizures. *Cochrane Database Syst Rev* 4:CD002217.

The Home Office. (2009) *Class A, B and C drugs [online]*. The Home Office via The National Archives website, London. Available at: http://webarchive.nationalarchives.gov.uk/+/http://www.homeoffice.gov.uk/drugs/drugs-law/class-a-b-c/ [Accessed August 16, 2012].

The Misuse of Drugs Act 1971 (Modification). (1984) London. Available at: http://www.legislation.gov.uk/uksi/1984/859/contents/made [Accessed September 4, 2012].

The Misuse of Drugs Regulations. (2001). London. Available at: http://www.legislation.gov.uk/uksi/2001/3998/made [Accessed September 4, 2012].

Thilothammal N, Kannan S, Krishnamurthy PV, Kamala KG, Ahamed S, Banu K. (1993) Role of phenobarbitone in preventing recurrence of febrile convulsions. *Indian Pediatr* 30:637–642.

Thilothammal N, Banu K, Ratnam RS. (1996) Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. *Indian Pediatr* 33:549–555.

Tholl DA, Miller TQ, Henderson WG, Myers TF. (1994) Meta-analysis of phenobarbital usage for prevention of intraventricular hemorrhage in premature infants: factors related to variation in outcome. *Clin Trials Metaanal* 29:177–190.

Tiamkao S, Mayurasakorn N, Suko P, Jitpimolmard S, Arunpongpaisal S, Phuttharak W, Auevitchayapat N, Vannaprasaht S, Phunikhom K, Chaiyakum A, Saengsuwan J. (2007) Very high dose phenobarbital for refractory status epilepticus. *J Med Assoc Thai* 90:2597–2600.

Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. (1998) A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 339:792–798.

Tsiropoulos I, Gichangi A, Andersen M, Bjerrum L, Gaist D, Hallas J. (2006) Trends in utilization of antiepileptic drugs in Denmark. *Acta Neurol Scand* 113:405–411.

Tudur Smith C, Marson AG, Williamson PR. (2003) Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database Syst Rev* 1:CD001904.

UN. (1971) Convention on psychotrpic substances, 1971. The United Nations Conference for the adoption of a protocol on psychotropic substances, Vienna.

Van Creveld S. (1958) New aspects of hemorrhagic disease of the newborn. *Arch Fr Pediatr* 15:721–735.

Van De Vrie-Hoekstra NW, De Vries TW, Van Den Berg PB, Brouwer OF, De Jong-Van Den Berg LTW. (2008) Antiepileptic drug utilization in children from 1997–2005 – a study from the Netherlands. *Eur J Clin Pharmacol* 64:1013–1020.

Van Der Korst JK, Colenbrander H, Cats A. (1966) Phenobarbital and the shoulder-hand syndrome. *Ann Rheum Dis* 25:553–555.

Vargas-Origel A, Espinosa-Garcia JO, Muniz-Quezada E, Vargas-Nieto MA, Aguilar-Garcia G. (2004) Prevention of hypoxic-ischemic encephalopathy with high-dose, early phenobarbital therapy. *Gac Med Mex* 140:147–153.

von Baeyer A. (1864) Untersuchungen über die harnsäuregruppe. *Der Chemie Und Pharmacie* 131:291.

Walton J. (1977) *Brain's diseases of the nervous system*. Oxford University Press, Oxford.

Wang WZ, Wu JZ, Ma GY, Dai XY, Yang B, Wang TP, Yuan CL, Hong Z, Bell GS, Prilipko l, De Boer HM, Sander JW. (2006) Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol* 5:46–52.

Wapner I, Thurston DL, Holowah J. (1962) Phenobarbital. Its effect on learning in epileptic children. *JAMA* 182:937.

Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. (2007) Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord* 9:353–412.

Whitelaw A, Odd D. (2007) Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. *Cochrane Database Syst Rev* 4:CD001691.

WHO. (1977) *The selection of essential drugs: a report of a WHO expert committee*. *WHO Technical Report Series*, 615. World Health Organization, Geneva.

WHO. (1979) *The use of essential drugs: second report of a who expert committee*. *WHO Technical Report Series*, 641. World Health organization, Geneva.

WHO. (1987) *The use of essential drugs. Third report of the who expert committee*. *WHO Technical Report Series, 770*. World Health Organization, Geneva.

WHO. (2001) *How to develop and implement a national drug policy, updates and replaces guidelines for developing national drug policies, 1988*. World Health Organization, Geneva.

WHO. (2005) Antiepileptic drugs. In *Atlas: epilepsy care in the world*. World Health Organization, Geneva.

WHO. (2007) *The selection and use of essential drugs: report of WHO expert committee: 2007 (including the 15th model list of essential drugs)*. *WHO Technical Report Series*, 946. World Health Organization, Geneva.

WHO. (2008) Phenobarbital [online]. Available at: http://archives.who.int/emlib/medicinedisplay6199.html?language=en&medidname=244%40phenobarbital [Accessed July 31, 2012].

WHO. (2010a) *Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children [online]*. World Health Organization, Geneva. Available at: http://www.who.int/mental_health/mhgap/evidence/epilepsy/mh_evidence_prof_epilpesy_q7_aed_2010_en.pdf.

WHO. (2010b) *Medicines: access to controlled medicines (narcotic and psychotropic substances) [online]*. World Health Organization, Geneva. Available at: http://www.who.int/mediacentre/factsheets/fs336/en/ [Accessed August 17, 2012].

Wilmshurst JM, Van Der Walt JS, Ackermann S, Karlsson MO, Blockman M. (2010) Rescue therapy with high-dose oral phenobarbitone loading for refractory status epilepticus. *J Paediatr Child Health* 46:17–22.

Wilson SA. (1940) *Neurology*. Edward Arnold, London.

Wolf SM, Carr A, Davis DC, Davidson S, Dale EP, Forsythe A, Goldenberg ED, Hanson R, Lulejian GA, Nelson MA, Treitman P, Weinstein A. (1977) The value of phenobarbital in the child who has had a single febrile seizure: a controlled prospective study. *Pediatrics* 59:378–385.

Woodbury DM, Penry JK, Schmidt RP. (1972) *Antiepileptic drugs*. Raven Press, New York.

World Health Assembly. (1975) *Resolution WHA28.66*. World Health Organization, Geneva.