URÆMIA IN METHYL BROMIDE POISONING: A CASE REPORT

BY

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Publications on methyl bromide poisoning have become more frequent in recent years; and it appears that delayed drunken sensation, giddiness, headache, epigastric discomfort, vomiting, hesitant and indistinct speech, numbness and tingling sensations of the feet, ataxia,smarting of the eyes, suffusion of the cornea, and, occasionally, diplopia and nystagmus, are the salient clinical features. Where methyl bromide has come into prolonged contact with the skin, a burning sensation for several hours with delayed blister formation has been described. The contents of the blisters are said to be of a gelatinous character. In the fatal cases convulsions and often twitching precede death. An excellent review on this subject has appeared recently in this Journal, in which, based on their own experiences, Clarke and others (1945), Wyers (1945), and Butler and others (1945) related a number of instances, reviewed the literature, and described the chemical properties of the gas and its industrial uses.

Some authors mention the occurrence of albuminuria, and a few necropsy reports refer to the involvement of the kidneys. Degenerative nephritis has been described by Viner (1945); and glomerular dilatation and degenerative changes in the tubules, "most severe in the convoluted tubules in which they have gone on to virtual necrosis," by Clarke and others (1945). But, "in view of the toxic effect of methyl bromide on the kidneys which is seen at autopsy, it is remarkable that cases so far described show no signs of renal dysfunctions" (Holling and Clarke, 1944). Our perusal of the literature seems to corroborate this statement, but it should be noted that Leffler and Ruetimeyer (1920) found hyaline casts and white blood cells in the urine of one patient, who also showed a blood urea of 85 mg. per 100 c.c.m. of blood. The description of a case exhibiting the symptoms of uræmia may, therefore, be of interest.

Case Report

A. B., aged 28, was admitted to hospital on April 13, 1946, as a casualty. He said he had been involved in a fire on the previous day and had fought it, with several other men, for about an hour and a half. After the incident he was nauseated and vomited several times. He was giddy and his eyes were very sore, but he was able to walk the several hundred yards necessary to go home. He retired to bed at once "feeling like passing out" and went to sleep easily. He awoke some hours later feeling his feet "burning," and discovered they were grossly blistered.

Examination.—On the dorsum of each foot was a huge blister and several smaller ones, together covering an area corresponding to the uppers of his shoes. The blistered areas were surrounded by a thin erythematous zone. The patient was well nourished and well developed. He was bright and co-operative but looked ill. His feet were giving him moderate pain. Examination of the heart, lungs, and abdomen did not reveal any abnormality. His tongue was furred, the temperature 98° F., the pulse rate 80 per minute, and blood pressure 110/80 mm. Hg.

Operation.—Under general anaesthesia the blistered areas were cleansed with soap and water and Cetavlon. Almost all the blisters were found to contain a grey gelatinous fluid and not the usual aqueous material. All blisters and contents were removed. The raw area was dusted with penicillin and magnesium carbonate powder, and dressed with vaseline gauze. A course of sulphamezathine was instituted, and the patient had a total of 12 g. A full course was not given because of the patient's later condition. The burnt areas healed well and comfortably in twenty days without redressing.

Course of Systemic Disease.—On April 14, one day after admission, the patient appeared bright and comfortable in the morning. In the afternoon he recommenced vomiting and developed persistent hiccoughs. Urine was scant on this and the following day, when vomiting and hiccoughing persisted, and an intravenous glucose-saline drip was administered. On April 17 the patient became more and more apathetic and sleepy, and found it a strain to talk. There was no oedema, and no neck
rigidity; Kernig's sign was negative, and fundi and discs were clear. The tongue was dry and coated. On the basis of the above findings, and those shown in the Table, a diagnosis of uremia was made. The temperature on this day was 97° F. The urine was loaded with albumin and microscopically revealed a moderate number of red cells and granular casts and a few leucocytes.

On April 18 the patient was slightly better and less sleepy, but his blood urea was still high (see Table). His face appeared somewhat puffy. He passed 8 oz. of urine, and 30 oz. during the following day. On April 20 the urine contained less albumin, and scanty red cells and granular casts.

