Field, E. J. (1973). *Lancet*, 2, 1080.
Field, E. J. (1974). *British Medical Journal*, 1, 245.
Field, E. J., Shenton, B. K., and Joyce, G. (1974). *British Medical Journal*, 1, 412.
Foster, J. B., Mertin, J., and Thomson, A. M. (1974). *British Medical Journal*, 1, 452.
McAlpine, D., Lumsden, C. E., and Acheson, E. D. (1972). *Multiple Sclerosis: A Reappraisal*. Edinburgh and London, Churchill Livingstone.
Mertin, J., and Hughes, D. (1974). *International Archives of Allergy and Applied Immunology*. In press.
Mertin, J., Shenton, B. K., and Field, E. J. (1973). *British Medical Journal*, 2, 777.
Mertin, J., Hughes, D., and Stewart-Wynne, E. (1974). *Lancet*, 1, 1005.
Pritchard, J. A. V., *et al.* (1972). *Lancet*, 2, 627.
Shenton, B. K. (1974). *British Medical Journal*, 1, 574.
Shenton, B. K., Hughes, D., and Field, E. J. (1973). *British Journal of Cancer*, 28, Suppl. No. 1, p. 215.

PRELIMINARY COMMUNICATION

Effective Treatment for Paraquat Poisoning in Rats and its Relevance to Treatment of Paraquat Poisoning in Man

L. L. SMITH, A. WRIGHT, I. WYATT, M. S. ROSE

British Medical Journal, 1974, 4, 569-571

Summary

After oral administration of a lethal dose of paraquat to rats the plasma concentration remained relatively constant over four to 30 hours and was related to the paraquat content of the small intestine over the first 16 hours. During the first 30 hours the concentration of paraquat in the lung rose progressively above that of the plasma to levels which are known to cause pulmonary damage. A treatment has been devised which prevents the absorption of paraquat into the plasma and prevents accumulation of paraquat in the lung. This treatment consists of a stomach wash followed by four administrations of bentonite plus purgatives at two- to three-hour intervals. Even when treatment was delayed until 10 hours after administration of paraquat 80% survival was obtained. The relevance of this treatment to paraquat poisoning in man is discussed in the light of the finding that slices of human lung accumulate paraquat in the same way as those of rat lung.

Introduction

Paraquat, a widely used herbicide, has caused death in man after ingestion. In most cases death has resulted from extensive pulmonary damage, characterized initially by oedema, haemorrhage, and at later stages fibrosis (Bullivant, 1966; Bronkhorst *et al.*, 1968; Matthew *et al.*, 1968). Except when extremely large amounts are taken signs of pulmonary damage are not usually seen for several days after ingestion and death may not occur for several weeks.

Paraquat has been shown to have a similar effect in experimental animals, the lungs being severely affected (Clark *et al.*, 1966; Conning *et al.*, 1969; Murray and Gibson, 1972). The discovery of an energy-dependent accumulation of paraquat by rat lung in vitro (Rose *et al.*, in press) shows the propensity of lung to take up paraquat over a long period of time from a low concentration in plasma, and, therefore, offers a possible explanation for the selectivity of paraquat for the lung and also, possibly, for the delay in onset of pulmonary changes.

Previous work in animals (Clark, 1971) has shown the efficacy of fuller's earth and bentonite in binding paraquat and preventing absorption from the gut. It was found, however, that a single dose of these materials was effective only when given within a few hours after paraquat administration. Our experiments were carried out to investigate in greater detail the relationships between gastrointestinal paraquat content and plasma and lung concentrations. The effect on survival of thorough purging of the gastrointestinal tract after a lethal dose of paraquat was also examined.

Methods

Measurement of Paraquat after Oral Administration.—Male, Alderley Park (Wistar-derived), specific pathogen-free rats (body weight 180-200 g) were starved for 24 hours before being dosed by gavage with 0·2 ml/100 g body weight of an aqueous solution of pure paraquat dichloride containing paraquat 340 μmol/ml and 50 μCi/ml of methyl-^{14}C paraquat (specific activity 30 mCi/mmol, purchased from the Radiochemical Centre, Amersham). Animals were killed with halothane, blood taken by cardiac puncture, and the lungs, stomach, and small intestine removed. The contents of the stomach and small intestine were collected by thorough washing, and the amount of paraquat present in these contents and in plasma and lung was determined by measuring the radioactivity.

