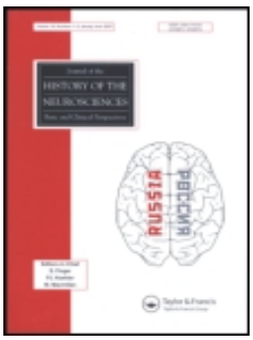

Routledge
Taylor & Francis Group

Journal of the History of the Neurosciences

ISSN: 0964-704X (Print) 1744-5213 (Online) Journal homepage: http://www.tandfonline.com/loi/njhn20

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To cite this article: B.J. Steinhoff (1992) Antiepileptic therapy with bromides— historical and actual importance, Journal of the History of the Neurosciences, 1:2, 119-123, DOI: 10.1080/09647049209525523

To link to this article: http://dx.doi.org/10.1080/09647049209525523

J Hist Neurosci (1992): 1, 119–123.

Antiepileptic therapy with bromides—historical and actual importance

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THE ERA OF DOMINANCE

The introduction of potassium bromide as an antiepileptic drug (AED) by Sir Charles Locock in 1857 (see also Friedlander, 1986) was a milestone in the history of epileptology. Up to that time anticonvulsive treatments included such drugs as turpentine, silver salts, indigo, belladonna and chloroform (Donath, 1914) but without avail. Other remedies tried included *Adonis vernalis* (Bechterew, 1894), hyoscyanus (Daly, 1915), thyroid extract (Dercum, 1916), pancreatic extract (Riggs, 1916), sodium bilborate (Kimber, 1923), calcium lactate (Kaufmann, 1916), other calcium containing compounds (Ivanov, 1937), benzedrine, amytal and ephedrine (Minski & Gillen, 1937), again in vain (Steinhoff, 1988). Such dangerous and ineffective invasive methods as cranial trepanation were occasionally performed (Lennox, 1940), expressing the general helplessness of antiepileptic therapy.

Sir Charles Locock, chairman of the Royal Medical and Chirurgical Society in London and obstetrician to the Royal Family (Lennox, 1960), reported that the application of 30 grains of potassium bromide daily had completely suppressed epileptic seizures in 14 of 15 female patients (Locock, 1857). It was tried, because epileptic attacks were thought to be related to masturbation and hysteria, and the sedative and antiaphrodisiac properties of bromides were well known (Dreifuss, 1989).

Only one year later (1858) Radciffe, Seé and Wilks definitively used bromides as AEDs (Steinhoff, 1988) and Wilks especially was responsible for its rapidly increasing use in the following years (Temkin, 1971).

The experience of some success at last in the treatment of epileptic disorders after such a long time of frustration and helplessness soon led to such enthusiastic comments as that of Radcliffe, only 4 years after Sir Charles Locock's first report: "The name of Sir Charles Locock ought to be remembered with gratitude by every epileptic" (Radcliffe, 1861).

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Soon, not only in epileptology bromides became widely used. In the middle 1870s, the annual bromide consumption at the National Hospital London was 2.5 tons (Lennox, 1960). Not only potassium bromide, but other salts such as sodium, calcium, strontium, nickel, rubidium, rubidium ammonium, arsenic, zinc, gold sodium, caesium, or cadmium bromides were tried in antiepileptic treatment (Steinhoff, 1988). Although some authors tried to prove the superiority of some over others, there was no significant difference between the various compounds, due to the fact that it is the bromine component that is the effective antiepileptic factor (Lennox, 1960).

For 55 years, there had been no real alternative antiepileptic treatment. Chloralhydrate (Ulrich, 1914) and the ketogenic diet (Schoenborn, 1930) were the only antiepileptic therapeutic possibilities which are still of limited importance but used in the period between the appearance of bromides and phenobarbitone (PB).

Bromide therapy was optimized. Toulouse and Richet, for example, developed the concept of bromide application together with limited salt intake, so that the average dosage of bromides could be reduced without lowering its efficacy (Richet, 1903; Richet & Toulouse, 1899; Toulouse, 1900), because high chloride intake shortens the half life of bromides (Dreifuss, 1989). This was an important step since undesired side-effects had become obvious.