On April 21, for the first time since admission, the urinary output was greater than the fluid intake. The following day he was much improved, but had developed an acne-like rash on his arms and legs. An electrocardiogram revealed sinus bradycardia. The T-wave was somewhat flattened, but there was no other abnormality. There was a small hæmatoma of the left conjunctiva. On April 23 improvement continued, though there was some conjunctivitis and the face was still puffy. The fundi were clear.

On April 24 he was sufficiently improved to take an interest in events around him. He spoke clearly and was mentally quite bright. The puffiness of his face had disappeared and his tongue was clean and moist. He had no headache or dizziness. Clinical and radiological examination of the lungs revealed nothing abnormal. The acne-like rash had disappeared. All tendon reflexes were normal though the plantars were not tested because of the foot lesions.

From now on his general condition improved rapidly (see Table). Haemoglobin was 79%, the red-cell count 4,960,000 per 100 c.mm. of blood, the white-cell count 7,850. By April 27 the urine was free from albumin and there were a few hyaline and granular casts in the deposit, but no red blood cells. On April 28 the patient had no residual symptoms except that he felt somewhat tired. On May 2 the urine was free from albumin, but there was an occasional granular cast still present. On May 4 he was discharged.

Two months later he was re-admitted for a check examination. The urine was clear and acid, with no albumin, specific gravity 1,018; the mean value of the urea clearance test was 55% of normal function. The urea concentration test was not conclusive.

On Dec. 24, 1946, he was re-admitted for renal function tests. His general condition was fairly good, and he was back at work. He had lost 13 lb. in weight since the fire incident. The urine was clear, and the urea clearance test 40% of normal function. An intravenous pyelogram showed normal excretion of the radio-opaque substance. No abnormalities of the kidneys were seen on the films.

On March 4, 1947, he was seen in the out-patient department. There had been no further loss of weight, but he still felt tired. He was now working 42 hours per week. The urine was clear.

The clinical features of this case of burns seemed so unusual that it was decided to investigate the aetiology as fully as possible.

### The Incident

On April 12, 1946, fire broke out in the machine room of a factory which purified and packed cotton wool for medical purposes. The room is about 100 ft. by 50 ft. and has a sloping roof of average height, approximately 10 ft. There are nine machines in the room, arranged in three rows of

#### Table

SHOWING PROGRESS OF PATIENT DESCRIBED IN THE TEXT

<table>
<thead>
<tr>
<th>Date</th>
<th>Blood urea (mg. per 100 c.cm. of blood)</th>
<th>Serum protein (mg. per 100 c.cm. of blood)</th>
<th>Serum bromide (mg. per 100 c.cm. of blood)</th>
<th>Serum chlorides (mg. per 100 c.cm. of blood)</th>
<th>Serum potassium (mg. per 100 c.cm. of blood)</th>
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three. These process the cotton from a washed and bleached stage to the final product. Fires are frequent in them and are usually due to metal, e.g. nails, etc., which are accidentally baled up with the cotton wool and which strike sparks against the machinery. The employees are highly trained to deal with these fires, and the following arrangement of extinguishers is installed.

1. Carbon dioxide is stored in cylinders on the wall of the room. From these cylinders pipes lead to sprays, three of which are situated above each machine, controlled individually by switch. Also there is a master switch beside the cylinders. It is stressed that the gas is pure carbon dioxide.

2. Methyl bromide hand extinguishers, containing pure methyl bromide, are at hand.

In the incident with which we are concerned, fire broke out and progressed with great ferocity. All the carbon dioxide switches were opened, and in addition forty methyl bromide extinguishers were used very lavishly indeed and, as it appears, rather haphazardly; for example, they were at times directed into the faces of the fire-fighters.

The fire lasted approximately two hours and the patient, a machinist, was present in the room for approximately an hour and a half. On three occasions he went outside for a few minutes' rest. He said that while in the room the atmosphere became thick and misty with spray and smoke. His throat was irritated and his eyes became sore. When he finally left the building he felt ill, but with help walked half a mile to his home. He vomited on the way home and again on going to bed. He felt "as if he had too much to drink." The blisters on his feet became manifest a few hours later.