Treatment after Paraquat Administration.—After dosing with paraquat animals were left for four to 10 hours. The stomachs were then washed out with 5 ml of 0·9% saline and each of the rats was given by mouth castor oil 0·5 ml, magnesium sulphate 250 mg/kg body weight in a small volume (about 0·4 ml), and a suspension of bentonite 7-10 ml (7% w/v). The castor oil and bentonite were administered a further three times at two- to three-hour intervals.

Measurement of Paraquat Accumulation in Slices of Human Lung.—Samples of fresh human lung were sliced and stored at room temperature in Krebs-Ringer phosphate buffer containing 200 mg/100 ml (w/v) glucose. Only slices with two cut surfaces were used. Slices (30-100 mg wet weight) were incubated in Krebs-Ringer phosphate (Umbreit *et al.*, 1964) glucose (3·0 ml) containing 0·1 μCi methyl-^{14}C paraquat (specific radioactivity 32 mCi/mmol) and the required amount of paraquat dichloride to give final concentrations of 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} mol/l. Incubation was carried out in air in a shaking water bath at 37°C. After incubation slices were blotted and dissolved in 1·0 ml Soluene (Packard Instrument Co. Ltd) then 10 ml of Dimilume scintillator (Packard Instrument Co. Ltd.) was added. Samples of incubation media (0·1 ml) were diluted to 1·0 ml with water, and 10 ml of Instagel scintillator (Packard Instrument Co. Ltd.) was added. The radioactivity of all samples was measured using a liquid scintillation spectrometer.

Central Toxicology Laboratory, Biochemical Mechanisms Unit, Imperial Chemical Industries Limited, Alderley Park, Cheshire SK10 4TJ

L. L. SMITH, B.SC., Biochemist
A. WRIGHT, L.I.BIOL., Biochemist
I. WYATT, L.R.I.C., Biochemist
M. S. ROSE, B.SC., PH.D., Head of Biochemical Mechanisms Unit

Results

After administration of paraquat 680 μmol/kg body weight to rats the plasma concentration of paraquat was more than 5 nmol/ml for at least 30 hours. During this time the lung concentration rose above that of the plasma to levels which are known to cause severe pulmonary damage (L. L. Smith and M. S. Rose, unpublished) and consequent death in three to six days (see table and fig. 2).

The paraquat present in the contents of the stomach and the small intestine of individual rats was measured one, four, eight, and 16 hours after dosing and compared with the plasma concentration at these times. At both one hour and 16 hours there was an apparent linear relationship between the paraquat content of the intestine and the plasma concentration of paraquat (fig. 1). There was no such relationship between the stomach contents and the plasma. Similar results were obtained at four and eight hours after dosing. Between 10% and 40% of the administered dose was found in the stomach of rats even after 16 hours.

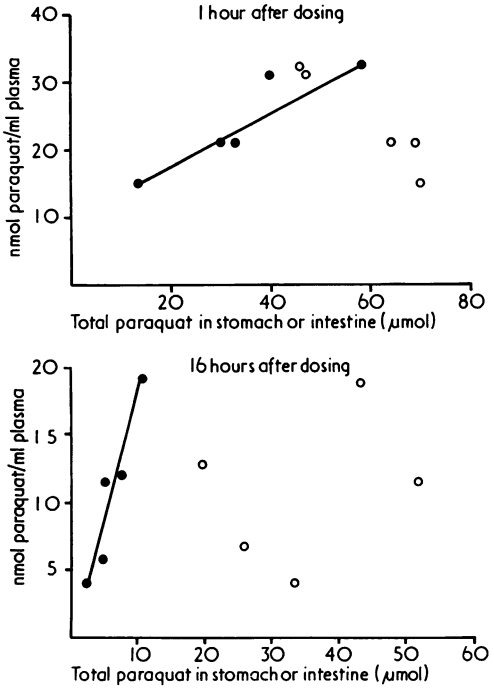

FIG. 1—Relationship between plasma concentration of paraquat and paraquat content of stomach and intestine. O = Stomach. ● = Intestine.

Rats were dosed with paraquat, left for four hours, and then treated in an attempt to remove the paraquat from the gastrointestinal tract. The plasma concentration of paraquat was considerably reduced by this treatment and by 30 hours was 6% of that in untreated paraquat-poisoned rats (fig. 2). The lung concentrations in the treated rats also did not rise to the high levels found without treatment. Groups of rats given the same treatment all survived a dose of paraquat which normally kills 90-100% of the rats (see table). Most rats survived after a lethal dose of paraquat even when treatment was delayed for 10 hours (see table).

