ARSINE POISONING IN INDUSTRY

A REPORT OF 2 CASES

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The dangers of arsine (arseniurated hydrogen) poisoning have been recognized since 1815, when Gehlen, a Munich chemist, in the course of some researches 'inspired a small portion and at the termination of one hour was seized with continual vomiting, shivering and weakness, which increased until the 9th day, when he died'.[1]

The first cases reported in industry occurred in 1873 in Germany,[1] during the process of recovering silver from lead and zinc ores. A considerable number of cases have since been reported. In 1908 Glaister[2] reviewed 120 cases, and in 1932 Meulberger *et al.*[3] stated that 247 cases were on record, of which 50 were fatal. In recent years comparatively few reports have appeared in the literature and in 1952 Locket observed that since 1935 only 10 cases had been reported in England.[4] Reports however still appear with sufficient frequency to emphasize the importance of arsine as a serious though preventable industrial hazard.

The majority of accidents in industry have been due to the use of acids, alloys or ores contaminated with arsenic, or arsenical compounds. Tin, lead, aluminium, and zinc ores have been most commonly incriminated. Many industrial processes are potential hazards, and cases have been reported in the tin refining,[4, 5] and lead smelting[6, 7] industries, in the cyanide extraction of gold,[3] and in the manufacture of arsenious acid.[9] Cases have also occurred in the galvanizing industry, in the manufacture of zinc chloride, zinc sulphate and hydrogen, and as a result of the cleaning of acid tanks. An unusual instance was that occurring in a submarine from the arsenic contamination of the lead in the accumulators.[23]

Arsine may be produced by the combination of nascent hydrogen and elemental arsenic

$$Zn + H_2SO_4 = ZnSO_4 + 2H$$
$$2As + 6H = 2AsH_3 \text{ (arsine gas)}$$

or by the reaction of water with a metallic arsenide.

$$AlAs + 3H_2O = Al(OH)_3 + AsH_3$$

Both types of reaction readily occur at room temperature and lethal quantities of arsine can be produced within a short space of time. No previous records of this condition occurring in South Africa have been found and, in view of the rapid development of industry in South Africa today, it seems important to report 2 cases of arsine poisoning which occurred recently. It is desired to draw the attention of industrial medical officers and general practitioners practising in the vicinity of industry to this condition, and to stress its importance as an industrial hazard.

CASE 1

J. 4148, an African male aged 25 years, was admitted to hospital on 1 May 1956 complaining of abdominal (peri-umbilical) pain and of passing black urine. The pain was severe and colicky and came on suddenly during the night. There had been no dietary indiscretion, and no other symptoms were referable to the gastro-intestinal tract. The black water was of maximum intensity from the outset and was unaccompanied by pain on micturition or other urinary symptoms.

The patient had been admitted to hospital 5 months before for a similar complaint. The chief complaint then was painful micturition, and ward records showed that later he developed jaundice, haemoglobinuria and abdominal pain. There was also an initial pyrexia and cough, accompanied by nausea and vomiting. He was treated with antibiotics and by the 4th day all symptoms and signs had disappeared. On discharge the haemoglobin value was 10·9 g.% and his white-cell count was 6,600 per c.mm. He remained well until the present episode.

For the past 10 months the patient had been employed in a chemical factory. He had not been outside Johannesburg during this period. Further details regarding the patient's occupation are given below.

Clinical Examination and Course. The patient was a well-nourished African male in no obvious distress. Temperature 100°F. The mucous membranes were pale but there was no jaundice, cyanosis, purpura, or skin rashes. Clinical examination was otherwise negative. There was no enlargement of the liver or spleen and no significant lymphadenopathy. Physical examination of the central nervous system was negative at the time of admission and has remained so, the last clinical examination being made 4 months later. The progress of the case was uneventful; the pyrexia settled by the 2nd day and the abdominal pain disappeared by the 3rd day. On the 4th day the urine was quite normal in colour. The patient received no specific therapy.

Laboratory Investigations. The urine was of port-wine colour. Albumen +++. Sugar absent. Bilirubin absent. Urobilin ++. Microscopic examinations of a centrifuged deposit showed no cells or casts. Bilharzia ova were not observed. The blood picture is shown in Table I. A moderately severe normochromic anaemia was found. The red-cell fragility test showed that haemolysis commenced at 0·5% saline and was complete in 0·3% saline. The incubation autolysis test[10] showed 0·5% lysis after 24 hours. The Coombs test, both direct and indirect, was negative. Ham's acid serum test and the Donath-Landsteiner test were negative. Paper electrophoresis of haemoglobin showed normal adult haemoglobin only. No malaria parasites were seen on thick or thin films, and Heinz bodies were not observed. The Schumm's test performed 2 days after admission was negative and the serum bilirubin was less than 0·5 mg.%. The modified Ide test was negative. A bone-marrow examination carried out on the 9th day in hospital showed an active hypercellular marrow, with a myeloid-erythroid ratio of 1 : 3. Erythropoiesis was normoblastic, but markedly hyperactive. In view of the haemoglobinuria,

anaemia, reticulocytosis and marked erythroid reaction in the marrow, a diagnosis of a haemolytic anaemia was made. The cause seemed most likely to be a factor of extrinsic origin, and a search for possble haemolytic agents to which the patient might have been exposed was accordingly undertaken. While these investigations were in progress a second case was admitted to the same hospital.