We interviewed three other men who were in the machine room during the fire as long as or longer than the patient.

J.S.—This man was in for two hours, during which he spent a considerable time in a confined space between a machine and a wall. He complained of sore throat and sore eyes, and of vomiting a great deal after coming out of the room. He went home and remained in bed the next week, suffering from malaise, anorexia, and headache. He was off work for three weeks. The day after the fire he saw his own doctor, who reported nothing seriously wrong.

C.W.—This man was in the fire for about an hour and a half. He gave a similar story to J.S., but reactions were less severe. He was off work for a week. He suffered a small first-degree burn of his forearm which he blamed on to the methyl bromide. It quickly healed and needed no treatment.

A.C.—The story was similar to that of C.W., but he was off duty two or three days only, and was not burned.

C.J.—He also fought the fire for some two hours. He suffered the same symptoms as the others, and was in bed one week and off duty three weeks.

Discussion and Conclusion

In our patient there was no history of kidney disease before the fire-fighting incident. There was no history of scarlet fever, tonsillitis, mercurial or mercuric chloride poisoning, or contact with any substance that could cause renal damage. The intravenous pyelogram appeared to rule out a congenital abnormality of the kidneys. Two months before the incident he was discharged Category A1 from the Army. In a period of six years in the Forces he once contracted jaundice during an outbreak of infective hepatitis in Italy in 1943. He was then sent to hospital for ten days. There was no other history of previous illness. No signs of residual liver damage were noted during the repeated hospital treatment for his present complaint, and frequent urobilinogen tests of his urine never showed undue increase. He had been fighting his first fire of the kind for six years. The fire itself consisted of burning cotton wool in a partly processed state. This gives off clouds of very thick, black, irritating smoke. Our inquiries into the amount of toxic gases which could evolve from burning cotton wool revealed that only negligibly small quantities could have been generated; of these, carbon monoxide would be the most important, particularly as the fire was partly of a smouldering nature. Our patient did not show any definite signs of carbon-monoxide poisoning. He did not suffer from muscular paralysis or the typical early sensation of tightness in his temples. His symptoms, however, were consistent with the known toxic effects of one of the fire-fighting materials employed, namely methyl bromide; They were: delayed drunken sensation, vomiting, suffusion of the cornea, and, though he was wearing boots and socks during the fire, gross blister formation on his feet. In accord with a similar case described by Gray (1944) and a note in Wyer's paper (1945), the blister content was of a gelatinous character in contrast to the more aqueous nature of blister fluids due to carbon dioxide burns. Moreover, the blood bromide was raised to 12.5 mg. per 100 c.c.m. of blood (0.1-5 mg. per 100 c.c.m. normal) on the fifth day after the incident. It may well be that the initial figure was higher and that elimination was promoted by saline drips. As it is understood that no bromide of any description was taken by the patient before or after the day of the fire, this rise indicates that considerable quantities of bromide or bromide compounds must have entered the blood stream in some other manner. According to an estimate by chemical experts the total amount of methyl bromide used in this fire was about 350 lb. It was handled in a rather
indiscriminate way with inadequate provision for ventilation and removal of the vapour. The presence of large volumes of carbon dioxide employed as the second fire fighting agent (150 lb. were discharged from pyrene cylinders) and an unknown quantity of the combustion products of the cotton wool, must have acted as a precipitating factor for a maximal inhalation of the methyl bromide vapours. Some of the initial symptoms, such as headache and irritation of the throat and eyes, may partly be ascribed to the high concentration of carbon dioxide present, but it can hardly be blamed for the subsequent clinical picture of uræmia with which this report is chiefly concerned.

