Edited by
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John Wright and Sons Limited
Bristol
1974

Paraquat Poisoning

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Paraquat is a herbicide introduced by Plant Protection Limited for commercial use in this country in 1963; the name strictly refers to the cation. The common paraquat salts are all apparently fully ionized and experiments have shown that the anions, chloride, sulphate, methylsulphate etc., do not affect the toxicity of paraquat. The compound belongs to a group of chemicals, the bipyridyls, and the molecules shown in *Fig.* 1 may be considered typical of the many hundreds that

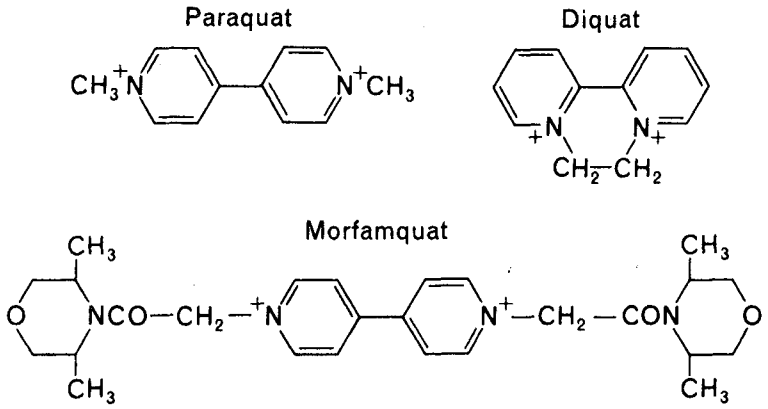

Fig. 1. Structures of typical herbicidal bipyridyls.

have been synthesized, variation usually being the result of introducing different quaternizing groups on the nitrogen atoms. Although they resemble one another to some extent, both in their action on plants and animals, the bipyridyls show major differences in both areas, and the effects of each, particularly in its toxicology, are best considered separately. Paraquat kills plants by effects on the green parts, not on woody stems, and is completely and rapidly inactivated by contact with clay in the soil. The paraquat molecule is flat and can penetrate into the crystal lattice of clay minerals where it is extremely firmly held by physical bonding; in this situation it cannot be attacked by soil organisms which are unable to penetrate the lattice. The only feasible way at present for removing the paraquat is to boil the soil with sulphuric acid and destroy the clay. Paraquat in its bound form is biologically completely inert and has been shown to cause no harm to either plant or animal life. Virtually all soils contain some clay, those that do not being extremely rare, and if paraquat somehow were to be free in the soil, it has been shown that it could be degraded by microorganisms. There is therefore every reason to believe

that environmental contamination and a possibly associated toxicological hazard presents no problem with paraquat. These properties enable one to kill weeds on the ground and then plant or seed directly through the killed vegetation and this can, in favourable circumstances, lead to the elimination of ploughing and other traditional cultivation techniques (for a review of the agricultural properties and uses of paraquat see Calderbank (1968)). Because of these properties, paraquat, the best of the bipyridyls, has become widely accepted and is now used in over 130 countries.

Paraquat, for agricultural purposes, is sold primarily as a 20 per cent aqueous solution under the trade name of Gramoxone, although other formulations are in limited use. On the domestic market, paraquat is sold as Weedol, a solid granule, which, until 1971, contained 5 per cent paraquat, but now contains 2·5 per cent paraquat together with 2·5 per cent diquat. During the 10 years of use and in all countries of use, 232 deaths from paraquat poisoning have been reported, about half of these being suicidal. In those cases where we have adequate information all deaths, both suicidal and accidental, have been due to the drinking of concentrated material. (There is an exception to this where a man killed himself by injecting the material (Almog and Tal, 1967).) In the accidental cases swallowing of the material has occurred after it has been put into an unlabelled container in some inappropriate place. Gramoxone has been drunk from a squash bottle in a drinks cupboard, from a beer bottle in a refrigerator, from a whiskey bottle in a larder; children have died after drinking Gramoxone from cordial bottles found in a field or in a farm outhouse or from measuring vessels left unattended. These cases are not exceptional but typical.

Table 1. Paraquat poisoning deaths 1964–1973 (All countries)

	Accident	*Suicide*	*Total**
England and Wales	15	26	49
Scotland	7	6	15
Ireland	22	15	42
W. Germany	9	19	29
Malaysia	8	15	24
Japan	2	10	12
U.S.A.	3	0	3
Other countries (24)	30	18	58
Totals	96	109	232

*The total includes those in which the circumstances of death are unknown.

Table 1 shows the distribution of notified fatal poisoning cases by country, only those countries where several cases have occurred being included. It can be seen that the cases occur predominantly in Western Europe – Ireland, England, and Germany having the most. In the U.S.A., a major user, few cases have occurred. Of the developing territories only Malaysia has a significant number and these are predominantly suicides. There is some tendency for the incidence to reflect total usage, but this is not invariable, and it is noticeable that where one might expect unskilled handling, such as Africa or India, the incidence of poisoning is nil or low. It is apparent that the application of paraquat is not accompanied by any serious risk of poisoning.

