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BROMIDE INTOXICATION

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The cumulative effect of drugs is a well-known phenomenon, and in prescribing certain medicines—for instance, digitalis—the signs of toxicity are kept constantly in mind. The cumulative action of bromide has not, however, always received the attention it deserves, with the result that bromide intoxication is by no means rare.

Bromide is one of the more commonly prescribed toxic drugs. A fairly comprehensive investigation of the prescriptions issued in 1928 under the national health insurance medical scheme showed *inter alia* that the drugs most commonly prescribed were, in the following order: (1) sodium bicarbonate; (2) ammonium carbonate; (3) sodium salicylate; (4) tinct. nuc. vom.; (5) potassium bromide; with ammonium bromide and sodium bromide much lower in the list. About one out of every ten prescriptions contains bromide as a principal ingredient. Since the total number of prescriptions issued in 1928 was 52,000,000, the inference is that something like 5,000,000 prescriptions containing bromide were dispensed in that year under the insurance medical service. An analysis made by one of us this year of 200 consecutive prescriptions at each of three different chemists showed that bromide was the chief ingredient in one out of every seven prescriptions for internal use (prescriptions for internal use form approximately 80 per cent. of all prescriptions), potassium bromide being the form in which it was most commonly prescribed. These figures give some idea of the widespread use of bromides; this prevalence is probably partly due to the fear of the barbiturates, and is likely to be increased rather than lessened by the recent changes in the Dangerous Drugs Act (see Case 3).

The fact that bromides may be toxic is well recognized, and most textbooks of pharmacology describe the physical and mental symptoms of bromism. The warning sign that is usually stressed is the skin eruption, particularly bromide acne. We have found skin lesions to be relatively rare, and it is significant that Craven¹ observed them only once in eight cases of severe bromide intoxication, while Sharpe² reports them as being present in only one out of his ten cases. It has been our experience that when a patient who is having bromide develops mental symptoms the possibility of intoxication is usually overlooked unless a definite rash is present.

It is difficult to give figures regarding the frequency of bromide intoxication, but data on this point are being collected. Some idea of the problem can be gathered from the fact that the cases quoted in this paper came under our care within a period of five months, and they are only a selection of the available material. In common with other observers, we have failed to find any clinical signs or symptoms that are peculiar to bromide intoxication alone, and the diagnosis must therefore ultimately

depend upon the presence of the toxic symptoms, together with a raised blood bromide, the symptoms disappearing on the withdrawal of bromide and administration of sodium chloride.

Technique of Blood Bromide Estimation

In order to estimate the blood bromide use was made of Walter's test as modified by Hauptmann³ and later by Dixon. This test has been in general use at the Central Pathological Laboratory of the London County Council Mental Hospitals Service for the past two years.

Two c.cm. of serum are delivered into a test tube and 4 c.cm. of water and 1.2 c.cm. of 20 per cent trichloroacetic acid are added. After shaking well and allowing to stand for ten minutes the mixture is filtered through No. 1 Whatman 7 cm. filter paper into another test tube. Two c.cm. of the filtrate are then taken and 0.4 c.cm. of 0.5 per cent. gold chloride solution added in a special comparison tube. The colour produced by this mixture is then compared against a series of gold-bromide standard tubes by eye, or in the colorimeter against the nearest of them.

Preparation of standard solutions for serum: 1.45 grams of pure dry sodium bromide are dissolved in 1 litre of water to make a stock solution. The standard sodium bromide solutions made as the table indicates are corrected to eliminate the error due to absorption of sodium bromide in the precipitation of protein from serum.

0.5 c.cm. of stock solution diluted to 10 c.cm.	= 25 mg. %
1.0 c.cm. " " " " 10 c.cm.	= 50 mg. %
1.5 c.cm. " " " " 10 c.cm.	= 75 mg. %
2.0 c.cm. " " " " 10 c.cm.	= 100 mg. %
etc. ranging up to 500 mg. per cent. of sodium bromide.	

