

## HISTORICAL NOTE

### Bromide, the first effective antiepileptic agent

The 2001 issue of the *British National Formulary* contains many antiepileptic agents listed under some 10 classes of anticonvulsants. Historically there had been no effective new antiepileptic drugs until the introduction of phenobarbitone. Hauptmann (1881–1948) in 1912<sup>1</sup> discovered its antiepileptic properties by accident when studying the anxiolytic effects of various drugs. Before that date, the only effective agent was potassium bromide, and like its more recent successors, the major therapeutic problem was obtaining a balance between suppressing fits and the frequent side effects.

At a meeting of the Royal Medical and Chirurgical Society in London on Tuesday 11 May 1857, Edward H Sieveking presented 52 cases of epilepsy (*Lancet* 1857;i:528). In the subsequent discussion, the President of the Society, Sir Charles Locock, Queen Victoria's physician accoucheur, made comment. He had used potassium bromide to treat what he called hysterical epilepsy. In most instances the fits were mainly menstrual or catamenial or uterine as they were called. Locock cited a German report that 10 grains (0.66 g) of potassium bromide taken three times a day caused reversible impotence. Locock therefore tried bromide on non-epileptic hysterical women troubled by "sexual excitement", and found that it calmed that excitement. The report in the *Medical Times* and *Gazette* of 23 May 1857 (cited by (Bazire 1882<sup>2</sup>) noted:

"... a lady who had hysterical epilepsy for nine years and had tried all the remedies that could be thought of by various Medical men (myself (Locock) among the number) without effect. This patient began to take bromide of potassium last March twelve month, having just passed one of her menstrual periods in which she had two attacks. She took ten grains three times a day for three months; then the same dose for a fortnight previous to each menstrual period and for the last three or four months she had taken them for only a week before menstruation the result had been, that she had not had an attack during the whole of the period. He had tried the remedy in fourteen or fifteen cases, and it had only failed in one..."

Locock thought that a drug, which calmed "sexual excitement", might therefore modify the epilepsy. He obtained good results, but curiously failed to publish them. Gradually bromides were more widely used for non-menstrual epilepsy. Dr Charles Bland Radcliffe reported his experience<sup>3</sup> of bromide therapy:

"... I put this mode of treatment into practice in five or six cases of epilepsy in which uterine irritation was a prominent feature, and with very satisfactory results upon the whole. In the summer of 1858, I began to give this medicine almost promiscuously at epilepsy and epileptiform disorder

... and the conclusion at which I have arrived is, that bromide potassium is the only remedy in epilepsy upon which most dependance can be placed, and that a brighter future in the fortunes of epileptics may be dated from the evening when Sir Charles Locock gave utterance to the words which have just been quoted."

In his Lecture *Diseases of the Nervous System* (1878) Wilks observed:

"... being in the habit of using the iodide in epilepsy. I substituted the bromide for it. I was at first under the impression that it was acting as an absorbent, and was picking out for its operations those cases where the disease had a syphilitic or local origin; but when the cures came to be numerous, the explanation would not apply, and it was evident that a very valuable specific remedy had been obtained. ... I was not aware at that time that Sir C Locock had recommended its use..."

Sir Samuel Wilks (1824–1911), observed that:

"It is a great question whether this remedy which has so powerful an influence in checking the fits is really curative; whether indeed it has a permanent effect on the brain to render it less unstable."

He realised the lack of efficacy of other remedies:

"If any old woman had the possession of a herb or a salt which could antagonise the disease, the knowledge would be worth more than that of the whole College of Physicians."

Wilks was born at Camberwell, graduated from Guy's in 1848, and obtained the MD with gold medal in 1850. He was to become a highly successful physician, President of the Royal College of Physicians in 1869, and an influential, intellectual, and accomplished writer.

Russell Reynolds, physician at the National Hospital, Queen Square, in his monograph in 1861, said that he was aware of the reports about the efficacy of potassium bromide but had not then had opportunity to use it. Charles Bland Radcliffe from Queen Square, had employed bromides often, but curiously believed that potassium bromide acted by correcting a "semi-gouty" condition of the blood. Belladonna he thought was of doubtful efficacy, that opium was sometimes useful, and that alcoholic stimulants were trustworthy.

Trousseau, in his famous *Lectures on Clinical Medicine Delivered at the Hotel Dieu, Paris*, Lecture iii<sup>4</sup> contains an exemplary, detailed account of almost all the types of epileptic attacks with which the 21st century neurologist is familiar. Apart from belladonna, he is

dismissive of attempts at treatment, and shows his frustration in a way that many of us can share today:

"Is medicine, then, entirely powerless against this terrible disease? Not completely so..."

A footnote (p 98) by the editor Bazire rightly observes that curiously, Trousseau, though he mentions the use of bromides (by Dr Henry Guéneau)

"introduced by Sir Charles Locock in May 1853,\* appears not to have tried this drug in epilepsy, although it was the mainstay of treatment, far more effective than belladonna, until the advent of phenobarbitone".

Trousseau followed this remark by saying:

if bromide "... be capable of warding off epileptic seizures for a time, it should then be regarded as one of the most valuable remedies at our command." (p.99)

Gowers in chapter XIII. Of his *Epilepsy and Other Chronic Convulsive Diseases*,<sup>5</sup> observed that potassium bromide

"has almost superseded other drugs in the treatment for the disease ... the influence of bromide is in the majority of cases, transient not permanent. ... They have a direct effect on the nerve elements, diminishing for instance, reflex action in the spinal cord, and ... on the nerve cells of the brain."

Gowers' idea of modifying intrinsic neural activity was an important and new concept. Bromides, although initially slow to gain acceptance, held sway from the 1870s until well into the 20th century. Much experimental and clinical pharmacology has succeeded these pioneering efforts, but present day dilemmas clearly mirror the images of the past.

\*Bazire is in error in the year, which was 1857

J M S Pearce

304 Beverley Road, Anlaby, Hull HU10 7BG, UK;  
jmspearce@freenet.co.uk

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- 2 Bazire PV. Note by the editor. In: Trousseau A. In: Lecture iii. On epilepsy. In: PV Bazire, ed (translator). *Lectures on clinical medicine delivered at the Hotel Dieu, Paris*. Vol 1. London: New Sydenham Society, 1868:98–9.
- 3 Radcliffe CB. *Lectures on epilepsy, pain, and paralysis*. London: 1864:223. (Cited by Bazire ref 2 1868:116.)
- 4 Trousseau A. In: Lecture iii. On epilepsy. In: PV Bazire, ed (translator). *Lectures on clinical medicine delivered at the Hotel Dieu, Paris*. Vol 1. London, New Sydenham society, 1868:33–98.
- 5 Gowers WR. *Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment*. New York and Dover: Wm Wood, 1885, reprinted 1964.