Early Clinical Neurochemistry of CNS-Active Drugs. Bromides¹

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ABSTRACT

The use of bromides in medicine dates back to the beginning of the 19th century. The salts were used in neurological and mental diseases, particularly in epilepsy, up until their partial replacement by phenobarbital and ultimate displacement by dilantin. This article reviews the analytical methodology as it developed historically, and traces the application of chemical analysis of body fluids to monitoring for bromide toxicity (bromism) and then to investigation of the blood-brain barrier in various disorders of the central nervous system.

Index Entries: Bromides; analytical methods for bromides; history of bromides; bromides and the blood-brain barrier.

INTRODUCTION OF BROMIDES FOR THE TREATMENT OF EPILEPSY

Although clinical chemistry has had its main development starting well into the present century, its beginnings can be traced to the application of chemistry to problems of physiology in the last century. The same is true for clinical neurochemistry, but in a more primordial fashion. Few effective drugs were known for the treatment of nervous and mental

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diseases, and the compounded requirement for the application of chemical procedures to the analysis of bodily constituents and drugs in the body’s tissues and fluids ensured that the literature in this area would be limited.

One drug active in the central nervous system (CNS) that played an important role in medicine in the 19th century, continuing until the 1940s, was bromide. Potassium bromide, discovered in 1826, became known to medicine when it was included as a treatment for splenomegaly in the British Pharmacopoeia. It lasted there only a few years (1835–1851), but soon afterwards was recognized as a CNS-active drug. In the 12th edition of his textbook of materia medica and therapeutics, Alfred Baring Garrod (1886) stated:

“Bromide of potassium was first used for the purpose of causing absorption of the products of inflammation... About the year 1854, the author made somewhat extensive trials of it, in cases of syphilitic skin disease, in patients who were found to be intolerant of the action of iodine. In these trials he found that it caused much drowsiness, and in very large doses, want of power over the extremities; he also was informed by several patients that it had a great effect upon the sexual function, acting as an antaphrodisiac, causing loss of virile power, and diminished venereal desire. Its prolonged administration often causes an eruption of acne. In 1857, Sir Charles Locock showed its efficacy in epilepsy connected with hysteria, and in nymphomania. Previously to these dates it had been stated to produce anaesthesia of the palate and fauces... It is still undecided how far its sedative effect on the nerve-centres, and its depressant action on the heart, are due to bromine, and how far to the alkali-metal with which the bromine is combined.”

Garrod went on to list various indications for potassium bromide, of which extensive use had been made in diseases of the nervous system: as a soporific in some forms of sleeplessness, when opium causes excitement, and henbane or belladonna fail to induce sleep; in convulsive nervous affections such as chorea and epilepsy, hysteria, and in the agitation of delirium tremens. The recommended dose was 5–30 grains (approx 0.3–1.8 g) of KBr; or 2–20 grains (approx 0.1–1.2 g) of ammonium bromide.

Locock’s recommendation for the use of bromide was not as direct as suggested by Garrod. Actually, it was following a lecture by E. H. Sieveking, a neurologist, to the Royal Medical and Chirurgical Society of London on May 12, 1857, on the pharmacological treatment of epilepsy, that Locock spoke about potassium bromide. Having read of its effect in causing impotence, he tried the compound in some hysterical women, one of whom was an epileptic, and had considerable success. At that time, onanism was regarded as a cause of epilepsy, so a drug to reduce libido was considered important in treatment. His statement was included in the report of the meeting, but Locock, an obstetrician, figured no further in the bromide story. Soon after that meeting Sieveking’s book on