PAPERS AND ORIGINALS

Arsine Toxicity Aboard the Asiafreighter

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Summary

Eight sailors on board the Asiafreighter were exposed to arsine that had escaped from a cylinder in the cargo hold. Four suffered severe toxicity and within a few hours had developed fever, weakness, nausea, vomiting, diarrhoea, abdominal pain, and haemoglobinuria. These patients had pronounced intravascular haemolysis, which in one patient was complete.

This patient was also stuporose and anoxic, a condition attributed to failure of oxygen transport and sludging of red cell debris in the cerebral and pulmonary circulations, but he regained a normal level of consciousness after exchange transfusion. Evidence of marrow depression was present: the reticulocyte response to the haemolysis was poor and there was a thrombocytopenia. All four patients developed renal failure, one being totally anuric for five weeks. Two patients developed peripheral neuropathy, and one was still severely disabled six months after the incident. The other four patients had a similar, though less severe, illness.

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Introduction

Arsine (arsenous hydride), a colourless gas, is an important environmental hazard in those industries concerned with refining and processing metals such as steel,¹ gold,² and tin,³ where it is formed by the action of acids or nascent hydrogen on arsenite impurities. In sewage plants arsine may also be liberated from fungi.⁴ The use of arsine in the transistor industry to stabilize selenium is not well known, and it was leakage of gas destined for this purpose, from a cylinder aboard a container ship, that led to the poisoning of the eight sailors described in this paper.

The Incident and Initial Symptoms

The Asiafreighter was transporting a mixed cargo from the U.S.A. to Europe in November 1974. After three days of heavy seas three of the crew and the first mate (cases 1-4) entered cargo hold no. 2 to gain access to the double bottom tanks of the hull and check for possible damage. The total time spent in the hold or the hull tanks ranged from 1 hour 5 minutes to 3 hours 45 minutes. The cargo in the hold was arranged in seven layers of containers, the two cylinders of arsine being in the second from bottom level. Though there was no external evidence of damage to that container one of the cylinders had leaked the whole of its contents through the cylinder valve, which had presumably opened as a result of repeated buffeting within the container during the storm.

None of the four men noticed the characteristic garlic-like smell of arsine because of other odours in the hold. By the next day they were very ill, but fortunately the ship was then approaching the Cornish coast and they were airlifted by helicopter to Falmouth and from there taken by road to the Royal County Hospital, Treliſke, Truro. Later the same day they were flown to King's College Hospital. The four other sailors who were affected had a shorter exposure. One was in the hold for 15 minutes only, another for a similar length of time wearing a protective helmet, and the other two had only stood at the entrance to the hold. These four sailors had a less severe illness than the first four, and were treated throughout in Truro. The arsine gas in the hold was eventually dispersed by a volunteer crew who opened the hold near Rotterdam, the drama of the incident having been well highlighted in the national press.

The first symptoms—fever, headache, muscular pains, epigastric pain, nausea, and vomiting—occurred between one and 12 hours after initial entry into the cargo hold. Shortly afterwards diarrhoea and loin pain occurred and the first specimen of urine passed was dark red. Three of the patients complained of watering eyes and two of shortness of breath. The severity of all symptoms seemed closely related to the duration of exposure.

TABLE 1—Relevant Haematological Data in Eight Cases Affected. Figures in Parentheses Refer to Day after Exposure to Arsin

Case No.	Age (Years)	Lowest Blood Haemoglobin (g/dl)	Highest Plasma Haemoglobin (g/dl)	Lowest P.C.V. (%)	No. of Days of Continuing Haemolysis	Maximum Reticulocytosis (%)	Spontaneous Rise in Haemoglobin (Day First Noted)	Lowest Platelet Count ($\times 10^9/l$)
1	44	6.8* (22)	7 (1)	0 (1)	3	4.5 (20)	90	27 (4)
2	20	8.3* (4)	2 (1)	24 (4)	4	4.8 (10)	15	83 (6)
3	41	9.0* (4)	2 (1)	26 (4)	4	8 (8)	6	133 (2)
4	22	6.3 (5)	1.5 (1)	18 (5)	4	6.4 (10)	6	156 (4)
5	38	8.6* (8)		26 (8)		9.4 (10)	10	
6	37	10.1 (11)		31 (11)	4	5 (5)	12	
7	42	9.8 (8)		30 (8)	4	6 (7)	11	
8	51	14.5 (7)		44 (7)	3			

*Received blood transfusion.