Five c.cm. of these standard bromide solutions are added to 1 c.cm. of 0.5 per cent. gold chloride and 1 c.cm. of 20 per cent. trichloroacetic acid in the comparison tubes, usually a rack of fifteen tubes from 25 mg. to 375 mg. per cent. by 25 mg. steps being required. The above standards are so arranged that direct comparison gives the milligrams of sodium bromide percentage in the serum treated as described. Provided the tubes are hermetically sealed and kept in the dark they may be used for some months.

The test is a very simple one, and has been found sufficient for all clinical purposes, the results being accurate to 5 per cent. either way. The more accurate microtitration methods are not required when dealing with the problem of intoxication; since it is only when the blood bromide reaches levels of 50 mg. and upwards (normal is 0.5-2.5 mg.) that it begins to be of clinical importance.

Symptomatology and Case Records

The degree of intoxication varies greatly from case to case, and in our present state of knowledge any classification must necessarily be arbitrary. For the sake of convenience we have grouped our cases under three headings: fatal, severe, and mild.

1.—FATAL INTOXICATION

Bromides when introduced into the body replace the chlorides, the total blood halide remaining constant. In experimental work on animals Bernoulli⁴ found that a 40 per cent. replacement in the blood of chlorides by bromides was fatal to rabbits. In the following case there was a blood bromide of 500 mg. per cent., which is equivalent to a 47 per cent. replacement of sodium chloride in the blood.

Case 1.—Mrs. A., aged 29, was referred to a psychiatric clinic on March 6th, 1936, by a general hospital, to which she had been admitted suffering from depression and insomnia. There was no history of previous mental symptoms, and her general health had been fair up to 1934, when she had "pneumonia." In 1935 she had bronchitis with pleurisy, and in February, 1936, "slight rheumatic fever," together with a recurrence of the pleurisy. On examination there were no signs of physical disease, and the diagnosis of "mild depression" was made. She was advised, however, to remain at the general hospital for a further period. This she did, and made an uneventful recovery, being discharged to a convalescent home on April 8th. During this illness the only drug she received was luminal, 1/2 grain o.n.

A week later she attended the clinic again as an out-patient, complaining of a recurrence of insomnia, and she was then put on mist. ammon. brom., 5 grains t.d.s. However, a relapse set in, necessitating her readmission to the same general hospital on April 25th, where, three days later, she was put on mist. tribromide, 30 grains t.d.s. She was seen again at the clinic on April 28th, when a diagnosis was made of "depression with hysterical features." One month later she was reported as "still in a very hysterical state, depressed, unable to stand, loses her voice." On May 30th she was "very depressed, delusional, and noisy." She became increasingly noisy, and was removed to the local observation ward on June 3rd in a condition thought to be "hysterical stupor." During the preceding six weeks she had received the bromides regularly, but no other medicine had been given excepting luminal, 2 grains, on May 31st and June 1st. On June 10th she was seen by one of us, and the diagnosis of bromide intoxication was made. At that time she was extremely ill and dehydrated. Temperature 100°; pulse 116. The skin was very dry, but there was no rash. The heart was not enlarged, the sounds were clear; blood pressure 120/85. Mentally she presented a typical picture of low muttering delirium, being disorientated and terrified by visual hallucinations. A blood bromide estimation gave a reading of 500 mg. per cent. Treatment by intravenous salt solution and the forcing of fluids was instituted, but, in spite of the blood bromide dropping to 420 mg. per cent., the patient died within forty-eight hours.

At the necropsy the heart was found to be small; the heart muscle was flabby and showed some myocardial degeneration, not of recent origin. There were some old pleural adhesions, and the lungs showed a slight terminal hypostatic pneumonia; there was also a recent cystitis.