TABLE I. CASE 1. HAEMATOLOGICAL DATA

	18 Dec. 1955	1 May 1956	3 May 1956	9 May 1956	28 May 1956	1 Aug. 1956
Haemoglobin (g.%)	10·9	10·3	9·6	10·2	13·5	16·7
Red-cell count (millions per c.mm.)			3·2		4·7	5·4
Packed cell volume %			29		42	
Reticulocytes %		7·2	15·0	6·0	2·0	4·0
Normoblasts (per 200 w.b.c.)		13	9	0	0	0
White blood cells (thousands per c.mm.)	6·6	6·4	4·2	9·6	1·9	4·0

CASE 2

On 10 May 1956, 9 days after the admission of case 1, J. 5908, an African male aged 30, was admitted complaining of passing black water. At first there was no pain but later he developed central colicky abdominal pain. There were no other gastro-intestinal symptoms. Apart from passing black urine there were no urinary symptoms. He gave a history of a previous similar attack, which had occurred 1 month before and for which he had been admitted to hospital. Haemoglobinuria was observed on that occasion, with pyrexia of 100·8°F. This patient had been employed at the same factory for the same length of time as case 1 and worked in the same section. These two men and a third were the only persons working in that particular section. Further details of the patient's occupation are outlined below.

Clinical Examination. The patient was a well-nourished African male. Temperature 100·6°F. There was no pallor of the mucous membranes, but slight jaundice was present. Physical examination revealed a 2-finger-breadth enlargement of the liver below the right costal margin. The liver was smooth and non-tender. The spleen was not palpable, nor was there any lymphadenopathy. The remainder of the clinical examination was negative.

Laboratory Investigations. The urine was of port-wine colour. Albumen +++. Sugar absent. Bilirubin absent. Urobilin ++. Urobilinogen +. Spectroscopic examination showed the presence of haemoglobin derivatives and methaemoglobin. Microscopic examination of a centrifuged deposit showed the presence of 1-2 leucocytes per high-power field and calcium-oxalate crystals. The blood findings in this case are shown in Table II. All the special haematological tests outlined in the investigation of case 1 were negative in this case, with the exception of the Schumm's test, which was positive. The serum bilirubin was 0·6 mg. % 2 days after admission. The modified Ide test was negative. Malaria parasites were not detected. A bone-marrow examination on the 4th day in hospital showed a hypercellular active marrow with a myeloid-erythroid ratio of 1-2 : 2. Erythropoiesis was hyperplastic and normoblastic in type. Subsequent progress of this patient was uneventful, the temperature returned to normal in 3 days, by which time the jaundice had disappeared and spectroscopic examination of the urine did not show the presence of haemoglobin or any of its derivatives. The liver could no longer be felt by the 5th day. In 10 days the haemoglobin value had risen to within normal limits.

TABLE II. CASE 2. HAEMATOLOGICAL DATA

	11 May 1956	13 May 1956	28 May 1956	1 Aug. 1956
Haemoglobin (g.%)	13·5	10·6	14·6	16·9
Red-cell count (millions per c.mm.)		3·7	4·9	5·4
Packed cell volume %		30	46	
Reticulocytes %	5·0	13·5	1·5	1·0
Normoblasts (per 200 w.b.c.)	0	0	0	0
White blood cells (thousands per c.mm.)	9·1	7·2	2·4	3·9

DISCUSSION

Two cases occurring in the same section of the same factory and presenting as haemolytic anaemias pointed obviously to the operation of some extrinsic factor connected with their occupation. A search for a history of exposure to a haemolytic agent at the place of employment was accordingly made. A third man who worked with these two patients was also examined. This man, an African male aged 25, had been employed in the same work as cases 1 and 2 since May 1955. He did not volunteer any complaints, but on direct questioning admitted to a recent episode of passing black urine; he was unable to specify the time of the attack with accuracy. There were no symptoms with this attack, which cleared up within a few days without treatment. Clinical examination revealed no abnormalities of significance. Urine examination revealed the presence of macroscopic haematuria and numerous bilharzia ova. A full blood count performed on 28 May 1956 showed a haemoglobin value of 13·5 g.%, packed cell volume 35%, and red-cell count 4·7 million per c.mm. The white-cell count was 6,000 per c.mm., with a mild eosinophilia in the differential count. A reticulocytosis of 4·5% was found. In view of the history of having passed black water and the presence of mild anaemia and a reticulocytosis, the possibility of haemolytic anaemia was considered. However, the bilharzia could have accounted for all these observations, and this case cannot be considered a proved haemolytic anaemia. Arsenic estimations were carried out on this patient nevertheless and are reported below.