Clinical Findings and Subsequent Course

Physical signs on admission in the four most severely affected patients were a pyrexia of up to 39°C, a striking orange pigmentation to the skin and sclerae, a tender, slightly enlarged liver, and tenderness in the renal angles. One patient (case 1) who was desperately ill, was also cyanosed, confused, and disoriented for time and place. The course of the illness and abnormalities found on investigation are most easily described by specific reference to the various systems involved.

HAEMATOLOGICAL SYSTEM

The most striking feature initially was the degree of intravascular haemolysis. In case 1 the haemolysis seemed to be complete: packed cell volume (P.C.V.) was 0% and plasma haemoglobin concentration was 7 g/dl (fig. 1 and table I). This patient received an exchange transfusion of 5 units of blood at Truro, and when he arrived at King's College Hospital the P.C.V. was 24% and the total haemoglobin

FIG. 1—Case 1. Serial haematological data. X.T. = Exchange transfusion. T. = Whole blood transfusion.

concentration 11.8 g/dl, of which free haemoglobin in the plasma amounted to about 4 g/dl. Many ghost cells were noted on the peripheral blood film (fig. 2). Over the next 12 hours a further continuous exchange transfusion of 12 units of fresh blood was carried out, after which there was no evidence of continuing haemolysis. In spite of the severe haemolysis the reticulocyte count remained below 1% for two weeks and only reached a maximum of 4.5% on day 20 (fig. 1), which suggested that there was some degree of marrow depression. During these three weeks his haemoglobin was only maintained by repeated transfusions, and it was not until the 12th week that the haemoglobin level began to rise spontaneously. Other evidence of marrow depression included a reduction in platelet count to a minimum of $27 \times 10^9/l$ on day four, with a slow rise to normal by day 15. Marrow aspiration on day six showed reduced cellularity with bizarre dyserythropoiesis. The red cell precursors were grossly abnormal with definite nuclear distortion (fig. 3). Granulopoiesis was reduced and showed some toxic changes, while megakaryocytes were

FIG. 2—Case 1. Peripheral blood film on arrival at King's College Hospital. Ghost red cells contrast with transfused normal cells. (Jenner-Giemsa stain. $\times 1087$).

FIG. 3—Case 1. Bone marrow aspirated on day six. Normoblasts (arrowed in b, e, and f) show varying degrees of nuclear distortion and fragmentation. (Jenner-Giemsa stain. $\times 1087$).

scanty. Tests for intravascular coagulation, including prothrombin time, partial thromboplastin time, thrombin clotting time, estimation of plasma fibrinogen and fibrin degradation products, and factor VIII and IX assays gave normal results. Four other patients (cases 2, 3, 4, and 5) had severe haemolysis (table I), though exchange transfusion was not required. The reticulocytosis was greater in these cases and the thrombocytopenia less pronounced. Haemolysis was relatively mild in the other three cases.

TABLE II—Results of Renal and Hepatic Function Tests. Maximum Abnormalities are Shown. Figures in Parentheses Refer to Day after Exposure to Arsenic

Case No.	Plasma Urea (mmol/l)	Plasma Creatinine (μ mol/l)	Creatinine Clearance (ml/min)	Aspartate Aminotransferase (I.U./l)	Alanine Aminotransferase (I.U./l)
1	55 (3)*	910 (3)	0 (1), 58 (95), 44 (184)	460 (3)	
2	37 (4)*	610 (4)	1 (1), 99 (95)	208 (3)	
3	31 (2)	360 (4)	12 (1), 114 (95)	71 (3)	
4	26 (2)	330 (2)	15 (1), 129 (95)	86 (3)	
5	10 (4)				
6	11 (1)				30 (3)
7	9 (1)				21 (4)
8	12 (2)				74 (3)
Normal range	3.3–6.7	40–110		10–50	3–38

*Received Dialysis.