The first uræmic symptoms started two days after the fire-fighting incident, when our patient developed hiccoughs, recommenced vomiting, and became drowsy. His urine was then scanty and loaded with albumin, and contained red and white blood cells and granular casts. Further manifestations were: a marked rise of his blood-urea to over 250 mg. per 100 c.c.m. of blood, some increase of indican in the serum, and a lowered total serum protein (5-5 mg. to 4.4 mg. per 100 c.c.m.) the albumin fraction being mainly affected. Though it has to be borne in mind that some protein loss may be accounted for by the amount of gelatinous fluid in the blisters, a further diminution occurred at the stage when puffiness of his face developed. All these signs and symptoms cleared within a few days, and after three weeks' hospital treatment he appeared fit enough for discharge. The follow-up examination one month later, however, revealed that his blood-urea was still slightly raised and his renal function impaired, as demonstrated by the urea clearance test. His convalescence was then slow, a fact which corroborates an observation made by Holling and Clarke (1944), who also mention the diminished capacity for work after methyl bromide poisoning. Eight months after the incident, though the patient was at work, he still did not feel fit. His blood-urea had risen again to 80 mg. per 100 c.c.m. and the urea clearance test showed deterioration of his renal function, though no abnormal constituents were present in his urine. An improvement was, however, noticeable eleven months after the fire.

The following points emerge from the discussion. A perfectly fit man with no past history of renal disease, who became engaged in fighting a fire with carbon dioxide and methyl bromide, exhibited the signs and symptoms of acute methyl bromide poisoning with subsequent development of uræmia and mildly progressive impairment of his renal function. Fellow workers who fought the fire for an equally long period and who also developed acute symptoms of methyl bromide poisoning, some of them with several days sickness, did not show uræmic symptoms and returned to work after a short time of absence feeling as fit as before the incident. What then are the reasons for the difference in the clinical picture? The following considerations should be evaluated.

1. Our patient was the only one who contracted larger blisters. They were due to second-degree chemical burns, and were probably caused by directing the jet of the methyl bromide apparatus on to his shoes and between them and his socks. Only the superficial layers of the skin were affected, and it is, therefore, unlikely that this type of burn can account for the renal disturbance.

2. Our patient was given sulphonamides, but the total dose did not exceed 15 g. of sulphafurazan within two days, and there was adequate administration of fluids during this period. Here again, it does not appear reasonable to suggest that such a small amount of the drug could have been responsible for the renal disturbance.

3. Our patient may have inhaled a far greater volume of methyl bromide than his fellow workers. It is certain that some of the employees who had milder symptoms were fighting the fire from a confined space inside the machine in question and did not come in contact with the gas in such concentrations as he did. In addition, those workers who like our patient were exposed to the higher concentration of the vapours for such a long period must have sustained a proportionately greater absorption of the gas than those exposed to lesser concentrations, since respiration was obviously stimulated by the presence of increased quantities of carbon dioxide in the atmosphere. We assume, therefore, that our patient did inhale more of the toxic gas than his fellow workers. As it is pointed out in the introduction to this paper, there is sufficient anatomical evidence in the literature to show that renal damage does occur in methyl bromide poisoning; therefore one may be justified in regarding this chemical as the causative agent of the clinical symptoms of impaired kidney function and uræmia manifest in our case.

This conclusion is based on the absence of evidence of any renal disease in our patient's past history. The possibility of a clinically silent lesion of course cannot be excluded for certain, though it is unlikely. A detailed explanation as to how the kidneys could have been affected by methyl bromide cannot be given; for the mechanism of its action is not yet known. However, it can be stated that one of the most toxic decomposition products, namely hydrobromic acid, was probably not present to any appreciable amount. A temperature of
1,000° C. would have been necessary to evolve it, and in this fire incident the temperature could have been nowhere near this point.

Summary

A fit man with no history of renal disease, who became engaged in fighting a fire with carbon dioxide and methyl bromide, showed the signs and symptoms of acute methyl bromide poisoning with subsequent development of uræmia and mildly progressive impairment of renal function.

It is assumed that an unusually large quantity of methyl bromide was inhaled during the fire, in which the patient had remained for about one and a half hours, and that the presence of a high concentration of carbon dioxide in the atmosphere by its stimulating action on respiration has precipitated the toxic effect.

We wish to thank Dr. John Humphrey for all the laboratory tests and his interest in this case, and Dr. H. A. Warbrick-Smith for the follow-up examinations.

REFERENCES