Describing bromism Cushny⁵ states: "The symptoms generally disappear on the withdrawal of the drug, but in his reduced condition the patient is liable to infectious disease, and in a number of cases of chronic bromide poisoning the immediate cause of death has been an attack of bronchitis or pneumonia." In the previously described case, although a mild terminal infection was present, we feel that death was due to bromide overdosage. Although death directly due to bromide is rare, Bunbury and Wagner⁶ mention two cases. These investigators, studying the incidence of bromism among psychotic patients, examined 1,000 routine admissions to the Colorado Psychopathic Hospital, and found that seventeen of the patients were admitted purely on account of bromide intoxication. Two of these patients died, and the authors state that they "feel that in these two cases death was due to the indiscriminate use of bromides only."

Even if a direct bromide death is quite exceptional, the intoxication may often contribute to the fatal termination.

We have recently seen an old lady become semi-comatose (with a blood bromide figure of 360 mg. per cent.) and then rapidly succumb to bronchopneumonia before the drug could be eliminated. Bunbury and Wagner⁶ mention four cases that died of cardiac decompensation, in which they felt that the excitement due to the bromide delirium had been an important contributory cause of the patients' death through placing an undue strain on an already weakened heart.

2.—SEVERE INTOXICATION

In this group either the mental or the physical symptoms may predominate. In evaluating the former it is important to know the patient's mental state before receiving bromide. If bromide intoxication is superimposed on any other mental illness it tends to give rise to a mixed picture, which often simulates schizophrenia. In the absence of any pre-existing psychosis it is usually a delirium or confusional state that is produced, with hallucinations and varying degrees of disorientation. These toxic states frequently necessitate the patient being removed to the observation ward or mental hospital. The common physical signs of intoxication are the dry skin, furred tongue, tremulous hands, slurred speech, and unsteady gait. The gag reflex tends to be lost early. Whether the mental or physical symptoms preponderate in any given individual would appear to depend upon the underlying constitution and personality of that individual.

The second case illustrates bromide intoxication arising in a patient admitted to a general medical ward for investigation of an enlarged thyroid.

Case 2.—Miss B., aged 42, was admitted on March 17th, 1936. On physical examination the thyroid was found to be enlarged, but no exophthalmos was present. The pulse rate was 92. The heart was not enlarged. The medical consultant found "no marked toxicosis." The patient's mental state was normal, and there was no previous history of nervous or mental symptoms. She was put on mist. tribromide, 30 grains t.d.s., on admission, which was later reduced to twice daily. Five weeks later (on April 22nd) she began to complain of dizziness, and was noted as being "hysterical and delusional." (At this time the basal metabolic rate was +14.) On May 12th she was seen by one of us, and was found to be confused, partially disorientated, and to have delusions that the other patients were talking about her. Physical examination revealed a coarse tremor of the hands and an unsteady gait. She had no bromide rash. Bromide intoxication was suspected, and her blood bromide figure was found to be 270 mg. per cent. The bromide was discontinued and salt given. She made a rapid improvement, was discharged on May 29th, and has remained well since.

The third case illustrates a more severe intoxication, occurring in a patient who had recently substituted bromide for medinal to overcome sleeplessness.

Case 3.—Miss C., aged 64, a school teacher, was admitted to the Maudsley Hospital on July 10th, 1936, in a state of great restlessness and confusion. She had no previous history of mental or nervous symptoms, and her memory was unimpaired. She had occasionally taken medinal for insomnia, but since May, 1936, when the sale of this drug was further restricted under the Dangerous Drugs Acts, she started to take sedobrol, for which no prescription was required. Each cube of sedobrol contains 17 grains of sodium bromide. The cubes were pleasant to suck, and she would on occasion take them during the day. She remained in normal health until about June 19th, when she started to have difficulty in remembering words. This increased, and on July 1st she was forced to stop work. During the week following she became increasingly restless and confused, and was terrified by visual and auditory hallucinations.