Conversion: SI to Traditional Units—Urea: 1 mmol/l $\approx$ 6 mg/100 ml. Creatinine: 1 μ mol/l $\approx$ 0.0113 mg/100 ml.

Except in the patient who was treated by exchange transfusion (case 1) there was evidence of continuing haemolysis with haemoglobinuria, free haemoglobin in the plasma, or excess urobilinurina for the four days after exposure to arsenic.

In each case there was a neutrophil leucocytosis of up to $14 \times 10^9/l$ lasting for three or four days and a monocytosis of up to $1.7 \times 10^9/l$ persisting for 10 days. There was, however, no monocytosis in case 1 after the patient had received his second exchange transfusion.

RENAL SYSTEM

All eight patients had some renal impairment (table II). One patient (case 1) was totally anuric for five weeks and was treated by peritoneal dialysis for the first two weeks, followed by haemodialysis for four weeks. Another (case 2) also had severe renal failure and was treated by peritoneal dialysis for four days. While haemolysis was continuing the peritoneal dialysate was red owing to free haemoglobin. The other patients did not require dialysis and renal function in cases 2, 3, and 4 returned essentially to normal at four and a half months, though it was still impaired in case 1 at six months (creatinine clearance 44 ml/min). Though the urine sediment was repeatedly examined during the period of renal failure casts were never found.

NEUROLOGICAL SYSTEM

The encephalopathy in case 1, already referred to, rapidly improved after exchange transfusion and dexamethasone. On day 10 the patient complained of paraesthesia and a burning sensation in the hands and feet. This was followed by weakness of the arms and, particularly, the legs which rapidly became worse, so that by day 30 he was unable to walk. Muscle wasting involved proximal and distal groups (fig. 4),

FIG. 4—Case 1. Muscle wasting of thighs at five months.

but changes in sensation were confined to the periphery. Nerve conduction studies in arms and legs showed definite slowing in sensory and motor nerves with reduced voltage of action potentials. On electromyography the changes were typical of a denervation myopathy. The neuropathy began to improve at seven weeks, but at six months he still could walk only with the aid of crutches.

Another of the severely affected patients (case 2) also complained of paraesthesia in the feet on day 10. These symptoms persisted for seven days, but there were no objective signs of a neuropathy, and both nerve conduction studies and electromyogram showed nothing abnormal.

PULMONARY AND CARDIOVASCULAR SYSTEMS

Two patients (cases 1 and 2) were clinically cyanosed on admission. Blood gas determinations showed hypoxia and hypocapnia: PO_2 was 5.59 and 7.98 kPa (41.9 and 59.9 mm Hg) respectively (normal range 12–15 kPa (90–113 mm Hg)); and PCO_2 was 3.90 and 3.99 kPa (29.3 and 29.9 mm Hg) (normal range 4.5–6.1 kPa (33.8–45.8 mm Hg)). These returned to normal values within 24 hours. Clinical examination of the lungs and chest x-ray examination showed nothing abnormal, and there was no evidence of heart failure of cardiac arrhythmias. Electrocardiograms taken in cases 1, 2 and 5 were normal.

OTHER SYSTEMS

At one month the patient in case 1 had developed a superficial cutaneous desquamation of palms and soles. This resolved within two weeks. Transverse white lines in the nails (Mee's lines) were first noticed at two months and persisted until the nail had grown out (fig. 5). His hair did not change colour though arsenic levels were grossly raised (table III). One week after the incident the arsenic level was more than 200 times that normally found in the root segment. Over the following months the measured arsenic contents became progressively less as the hair grew out.

Though each patient had tender hepatomegaly, evidence of liver damage was minimal. The highest serum aspartate aminotransferase level observed was in case 1 (460 I.U./l), and this returned to normal

FIG. 5—Case 1. Mee's lines in fingernails at three months.