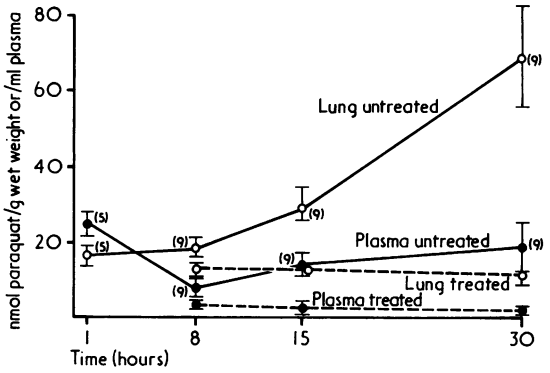

FIG. 2—Effect of treatment on relationship between lung and plasma concentrations of paraquat after paraquat by mouth. Treatment was started four hours after administration of paraquat. Numbers of untreated rats are given in parentheses; each point is mean ± S.E. of mean. Each point for treated rats is mean ± S.E. of mean from four rats.

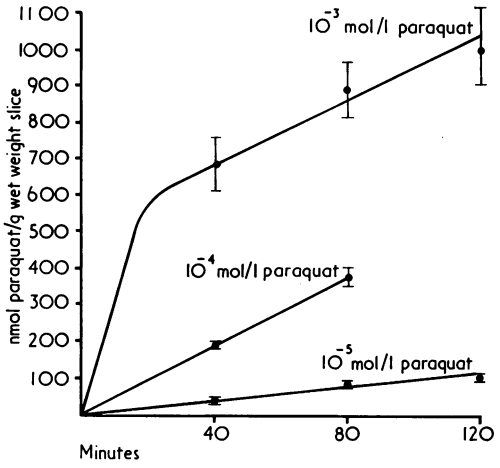

FIG. 3—Accumulation of paraquat by slices of human lung. Each point is mean ± S.E. of mean of three determinations.

Slices of human lung accumulated paraquat in vitro to concentrations greater than those present in the incubation medium (fig. 3). At high concentrations (10^{-3} mol/l.) there was an early rapid phase followed by a slower linear phase, as has been shown previously for slices of rat lung (Rose *et al.*, in press). The linear rate of accumulation increased with increasing paraquat concentration in the incubation medium (fig. 3) but approached a maximum at 10^{-3} mol/l. From the data shown in fig. 3, together with other data obtained with lower concentrations of paraquat, the process can be shown to exhibit saturation kinetics with a Vmax of about 300 nmol of paraquat accumulated/g tissue/hour and a Km of about 4×10^{-5} mol/l.

Discussion

The results show that after oral administration of paraquat to rats the lung is able to accumulate paraquat to a concentration greatly in excess of that of the plasma, as might be predicted from the discovery of energy-dependent accumulation in vitro

Number of Paraquat dosed Rats Dead at Each Day after Administration according to Treatment given

	No. of Rats given Paraquat	Days after Administration of Paraquat													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
No treatment	29	0	0	11	22	25	26	26	27	27	27	27	27	27	27
Treatment after 4hr	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Treatment after 10hr	10	0	0	0	1	2	2	2	2	2	2	2	2	2	2

(Rose *et al.*, in press). When measures are taken to remove free paraquat from the gut the concentration of paraquat in the plasma is considerably reduced, the lung no longer accumulates paraquat to high levels, and rats survive a dose of paraquat which is normally lethal. Hence, paraquat concentrations in the lung of 10-15 nmol/g do not cause sufficient damage to kill rats and it is the accumulation of paraquat to concentrations greater than these values which leads to severe pulmonary damage and death. It can also be concluded that it is not only the peak plasma concentration which is responsible for determining the lung level but also maintenance of plasma concentrations from which the lung can accumulate large amounts of paraquat. The maintenance of such plasma concentrations in the rat has been shown to be the result of continued absorption of paraquat from the gut over the first 30 hours after administration by mouth.

We have shown that slices of human lung accumulate paraquat in vitro and the kinetics of the process are very similar to those for the rat (V max for both about 300 nmol of paraquat/g tissue/hour; KM for both in the region 4×10^{-5}-8×10^{-5} mol/l.). Clearly, human lung has the capacity to accumulate paraquat from relatively low plasma concentrations and this process may be prolonged, as in the rat. That this might be the case is suggested by the delay of several days often seen in patients before signs of lung damage occur. In the treatment of cases of human poisoning measures which remove paraquat from the gastrointestinal tract should be effective in reducing plasma levels and thus might prevent the accumulation of damaging amounts of paraquat in the lung. In rats treatment consisting of a stomach wash followed by repeated administration of cathartics, together with large volumes of fuller's earth or bentonite, has been shown to be effective, and we suggest that this type of treatment continued for several days might be beneficial in cases of human poisoning. Other measures, such as haemoperfusion or haemodialysis, which act directly to reduce the plasma concentration of paraquat should also be considered since in man impairment of renal function is frequently an additional complication (Bullivant, 1966).