Critical comments regarding the side-effects of bromides became more frequent especially the chronic, sometimes even lethal, bromide intoxication. In 1905, for instance, Peterson mentioned dementia, intoxication, depression, mania and paranoia as typical undesirable effect of bromides. In spite of their remarkable antiepileptic efficacy he expressed the opinion that the epileptic patient would probably have been better off, if bromides had not been discovered.

THE APPEARANCE OF NEW ALTERNATIVE ANTIEPILEPTIC DRUGS

In 1912 Hauptmann introduced PB as a new AED with very good efficacy. Although bromides lost their importance, many authors as late as the 1930s, such as Rodhe, Winterseel, Sutherland, Szecsödy and Reitmann recommended them (Steinhoff, 1988).

With the appearance of phenytoin (PHT) in 1938 (Merrit & Putnam, 1938), antiepileptic therapy was enriched by a drug which was non-hypnotic. By 1940 Lennox suggested PHT as the only first-line AED. Table 1 shows the introduction of the main AEDs.

The introduction of carbamazepine (CBZ) and valproic acid (VPA) added further new drugs to worldwide accepted first-line treatments.

Bromides virtually vanished, mainly because of their side-effects and assumed lower efficacy compared with modern alternatives (Steinhoff, 1988). Twenty years ago, the Swiss epileptologist Schweingruber (1971) stated that bromides had no more than historical importance, and this was

Table 1. First announcement of antiepileptic efficacy of important antiepileptic drugs.

Bromides (BR)	1857 (Locock)
Phenobarbitone (PB)	1912 (Hauptmann)
Phenytoin (PHT)	1938 (Merrit & Putnam)
Primidone (PRM)	1952 (Richards & Everett)*
Ethosuximide (ESM)	1958 (Zimmermann & Burgemeister)*
Carbamazepine (CBZ)	1963 (Lorge)*
Valproic acid (VPA)	1964 (Meunier & Carraz)*

*See Kugler & Spatz (1984).

the common opinion of that time. But, this judgement was based either on case reports or non-controlled investigations and in some specialized epilepsy centres dealing with intractable epilepsies bromides were still used as add-on drugs in selected cases, mainly with generalized tonic–clonic seizures (GTCS) (Steinhoff, 1988).

THE COMEBACK

In spite of the use of modern first-line AEDs approximately 20–30% of all patients with epilepsies will not be completely seizure-free (Schmidt, 1988).

The observation of good bromide efficacy in selected cases encouraged the undertaking of a retrospective, controlled investigation (Steinhoff & Kruse, 1988). Antiepileptic treatment of 60 patients with GTCS, who had been treated with bromides alone (5 cases) or as an add-on drug, was analyzed. The results were compared with a very similar group of patients who had been on PHT and/or PB as basic medication. Surprisingly no significant difference was found regarding the antiepileptic efficacy and the frequency of side-effects between the bromide and the control groups. Of the 60 patients, 58% became free of GTCS or had a reduction of the GTCS-frequency of more than 50% without loss of efficacy for at least 3 years. All side-effects were reversible with dosage reduction or complete bromide withdrawal in a single case. Common side-effects were loss of appetite and weight, apathy, tiredness, psychomotor retardation and asynergic coordination. The success rate was 10% higher than in the control group. It was therefore claimed that there is an indication for bromides in every case of epilepsy with GTCS resistant to therapy with first line AEDs.

These observations are supported by various investigations of other epileptologists all published during recent years and reporting between 27% (Scheunemann, 1983) and 55% (Woody, 1990) improvement in the treatment of epilepsies with intractable seizures, so that several authors have very recently recommended bromides as an antiepileptic drug alter-

native (Boenigk *et al.*, 1985; Dreifuss & Bertram, 1986; Ernst *et al.*, 1988; Scheunemann, 1983; Steinhoff & Kruse, 1988; Woody, 1990).

The rather low rate of side-effects might be a result of the conditions of modern antiepileptic therapy with regular clinical and laboratory examinations of the patients, which allow the detection of undesired drug effects early enough to prevent serious complications.

Conclusion

More than 130 years after its introduction, bromide treatment in some patients with epilepsy of GTCS type has been re-established as an additional therapy in selected cases.

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