On admission she appeared toxic. Temperature was normal, pulse 100. Arteries slightly thickened; heart not enlarged; blood pressure 122/75. No skin lesions were present. Examination of the nervous system revealed sluggish pupils,

exaggerated deep reflexes, coarse tremors of the fingers, slurred speech, unsteady gait, Rombergism, and absent palatal reflex. There was incontinence of urine, but examination of the urine was negative. Examination of the blood showed a normal blood urea percentage and a blood bromide of 290 mg. per cent. The mental state showed great confusion and restlessness (she tried to climb a tree in the garden); she was disorientated for time and place; visual hallucinations were present by day, but more marked at night. She was placed on salt at once, and within forty-eight hours of admission showed definite improvement. On July 21st the blood bromide was 150 mg. per cent. At that time, although much improved physically and although the hallucinations had ceased, she was still suspicious and slightly confused. Thereafter her progress became more rapid, and by August 7th she was well excepting for slight physical weakness and a mild feeling of depression. Her blood bromide had dropped to 60 mg. per cent.

3.—MILD INTOXICATION

There is, finally, a very important mild toxic group, in which the symptoms are largely subjective and where the taking of a mental status may reveal little out of the ordinary. The patient, however, feels tired or weak, is "not his old self," or is "unable to concentrate"; complains of loss of appetite, failing memory, or broken sleep. These symptoms quickly clear up when the bromide is eliminated from the system. The next case is quoted to illustrate this group.

Case 4.—Miss D., aged 24, factory hand. Treated at hospital for hysterical fainting attacks. She first attended the out-patient department on May 28th, 1935, and continued to attend regularly until January, 1936. Her condition showed little change. On January 8th, 1936, she was first put on bromide, 5 grains t.d.s., which on February 8th was increased to 20 grains t.d.s. On February 26th she became puffy under the eyes and very pale, and her mother said she had become depressed and more bad-tempered. Her appearance suggested nephritis, but, except for a trace of albumin, investigations were normal. On March 18th she complained that she was losing her memory; when walking into shops she would forget things and have to walk out. Her conduct at home was becoming more erratic. Bromide intoxication was not thought of at this time, and it was only on carrying out an investigation on bromide levels in the out-patient department that it was found that her blood bromide was 310 mg. per cent. Removal of bromide and substitution of salt relieved these symptoms, her memory improved, and the depression vanished. The physical appearance suggestive of nephritis completely cleared up. She still attends the out-patient department in about the same condition as at her first visit.

Toxic Threshold

In our experience certain types of patients would appear to be especially susceptible to intoxication. Patients with arteriosclerosis, anaemia, impaired renal efficiency, or organic heart disease are more likely to show early evidence of toxicity. In general, the older the patient the greater the liability to intoxication, so that 150 mg. per cent. of blood bromide is significant in a man aged 50, while it could probably be ignored in a man aged 22. There is, however, a large "unknown" factor, for although the normal level is under 3 mg. per cent., yet it can sometimes be raised to 200 mg. without evidence of serious toxicity, and levels of over 350 mg. per cent. have been recorded without symptoms being observed. Owing to this wide variation of level at which toxic features appear it is impossible to give a definite toxic threshold that would apply to all cases, but it is our opinion that levels of under 100 mg. per cent. can usually be ignored; that in the range from 100 to 200 mg. per cent. symptoms are likely to appear in elderly patients or in those with impaired cardiovascular or renal efficiency; that levels of over 200 mg. per cent. produce symptoms in most cases. It is rare for a patient to be

able to tolerate a blood bromide of 300 mg. per cent. without ill effect.

The following case illustrates a severe intoxication in a man with arteriosclerosis with a blood bromide of only 190 mg. per cent.