TABLE III—Measurements of Arsenic Content in Hair Segments. Values in Parentheses Refer to Segment of Hair as Measured in cm from Root in which Highest Value for Arsenic Content was Found

Case No.	Arsenic Content* (p.p.m.)		
	9 Days	19 Days	99 Days
1	236 (Root)	107 (0-1)	53 (3-4)
2	107 (Root)	42 (0-1)	27 (3-4)
3	39 (Root)	22 (0-1)	
4	47 (Root)	22 (0-1)	9 (3-4)

*Normal Value <1 p.p.m.

by day 6. In one of the three cases in which the alanine aminotransferase was determined (case 8) a slightly raised level was found (table II).

On day 3 one patient (case 5) developed a painful arthropathy involving the knees, hips, and shoulders, but there were no abnormal physical signs. These symptoms persisted for two weeks.

Discussion

The mechanism of the haemolysis, which is such a striking feature of arsine toxicity,⁵⁻⁷ is almost certainly multifactorial.⁵ Among the postulated factors are the formation of elemental arsenic⁸ and arsenic dihydride,⁹ the inhibition of catalase,¹⁰ and the formation of irreversible complexes with sulphhydryl groups of essential enzymes within red cells.⁷ Haemolysis in one of our patients (case 1) seemed to be complete, and it is surprising that this patient did not suffer irreversible brain damage in view of the poor oxygen-carrying capacity of free haemoglobin. Teitelbaum *et al.*,⁶ have also reported a patient with a P.C.V. of zero who survived after an early exchange transfusion. In addition to removing red cell debris and replacing viable red cells arsine-protein complexes may also be removed by exchange transfusion. This might explain why this patient, though the most severely affected, subsequently had no further evidence of intravascular haemolysis, whereas the other patients who did not have exchange transfusions showed haemolysis for longer. The latter patients also showed another persisting response to circulating red cell debris—namely, continuing monocytosis.

The poor reticulocyte response, observed particularly in case 1, was presumably primarily the result of a direct toxic effect of arsine on the bone marrow, and consistent with this were the abnormal nuclei seen in the normoblasts, though renal failure may have been a contributing factor. Marrow depression has not been emphasized in most series, though Levinsky *et al.*,⁷ in a report of three cases, noted that reticulocytosis was arrested for up to seven weeks. The thrombocytopenia was probably also the result of the marrow depression, since marrow megakaryocytes were reduced in numbers, and there was no evidence of intravascular coagulation. The latter is known to be initiated by intravascular haemolysis, and it is surprising that our patients were not so affected.

Sludging of red cell debris within the microcirculation was probably responsible, at least in part, for the dysfunction of various systems observed, including the encephalopathy in case 1, which resembled the changes described in cerebral malaria. An encephalopathy with restlessness, agitation, and disorientation, beginning some days after exposure, has also been described and attributed to a toxic effect of arsine on the brain,⁷ but the time course is quite different to that seen in our patient. Sludging within the renal circulation may be an important feature in the pathogenesis of renal failure, though the degree of haemolysis and severity of renal failure do not always correlate closely,^{11 12} and other factors, discussed below, are likely to be involved. Sludging within the pulmonary circulation may have been responsible for the hypoxia seen in two cases, since the frank pulmonary oedema described by others^{13 14} was not found. Hepatic tenderness is characteristic of arsine toxicity and in fatal cases centrilobular necrosis may occur¹⁴—again

changes which might have been caused by sludging within the hepatic sinusoids.

One of our patients was anuric for five weeks and another survivor reported was anuric for 31 days.¹⁵ Survivors from such prolonged anuria due to other causes are unusual.¹⁶ Factors involved in the pathogenesis of the renal failure, other than sludging within the renal circulation, include a direct toxic effect of arsine on renal tubular metabolism,¹⁷ the precipitation of toxic arsine-haemoglobin complexes in the tubular lumen,¹⁵ and a considerable reduction in renal blood flow.¹⁸ Histological findings are those of a severe tubular necrosis.¹⁵ The absence of granular and cellular casts in the urine sediment, though surprising, has also been reported by others.^{5 6 14 19} Patients recovering from arsine poisoning may develop chronic renal failure with glomerular sclerosis, atrophic tubules, and interstitial fibrosis,¹⁵ and this may happen in our patient (case 1).