We thank Mr. Moussalli, Dr. K. Lodge, and Dr. R. Munro, cardiothoracic department, Wythenshawe Hospital, Manchester, for supplying samples of human lung.

References

Bronkhorst, F. B., Van Daal, J. M., and Tan, H. D. (1968). *Nederlandsch Tijdschrift voor Geneeksunde*, **112**, 310.
Bullivant, C. M. (1966). *British Medical Journal*, **1**, 1272.
Clark, D. G. (1971). *British Journal of Industrial Medicine*, **28**, 186.
Clark, D. G., McElligott, T. F., and Weston-Hurst, E. (1966). *British Journal of Industrial Medicine*, **23**, 126.
Conning, D. M., Fletcher, K., and Swan, A. A. B. (1969). *British Medical Bulletin*, **25**, 245.
Matthew, H., *et al.* (1968). *British Medical Journal*, **3**, 759.
Murray, R. E., and Gibson, J. E. (1972). *Experimental and Molecular Pathology*, **17**, 317.
Rose, M. S., Smith, L. L., and Wyatt, I., *Nature*. In press.
Umbreit, W. W., Burris, R. H., and Stauffer, J. F. (1964). In *Manometric Techniques*, p. 132. Minneapolis, Burgess Publishing Company.

MEDICAL MEMORANDA

Horseshoe Kidney: A Report of One Family

R. S. DAVID

British Medical Journal, 1974, 4, 571-572

This paper is a report of a family in which all three siblings had horseshoe kidneys, while the mother had a rotational abnormality of one kidney. *X*-ray examination showed other congenital bony abnormalities.

Case Reports

Case 1.—The youngest in the family had a lumbar meningomyelocoele and gross congenital deficiency of the left iliac bone. She was referred at the age of two for assessment of her urinary tract because of recurrent urinary infections and continuous dribbling incontinence. Intravenous pyelography showed a typical horseshoe kidney (fig. 1), and an expression cystogram showed gross reflux to a dilated pelvis and ureter on the right (fig. 2). Her problems were due to her neurogenic bladder rather than to her kidneys and she was managed accordingly.

Case 2.—The boy, aged six, was referred after a single episode of vague abdominal pain and haematuria lasting two days. His intravenous pyelogram (fig. 3) again showed a horseshoe kidney, with slight fullness of the left pelvis and ureter. The 12th ribs were seen to be short. A cystogram was normal, while a left retrograde pyelogram did not show any obstruction. He remained symptom free.

Case 3.—This 10-year-old girl had had no symptoms at all. but her intravenous pyelogram was again characteristic, and she had a short left 12th rib (fig. 4).

Case 4.—The mother, who was the only other member of the family to be *x*-rayed, had a different renal pattern. While her right kidney was entirely normal the left was abnormally rotated, with the lowest calyx pointing medially in typical horseshoe fashion. On her *x*-ray film six lumbar vertebrae are seen (fig. 5).

Comment

The frequency with which horseshoe kidney occurs, according to different estimates, varies between one in 400 (Glenn, 1959) and one in 1,000 (Walters and Priestley, 1932). A large post-mortem series (Bell, 1950) gives probably the most accurate estimate of frequency in the general population—one in 497.

The family reported here illustrates some of the clinical pictures. Many patients like the girl in case 3, are symptom free and may remain so throughout life, their horseshoe kidney being discovered accidentally at routine medicals, laparotomy, or necropsy. This must in part account for the variation in estimates of the frequency of the condition. As in case 1, many patients have associated congenital anomalies. A recent series (Kölln *et al.*, 1972) gives a figure of 30%, with 51 anomalies in 32 patients; of these 16 were urogenital, 11 musculoskeletal, and 10 cardiovascular, and seven were in the central nervous system, including three meningomyelocoeles.

Those horseshoe kidneys that cause symptoms do so usually either because of hypertension or because of partial obstruction to the ureters as they cross the bridge of kidney tissue. No

Booth Hall Children's Hospital, Blackley, Manchester 9
R. S. DAVID, F.R.C.S., Surgical Registrar