Case 5.—Dr. X., aged 55, a medical man, was admitted to the Maudsley Hospital on July 7th, 1936, for a confusional state. During the war he had had a nervous breakdown, but made a good recovery and had been at work steadily since. He took small doses of bromide for insomnia, but his general health had been very good excepting for a tendency to a blood pressure of about 200 mm. On June 2nd he was involved in a motor accident, and was dazed for an hour and a half with complete amnesia for most of this period; he also received injuries to the face, jaw, and back. He was able, however, to continue his work, and two days after the accident attended a medical meeting and a Masonic dinner. Six days after the accident he was x-rayed, owing to persistent pain in the shoulder and jaw, and was found to have fractures of the scapula and mandible. He was now put to bed and given bromide, 15 grains t.d.s., with an occasional extra dose at night. His condition rapidly changed: he became depressed and suffered from nightmares; during the day he had palpitations; the headache, present since the accident, was more severe, so that he had to give up all work. Photophobia developed, and his vision for colour became disturbed. His room had to be darkened. Five days previous to admission he began to experience alarming hallucinations, but retained sufficient insight to view these phenomena with objective curiosity. Bromide at this time had been taken for a period of one month.

On admission he was dull and confused. His sense of temporal perception was impaired, so that interviews with the doctor were either forgotten or misplaced in time. Hallucinations persisted. Examination of the nervous system was negative. There was no skin rash. The diagnosis of bromide intoxication was made, and the blood bromide level was found to be 190 mg. per cent. Treatment with sodium chloride, 50 grains four-hourly, and ample fluids produced a rapid amelioration of his symptoms. Medinal was substituted for the bromide to ensure sleep. In six days the hallucinations had completely disappeared and the blood bromide level had fallen to 75 mg. per cent. Eleven days after admission he felt sufficiently well to leave hospital and go to a large medical conference. The depression had been replaced by a mild euphoria, and on his return to London he reported residual symptoms of fatigue and a certain difficulty in concentration, probably the effect of the concussion and the arteriosclerotic complications. His blood pressure while in hospital was 170.

The severity of the intoxication in this case was probably due to the accompanying arteriosclerosis, since in many individuals a blood bromide of 190 mg. per cent. can be tolerated with little distress.

Therapeutic Considerations

Bromide is used chiefly in the treatment of epileptics, psychotics, and neurotics. A discussion of the treatment of epilepsy is outside the scope of this paper. With regard to patients in mental hospitals, it is the authors' opinion that it is possible and preferable to use methods other than that of prescribing large doses of bromide to obtain the necessary relaxation and rest. That bromide tends to be the regular "diet" of the neurotics was brought out very clearly by estimating the blood bromides of fifty consecutive admissions to the Maudsley Hospital—an analysis of these figures has been published elsewhere.⁷ It is difficult to escape the conclusion that in many cases bromides are given as a routine measure without any realization of the possible ill effects on the patient.

It is beyond dispute that a considerable number of "nervous" cases do benefit from taking bromide. It is difficult to delimit this group, but it probably comprises chiefly those in whom there is temporary increase in anxiety, and where there is reason to believe that outside

events are playing a prominent part in causing it. Menopausal conditions and certain cases of sexual excitability also appear to be particularly helped by bromide, as are cases in which there is much irritability.

Bromide acts by replacing the chlorides in the body, the rate of substitution depending upon the quantity of bromide given, the fluid and chloride intake, and the renal efficiency of the individual. As the salt intake varies from individual to individual, so the amount of bromide remaining in the body after a standard dose also varies. If 50 grains of bromide are given to one person who is on a low salt diet and has a small fluid intake the blood bromide at the end of twenty-four hours will be appreciably higher than when the same amount of bromide is given to a patient who is on a normal diet. Therefore prescribing bromides without knowing the chloride-fluid intake is tantamount to prescribing an indefinite quantity of bromide. This, in part, explains why certain patients, receiving 10 grains of bromide three times a day, develop toxic symptoms in four to five weeks, while others can take the same dose for twelve months and benefit from it. It is difficult, therefore, to lay down rules as to dosage for any given individual. This must be arrived at by observing the effect of varying amounts of the drug.