Description of Working Conditions

These three men worked together in one section of the factory and were the only persons employed in this particular section. Their task was to shovel zinc ash into large cauldrons of boiling sulphuric acid. The men stood on a platform above the cauldrons and might have been exposed to fumes arising from them. Arsenic is a frequent contaminant of zinc ash and the material in use in the factory was analysed by the factory analyst, who reported as follows on a sample received on 25 May 1956: 'Arsenic as arsenious oxide (As_2O_3) 8 parts per million (Gutzeit method), arsenic as free arsenic 6 parts per million. Addition of sulphuric acid to the zinc ash results in the liberation of a large proportion of the arsenic in the form of arsine.' Subsequent investigation failed to detect the presence of antimony in the zinc ash and stibine was not liberated by sulphuric acid. Arsenic estimations on the nails and hair and the urine of the patients were made, and urine estimations were also made on 3 healthy controls employed elsewhere in the factory. The results are shown in Table III. These findings confirmed the tentative diagnosis of arsine poisoning.

It is clear that in the circumstances described above the conditions were ideal for the production of arsine by combination of nascent hydrogen and free arsenic. Although the men had worked in the factory for nearly 12 months they had each suffered only two attacks (except case 3, who had

TABLE III. ARSENIC CONTENT OF NAILS, HAIR AND URINE

Specimen	*Date*	*Case 1*	*Case 2*	*Case 3*	*Controls* 1	2	3
Nails and Hair (estimated together)	4 June 1956	240 parts per mil.	14 parts per mil.	37 parts per mil.	—	—	—
Urine	19 Aug. 1956	0·5 mg. per litre	0·4 mg. per litre	0·6 mg. per litre	0·0 mg. per litre	0·0 mg. per litre	0·1 mg. per litre

only one attack). It is difficult to explain the infrequency of the attacks, and the nature of possible precipitating factors is not known. A possible explanation is the use of a particular batch of zinc ash or sulphuric acid more heavily contaminated with arsenic than usual.

Arsine Poisoning

In view of the long period of exposure to the potentially dangerous atmosphere it was not possible to determine the period of exposure responsible for the attacks in our cases. Reports in the literature, however, indicate that comparatively short periods of exposure sometimes produce symptoms. In a case reported by Locket *et al.*[9] symptoms dommenced within ½ hour of exposure, and in the Indiana outbreak reported by Spolyar and Harger[7] symptoms commenced 1½ to 7 hours after exposure.

The maximum safe concentration of arsine recommended by the American Conference on Governmental Industrial Hygiene is 0·05 parts per million (quoted by Morse and Setterlind[6]). Henderson and Hagard[11] state that 3-10 parts per million will cause symptoms after several hours' exposure and 16-60 parts per million are dangerous after ½ hour's exposure. Nau,[12] in animal experiments, was able to produce a mild chronic haemolytic anaemia in rats after exposure to an atmosphere containing 0·05-2 parts per million of arsine for 1-3 hours daily to a maximum of 144 hours.

The clinical features of arsine poisoning are well reviewed by Lockett *et al.*[9] and by Hunter.[1] The most striking features are the acute intravascular haemolysis and the frequent occurrence of oliguria and anuria. Abdominal pain, nausea, diarrhoea, vomiting and headache, followed by jaundice, anaemia, haemoglobinuria and methaemoglobinuria, are the common presenting symptoms. Wills[13] noted a par-boiled redness of the face in his fatal case, and a garlic-like odour of the breath was observed by Bulmer *et al.*[14] Severe cases rapidly develop oliguria and anuria with increasing uraemia and all the features of acute tubular necrosis. Of the reported cases which developed anuria the mortality approaches 100%.[9]

The cases reported here were mild attacks, the most striking feature of which was the haemoglobinuria and anaemia. Constitutional disturbances were mild and neither patient developed oliguria or anuria. Recovery occurred rapidly and appeared to be complete in spite of the persistence of arsenic in the urine 3 months after the attack.

The mortality of arsine poisoning is given as 20% by Kober,[15] as 31·4% by Glaister,[2] and as 28% by Bomford and Hunter.[4] In Spolyar and Harger's series,[7] 4 of 13 cases died. It is possible that these figures are unduly high owing to the fact that mild cases may have been missed.