Symptoms of a peripheral neuropathy can develop within hours of exposure,^{6 14} but more often, as in our two cases, do not develop for some days.^{7 20} Nerve biopsies have shown fragmentation of myelin and disintegration of the axis cylinder,²⁰ and the arsine may be neurotoxic through the effect of elemental arsenic in binding to the disulphide linkages of lipoic acid,⁹ an important cofactor in decarboxylation in the nervous system. Residual disability is not uncommon.²⁰ The cutaneous manifestations—namely, desquamation and Mee's lines—often coincide with the development of a peripheral neuropathy.²⁰ We are unaware of any reports of an arthropathy associated with arsine poisoning, and its explanation remains unknown.

Myocardial necrosis has been described in some fatal cases by Pinto *et al.*,¹⁴ and they also reported electrocardiographic abnormalities in all of their 13 cases. These were not present in our patients, however, or those of Teitelbaum *et al.*⁶

The diagnosis in these cases was made on the telephone by Dr. Roy Goulding of the poisons unit, Guy's Hospital, in the face of all arguments to the contrary and despite the lack of evidence that arsine was in the cargo hold—it was not specified on the manifest held by the captain but only on a bill of lading held by the dispatch company in the U.S.A. Two days passed before analytical proof of the presence of arsine was obtained. Early diagnosis is essential since exchange transfusion is undoubtedly life-saving. Though dimercaprol is an effective chelator of arsenic its administration even early after exposure has not been of value in preventing haemolysis, renal failure, or the neuropathy.^{6 14 19}

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References

- Muehlberger, C. W., Loevenhart, A. S., and O'Malley, T. S., *Journal of Industrial Hygiene*, 1928, **10**, 137.
- Bulmer, F. M. R., *et al.*, *Journal of Industrial Hygiene*, 1940, **22**, 111.
- Bomford, R. R., and Hunter, D., *Lancet*, 1932, **2**, 1446.
- Cox, D. P., and Alexander, M., *Bulletin of Environmental Contamination and Toxicology*, 1973, **9**, 84.
- Fowler, B. A., and Weissberg, J. B., *New England Journal of Medicine*, 1974, **291**, 1171.
- Teitelbaum, D. T., and Kier, L. C., *Archives of Environmental Health*, 1969, **19**, 133.
- Levinsky, W. J., *et al.*, *Archives of Environmental Health*, 1970, **20**, 436.
- Gramer, L., *Archiv für Gewerbepathologie und Gewerbehygiene*, 1955, **13**, 601.
- Heubner, W., and Wolff, K., *Archiv für Experimentelle Pathologie und Pharmakologie*, 1936, **181**, 149.
- Jung, F., *Biochemische Zeitschrift*, 1939, **302**, 294.
- Jenkins, G. C., *et al.*, *British Medical Journal*, 1965, **2**, 78.
- Gebert, F., *Biochemische Zeitschrift*, 1937, **293**, 157.
- Hocken, A. G., and Bradshaw, G., *British Journal of Industrial Medicine*, 1970, **27**, 56.

¹⁴ Pinto, S. S., *et al.*, *Archives of Industrial Hygiene*, 1950, 1, 437.¹⁵ Muehrcke, R. C., and Pirani, C. L., *Annals of Internal Medicine*, 1968, 68, 853.¹⁶ Siegler, R. L., and Bloomer, A., *Journal of the American Medical Association*, 1973, 225, 133.¹⁷ Hughes, W., and Levvy, G. A., *Biochemical Journal*, 1947, 41, 8.¹⁸ Pedersen, F., *et al.*, *Acta Medica Scandinavica*, 1968, 496, Suppl. p. 27.¹⁹ McKinstry, W. J., and Hickes, J. M., *Archives of Industrial Health*, 1957, 16, 32.²⁰ Heyman, A., *et al.*, *New England Journal of Medicine*, 1956, 254, 401.