The treatment of bromide intoxication when established or suspected is a simple procedure. The bromide is immediately stopped, large quantities of fluid, preferably normal saline, are given by the mouth, and sodium chloride, 20 to 40 grains, is administered four-hourly. Figures given in a previous paper by one of us⁷ showed that when no salt was given relatively high amounts of bromide were still present in the blood of patients one to three months after the medicine had been discontinued.

Conclusion

As a result of our investigations we have come to realize how little is known at present of the precise indications for bromide therapy and the best methods of employing it. We do not wish to appear to overstress its dangers nor to undervalue its use. However, within the last year three doctors have been admitted to the Maudsley Hospital suffering from bromide intoxication, none of whom had appreciated the true cause of their illness through ignorance of the cumulative effect of this drug. This and other evidence suggests that throughout the country there are many similar cases being overlooked, resulting in a preventable quota of admissions to mental hospitals and much chronic ill-health.

Summary

1. Figures are quoted to illustrate the widespread use of bromides.
2. The toxicity of bromides is discussed.
3. A simple test for estimating bromide in the blood is given.
4. Symptoms and signs of fatal, severe, and mild intoxication are described and illustrated by case records.
5. Conditions predisposing to intoxication are suggested. The toxic threshold is discussed.
6. Therapeutic considerations are briefly considered.

Our thanks are due to Sir Frederick Menzies and Dr. E. Mapother for permission to publish the cases, also to Dr. Golla and the staff of the Central Pathological Laboratory of the London County Council, Mental Hospitals Department, who very kindly did the chemical tests.

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DIABETES MELLITUS IN CHILDHOOD *

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The following is a summary of the cases I have seen personally during the last ten years at the Hospital for Sick Children, Great Ormond Street.

TABLE I

	Boys	Girls	Total
Number of cases	44	27	71
Deaths	4 (9 per cent.)	6 (22 per cent.)	10 (14 per cent.)
Left clinic	—	—	11*
Family history of diabetes	8 (18 per cent.)	8 (30 per cent.)	16 (23 per cent.)

* Seven of these are attending other clinics and were well when last heard of.

Diagnosis

The symptoms in children are in most cases the classical ones—thirst, polyuria, and wasting. Usually only one to four weeks elapse between apparent normal health and the appearance of clinically unmistakable disease; in some, however, the onset is more gradual, and a history of lack of well-being for several months before the onset of the typical symptoms may be obtained. The common complaints in this period have been lassitude, a stationary or decreasing weight, and occasionally enuresis; in one patient typical symptoms appeared within a week of an attempt to cure this lassitude by large doses of dextrose. Two patients who were in hospital for other reasons were found on routine examination to be passing sugar. Neither had any symptoms at the time; both have since developed into typical cases.

It is obviously incapable of proof, but I believe that some of these patients, if given a correctly balanced diet before the onset of symptoms, could be prevented from developing the disease for many years. It is therefore wise to test the urine in all cases showing debility and failure to gain weight. In a certain number sugar will be found, and it will be necessary to investigate further; the dextrose tolerance test, repeated if a doubtful or unusual type of response is obtained, will usually prove diagnostic. It is necessary to continue the test for three hours, as in some cases the only abnormality is a failure to return to normal within that time. The urine should of course be examined simultaneously to exclude a low renal threshold for sugar. It is often sufficient to give the dose of dextrose to the fasting child and to estimate the blood sugar two hours later. If it be below 0.12 gram per 100 c.cm. it is safe to exclude diabetes; if it is higher, a full investigation will be necessary.

Diet

In children the aim of treatment is twofold: first, to enable the child to be happy, active, and healthy, and, secondly, to prevent the progress of the disease. The first is relatively simple, but the second is difficult and often impossible.

Diet is still the most important factor in treatment. It must be sufficient to allow normal activity and growth, but any excess food above this is deleterious. There is no satisfactory formula whereby the caloric requirements can be calculated for any given child. The following table shows the average calorie intake which in the children in this series has allowed normal growth.

* Read in the Section of Diseases of Children at the Annual Meeting of the British Medical Association, Oxford, 1936.