were found in the first two serum samples, taken before the surgery and on the seventh day from the onset of the fever. Later a gradual rise in the titre to high values was demonstrated. A cytopathic agent with the characteristics of a cytomegalovirus has been isolated from the urine in human fibroblast cultures.

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Accidental Poisoning by Paraquat: Report of Two Cases in Man

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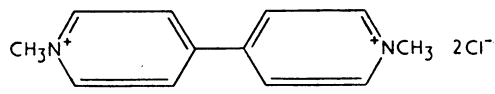
Brit. med. J., 1966, **1**, 1272–1273

Paraquat is the trade name of the dichloride salt of the radical 1,1'-dimethyl-4,4'-dipyridylium, a powerful herbicide developed in recent years by Imperial Chemical Industries Ltd. The structural formula of the substance is as follows:



The herbicidal activity has been investigated fully, and the substance is shown to be very rapidly absorbed into the aerial parts of plants, but its precise mode of action is unknown.

Contact with soil causes immediate absorption and complete inactivation. The substance is non-volatile, non-inflammable, non-explosive, and very soluble in water, giving an alkaline solution. Concentrated aqueous solutions will corrode mild steel, galvanized iron, and aluminium.

Clark, McElligott, and Hurst (1966) have determined the toxicity of Paraquat for a number of animal species, and have described in some detail the pathological appearances which follow its administration by various routes in rats, mice, and rabbits. Lesions developing in the lungs are very unusual in type.

Up to July 1964 one case of poisoning in a child had occurred in Ireland. The present paper describes two further human fatalities in New Zealand. The two victims were a European aged 28 (Case 1) and a Maori aged 23 (Case 2). While in an intoxicated state at a party on 31 October 1964 the former ingested about half a glassful (4 oz.; 114 ml.) of a 20% solution of Paraquat in water from a bottle which previously had contained stout, while the latter was believed to have taken only a mouthful of the liquid, most of which was said to have been rejected immediately.

Case 1

On 1 November 1964 a European man aged 28 complained of a sore throat, dysphagia, epigastric pain, and possible haemoptysis but gave no history of vomiting. He had some diarrhoea on 2 and 3 November, and jaundice began on the 3rd. He was admitted to the Lower Hutt Hospital on 4 November.

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On admission he was dehydrated, toxic, and moderately jaundiced, with excoriation of the lips, mouth, and fauces. He was apyrexic, with guarding in the upper abdomen, and had a decreased urinary output. The full blood count was normal. Initial liver-function tests showed a total bilirubin of 8 mg./100 ml., alkaline phosphatase 17.7 K.A. units, and thymol turbidity 11 units. These subsequently rose to 13, 27, and 27 respectively, with a decrease in serum proteins (albumin and globulin together). Initially his non-protein nitrogen was 127 mg./100 ml. and later 86 and 150 mg. Faeces were strongly positive for occult blood, and the urine showed a large amount of bilirubin but no increase in urobilinogen. His urinary albumin remained high. Schumm's test and tests for methaemoglobin were negative: serum S.G.O.T. 66 units, S.G.P.T. 160 units.

X-ray examination of the chest on 4 November showed nothing abnormal, but next day there was a widespread fine mottling suggestive of interstitial oedema. Changes on 7 November were even more marked, and at this stage the patient showed respiratory distress, despite a strict fluid balance and a reasonable urinary output (S.G. 1015) and electrolyte balance. An electrocardiogram (E.G.C.) suggested a conduction bundle defect of the heart, with associated toxic myocarditis.

Broadly treatment consisted of intravenous fluids, prophylactic penicillin, and pethidine for pain. On one occasion mannitol was given intravenously, to induce diuresis in an effort to reduce the pulmonary oedema. The effort was not successful. The patient died on 7 November, exactly one week after taking Paraquat.

Post-mortem Examination.—The pleural cavity contained slight blood-stained effusion. The mucous membrane of the larynx, trachea, and bronchi was slightly inflamed and thick mucus was present. The lungs were voluminous and solid, with haemorrhages and oedema. Histologically congestion and haemorrhages were conspicuous, and oedema fluid in some alveoli contained much fibrin. Much of the lung, however, was solid and airless from heavy proliferation in the alveolar walls and elsewhere of cells of fibroblastic type (cf. Clark *et al.*, 1966). In a few places considerable proliferation of the epithelium of the terminal bronchi had led to the formation of small gland-like structures. Focal or diffuse polymorphonuclear, mononuclear, or eosinophilic infiltration, and many macrophages, accompanied the other changes in some areas. The mouth was ulcerated, but not the oesophagus. The stomach was congested and areas of haemorrhage were apparent. The liver was enlarged by approximately one-half and was firm and yellow. Microscopically mid-zonal and centrilobular degeneration of the liver cells increased in severity, until, towards the centre of the lobules, the cells were on the verge of necrosis. Both kidneys were soft and swollen. Microscopically tubular degeneration was severe and ischaemic glomerular degeneration was seen, but probably the changes noted were at least in part due to post-mortem phenomena.

The myocardium was soft and discoloured, and on section showed a mild myocarditis. The spleen and other organs appeared normal.

Case 2

A Maori man aged 23 was admitted to hospital on 6 November 1964, mainly for observation. He was known to have vomited copiously after the ingestion of the Paraquat, and several times the following morning. He had abdominal pains on 1 and 2 November, and noticed that he coughed readily if he inhaled deep.