Analysis of Treatment in Childhood Leukaemia. I—Predisposition to Methotrexate-induced Neutropenia after Craniospinal Irradiation

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Summary

The degree of drug-induced neutropenia resulting from a controlled trial (UKALL I) of treatment in acute lymphoblastic leukaemia was analysed. The main agent associated with severe neutropenia was methotrexate, and methotrexate-induced neutropenia was significantly greater in patients who had received craniospinal irradiation. The synergistic toxic effect of irradiation followed by methotrexate treatment seems to have contributed to three of the five deaths which occurred in complete remission in this trial; all deaths in remission occurred in patients who had received central nervous system prophylaxis. Analysis of patients who subsequently relapsed compared with those still in remission after 18 months of treatment indicated that the former, on average, had slightly lower neutrophil counts. This suggests that the children who relapsed did not receive any less aggressive treatment than those who remained in remission.

Introduction

Combination chemotherapy in acute lymphoblastic leukaemia has greatly reduced the rate of haematological relapse. In the absence of specific preventive measures, however, a high proportion of patients with this disease relapse with central nervous system (C.N.S.) involvement.¹⁻³ The Memphis group pioneered successful C.N.S. prophylactic treatment and found that craniospinal irradiation greatly reduced the incidence of this complication.⁴ Subsequently the British Medical Research Council undertook a controlled trial (UKALL I) to confirm the Memphis observation. In the first 18 months of this trial it was shown that while 26 out of 80 patients not receiving C.N.S.

prophylaxis relapsed with C.N.S. leukaemia only one of the 75 receiving prophylaxis primarily relapsed with this complication.⁵ On the other hand, while none of the non-irradiated patients died in complete remission five such deaths occurred in the C.N.S. prophylaxis group. We have reported the considerable difference in lymphocyte counts between these groups and analysed the types of lymphocytes depleted 84 weeks after entry to the trial.⁶ At 84 weeks there was no apparent difference in neutrophil counts, but analysis of the deaths in remission showed that three out of four patients with available counts had pronounced neutropenia at the time of death. In this report we show that neutropenia is much more pronounced at certain stages of UKALL I maintenance chemotherapy than at others and that C.N.S. irradiation predisposes to drug-induced neutropenia for at least 18 months.

The Trial

The trial protocols are summarized in fig. 1. All methotrexate courses were of five daily doses except for the first two at 15 and 17 weeks, which were of three and four doses respectively. After week 24 12-week cycles as given between weeks 13 and 24 (but with full five-day courses of methotrexate) were administered. There were only two differences between the drug schedules for the two groups. Firstly, patients not receiving C.N.S. prophylaxis were given an extra five-day course of cytarabine during week 9. Secondly, and, more importantly, in each of the 11 methotrexate courses between weeks 17 and 55 the C.N.S. prophylaxis group received the first dose of methotrexate intrathecally. The main analysis in this study continues to the end of week 84, when patients were divided into subgroups receiving continued chemotherapy, no chemotherapy, or immunotherapy without chemotherapy.

The radiation was applied to the cranium to a total midline dose of 2500 rads by opposing lateral fields, which at most centres included the posterior part of the orbit. The apparatus used was not constant and included supervoltage, 250 kV, and cobalt sources. The cranial irradiation was usually completed within two and a half weeks but was sometimes protracted by another week or so mostly on account of myelodepression. During the second half of this time spinal irradiation to a total dose of 1000 rads (measured at the posterior surface of the vertebral bodies) was also given.

Because of the divergent views and facilities available at the different trial centres a fully randomized trial of C.N.S. prophylaxis could not be organized. Consequently some of the centres treated patients by only one of the schedules while other centres randomized patients into equal groups. Nevertheless, the distribution of patients was remarkably uniform on the basis of numbers, age, and presenting haematological features.⁵

Methods

The analysis in this study involved serial recording of neutrophil and lymphocyte counts from all patients in the trial. A total of 90 patients receiving no C.N.S. prophylaxis and 78 patients receiving C.N.S.

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