Arsine has been shown to act directly on haemoglobin[16] in the presence of oxygen to produce choleglobin, methaemoglobin, methaemalbumin and probably other haemoglobin pigments. Arsenite and arsenate rapidly convert methaemoglobin to haemoglobin,[9] so that intracorpuscular arsenite and arsenate are unlikely to be responsible for the presence of methaemoglobinuria. Pathogenesis of the renal lesion in arsenic poisoning is not clear, but Lockett *et al.*[9] suggest that it may be anoxic in origin. Josephson *et al.*,[17] believe that, in addition, arsine has a direct action on the heart. This view is based on autopsy and electrocardiographic findings indicative of acute myocarditis in their cases. Confirmation of these findings in further cases will be of considerable interest.

Prevention of arsine poisoning is primarily a problem of factory organization and design. Hunter[1] advised the use of respirators where arsenic is known to be present. Koelsh[18] suggested using small birds to detect arsine, and more recently Bamford[19] described the use of silver nitrate on mercuric-chloride test papers. Treatment of the established case follows standard therapeutic principles. Anaemias, if severe, should be treated with blood transfusion. Oliguria and anuria are best treated on the basis of the principles laid down by Bull, Joekes and Lowe.[20] B.A.L. has been used in many of the reported cases, but the results have been uniformly disappointing.[21, 8] Experimentally, Kensler *et al.*[22] have shown that B.A.L. could only produce beneficial effects if given within 45 minutes of exposure. This virtually excludes the possibility of benefit in most clinical cases. Locket *et al.*[9] also mention the use of exchange transfusions which may be of value during the first 6 hours of an attack.

SUMMARY

Two cases of arsine poisoning occurring in factory workers engaged in dissolving zinc in sulphuric acid are reported. A possible third case is also mentioned. These cases are believed to be the first reported in South Africa. The production of arsine in industry, the toxic action of the gas, its lethal dosage, and the clinical features of arsine poisoning are briefly discussed.

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REFERENCES

1. Hunter, D. (1957): *The Diseases of Occupations*, 2nd Ed. London: English University Press.
2. Glaister, J. (1908): *Poisoning by Arseniuretted Hydrogen or Hydrogen Arsenide*. Edinburgh: Livingstone.
3. Meulberger, C. W., Lovenhort, A. A. and O'Malley, T. S. (1928): J. Industr. Hyg., **10,** 137.
4. Bomford, R. R. and Hunter, D. (1932): Lancet, **2,** 1446.
5. Macaulay, D. B. and Stanley, D. A. (1956): Brit. J. Industr. Med., **13,** 217.
6. Morse, K. M. and Setterlind, A. N. (1950): Arch. Industr. Hyg., **2,** 148.
7. Spolyar, L. W. and Harger, R. N. (1950): *Ibid.*, **1,** 419.
8. Steel, M. and Feltham, D. V. G. (1950): Lancet, **1,** 108.
9. Locket, S., Grieve, W. S. M. and Phillips, L. (1952): Trans. Assoc. Industr. Med. Off., **2,** 14.
10. Dacie, J. V. (1956): *Practical Haematology*, 2nd ed., p. 99. London: Churchill.
11. Henderson, Y. and Haggard, H. W. (1943): *Noxious Gases and the Principles of Respiration Influencing their Action*, 2nd ed. New York: Chemical Catalog Co.

12. Nau, C. A. (1948): Sth. Med. J. (Bgham, Ala.), **41,** 341.
13. Wills, R. A. (1948): Industr. Med. Surg., **17,** 208.
14. Bulmer, F. M. R., Rothwell, H. E., Polack, S. S. and Stewart, D. W. (1940): J. Industr. Hyg., **22,** 111.
15. Kober, G. M. and Hayhurst, R. (1924): *Industrial Health.* Philadelphia: Blakiston.
16. Lemberg, R. (1939): J. Austral. Chem. Inst., **6,** 170.
17. Josephson, C. J., Pinto, S. S. and Petronella, S. J. (1951): Arch. Industr. Hyg., **4,** 43.
18. Koelsch, F. (1920): Zbl. GewHyg., **8,** 121.
19. Bamford, F. and Stewart, C. P. (1947): *Poisons, their Isolation and Identification*, 2nd. ed. London: Churchill.
20. Bull, G. M., Joekes, A. M. and Lowe, K. G. (1949): Lancet, **2,** 229.
21. Pinto, S. S., Petronella, S. J., Johns, D. R. and Arnold, M. F. (1950): Arch. Industr. Hyg., **1,** 437.
22. Kensler, C. J., Abel, J. C. and Rhoads, C. P. (1946): J. Pharmacol., **88,** 99.
23. Dudley, J. F. (1919-20): J. Industr. Hyg., **1,** 215.