On admission he had a slight cough with greyish sputum and slight swelling of the lips and tongue. He was a little giddy but apyrexic. There was no diarrhoea and nothing else of note on examination. His clinical picture may have been affected by his state of mind, as he was aware of the death of his friend (Case 1) and generally remained depressed during his stay in hospital.

The clinical course consisted in increasing shortness of breath and persistent tachycardia (100–160/min.). The E.C.G. showed a partial defect of conduction and evidence of a possible (toxic) myocarditis, with widespread effects of some congestive heart failure. The man was not obviously jaundiced, and the urinary output was satisfactory. There was an episode of cyanosis on 11 November, but he was much improved mentally and physically by the next day, though tachycardia was still present. He remained the same on the 13th, but on the 14th increasing shortness of breath with cyanosis was evident. He became frightened and apprehensive. Several lapses into semicoma occurred on 15 November. The blood-pressure was 110/80, the pulse 140/min., and the respiratory rate 40–50/min. He complained of pains "all over," but had no fits. He died on the 15th, 15 days after the ingestion of Paraquat.

Laboratory examination showed at first a normal blood count, but later the white blood corpuscles numbered 26,000/c.mm., with 83% polymorphs. Haemoglobin remained constant and normal. Serum protein was consistently high and electrophoresis showed a large increase in all globulin fractions. Initially bilirubin was slightly raised (3 mg./100 ml.), but later was normal. Other relevant data were: serial non-protein nitrogen estimations 82, 54, 80, 60, 70, 78, 112 mg./100 ml., casts present in the urine, electrolytes normal, serum S.G.O.T. 162 units, other tests of liver-function normal, faecal occult blood test negative. An early *x*-ray film of the chest showed patchy consolidation at the base of both lungs, and the appearances were more pronounced on 11 November.

Treatment consisted of tetracycline for four days, followed by ampicillin for four days. The patient was digitalized and given a mercurial diuretic once. Prednisone was given from 11 November and may have accounted for the temporary improvement in his general condition at this time.

Post-mortem Examination.—The trachea and bronchi contained a thin fluid, with some flecks of thick mucus. The lungs were dark, congested, and solid. Histologically they presented appearances similar to those described above, but on the whole were less severe. No important abnormality was present in the other viscera.

Comment

Case 1 initially showed the effects on the alimentary tract of a corrosive poison, followed shortly after by a phase of hepatic failure and renal insufficiency. The initial symptoms abated, while the hepatic failure tended to become more severe. Clinical and *x*-ray signs of respiratory failure and E.C.G. signs of toxic myocarditis and failure became apparent on the fifth day after ingestion of the poison. The abnormal *x*-ray appearances of the chest and the state of respiratory distress then became progressive until his death on the seventh day.

Case 2 also initially showed symptoms of a gastro-enteritis, followed shortly after by those of respiratory distress and toxic myocarditis. The hepato-renal episode, so evident in Case 1, was present to a much less extent and was overshadowed by the earlier onset of respiratory symptoms. Lapses into semicoma were thought to be secondary to cyanosis and cerebral anoxia. Vigorous treatment and the use of large doses of prednisone failed to bring about a permanent improvement.

In both cases the renal episodes consisted in initial anuria followed by a normal output, with persistently raised non-protein nitrogen and normal electrolytes. There was no evidence of true renal failure or uraemia in either patient. Both showed E.C.G. changes of "myocarditis" with conduction defects which did not improve appreciably with digitalis.

The findings at necropsy appeared to correspond to the amount of poison ingested. No attempt was made to assay the poison in the body because of the long delay between ingestion and the death of the patient, and the known transient presence of the substance. Case 1 exhibited toxic changes in the heart, liver, and kidneys, whereas in Case 2 these were not evident. However, the interesting feature common to both cases was the changes seen in the lungs. In each case both lungs were congested, haemorrhagic, oedematous, and almost wholly solid.

Microscopically all four lungs showed thickening of the alveolar walls with oedema and haemorrhage, and some infiltration by lymphocytes, macrophages, and eosinophils. Some of the alveolar spaces were filled with oedema fluid or with fluid containing large amounts of fibrin. Much of the lungs, however, was solid and airless, owing to fibroblastic proliferation in the alveolar walls and elsewhere. Essentially these are the lesions described in laboratory animals by Clark *et al.* (1966); they represent an unusual pulmonary reaction to a single dose of a toxic substance, which, while not persisting very long in the body, initiates during its stay progressive changes leading ultimately to death.

Minor liver damage such as was seen in Case 1 has been observed in rabbits, and renal tubular degeneration and necrosis has been found in rats, rabbits, and mice.

It is difficult to interpret the changes in man, especially in the absence of bacterial infection. A degree of pulmonary congestion and oedema may have resulted from interference with the conducting system of the heart and subsequent failure.

In many ways the microscopical appearances mimic those seen in "uraemic pneumonitis," a secondary to alterations in capillary permeability brought about by the azotaemia, but neither of these two patients was uraemic in the true sense.

The organ specificity of Paraquat raises some interesting questions in regard to its chemical structure and possible relationship to substances with a similar free radical, but there does not appear to be any substance of similar chemical configuration in general clinical use.

Summary

Two fatal human cases of poisoning due to the herbicide Paraquat are described and the histological features seen are compared with those observed in animals. Passing reference is made to another fatality reported from Ireland.

I wish to thank Drs. M. Watt and M. H. Watson for permission to publish these two cases, which were under their care.

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