The effects of paraquat poisoning were first studied in rats (Clark *et al.*, 1966); changes were seen in these animals which subsequently proved typical of those in other animals and man. The most striking effect is in the lung, the compound initially causing oedema and haemorrhage. If the animal survives this initial phase a fulminating fibrotic process develops and within some 7 to 14 days the lung is a mass of fibrous tissue. Death ensues from anoxia due to a gross impairment of gaseous exchange processes. A detailed description of these changes has now been published elsewhere (Kimbrough and Gaines, 1970). These changes occur whether paraquat is given orally or parenterally, but not when given by inhalation. These dramatic effects in the lung have tended to overshadow the effects of paraquat in other organs, but damage due to paraquat can be demonstrated in the kidneys, liver, and heart. The extent of this damage varies with different species: in the rat, for instance, there is virtually no liver damage and the kidneys are only slightly affected, whereas in the dog all the above organs may be involved. The rabbit appears to be anomalous in that the typical lung changes are not seen in this species (Butler and Kleinerman, 1971).

In man there are now several well investigated reports of the effects of paraquat. The first reaction consequent on the ingestion of Gramoxone is due to its irritancy and usually appears as burning and ulceration of the mouth, oesophagus, and gastrointestinal tract (McDonagh and Martin, 1970; Malone *et al.*, 1971). Diarrhoea is common, sometimes accompanied by blood; curiously vomiting is by no means invariable. The first signs of systemic poisoning are associated with renal damage, usually starting 1–3 days after poisoning, producing an elevated blood urea, reduced creatine clearance, and a diminished urine flow (Oreopoulos, *et al.*, 1968; Gardiner, 1972). The lesion in man is a tubular necrosis similar to that seen in animals. Such effects occur in most cases of poisoning and can be severe, but kidney failure has not been reported as a primary cause of death.

Jaundice as a consequence of damage to the liver is also of common occurrence in man (Fennelly *et al.*, 1971; Grabensee *et al.*, 1971). Post-mortem examination shows a centrilobular necrosis of the liver cells (Bullivant, 1966). The effects on the heart are more varied. Death from heart or circulatory failure has been reported in some instances (Lanzinger *et al.*, 1969; Iff *et al.*, 1971), whereas in many others no apparent defect exists. Post-mortem examination usually does not show any gross lesions, although a patchy degeneration or necrosis of some cardiac muscle fibres may be apparent (Masterson and Roche, 1970). It is possible that the failure of the heart is not entirely due to the direct effect of paraquat on this organ, but is a reflection of the total body damage.

In the majority of cases of poisoning, the above effects, although seriously complicating therapy, seem to be reversible and relatively normal function appears after a few days. The most serious threat to life and the cause of death in most instances is the damage to the lung. In the past, attention has been concentrated on the fibrosis developing after a long delay, rapidly leading to respiratory insufficiency. It is now apparent, however, that damage to the lung occurs early in paraquat poisoning, although this may not be clinically apparent. Yoneyama *et al.* (1969) have described a case of death in one day after a large dose of Gramoxone where lung haemorrhage was present, and von der Hardt and Cardesa (1971) found lung haemorrhage and almost complete loss of the alveolar and bronchiolar epithelium in a woman dying two days after swallowing Gramoxone. Similar findings have also been reported by others (Hargreave *et al.*, 1969; Nagi, 1970).

The more usual case of a delay before lung involvement is clinically apparent,

is typified by the reports of Bronkhorst *et al.* (1968), Fennelly *et al.* (1968), McDonagh and Martin (1970), Bony *et al.* (1971), and Grabensee *et al.* (1971), where death was delayed for up to 26 days. In an unreported case death from pulmonary fibrosis occurred 35 days after deliberate ingestion of Gramoxone. Two other cases are of interest in this respect. In the one reported by Matthew *et al.* (1968) at post-mortem fibrosis was seen not only in the patient's own lung, but also in a lung transplanted six days after ingestion. It is, however, possible that the fibrosis was part of a rejection reaction. These authors also stated that although three days prior to the transplant the patient was clinically and radiologically well, tests showed a pattern of deteriorating lung function; this observation has been confirmed (Matthew, 1971). In the case of Almog and Tal (1967), a patient who injected himself with Gramoxone developed signs of paraquat poisoning typical of those after ingestion and died in severe respiratory distress 18 days after injection. The proliferation of the terminal bronchiolar epithelium seen in animals (Clark *et al.*, 1966) was also noted in this case (Herczeg and Reif, 1968).

Unusual pathological findings at post-mortem include adrenal cortical necrosis (Yoneyama *et al.*, 1969; Nagi, 1970), and oedema and haemorrhage of the brain (Lanzinger *et al.*, 1969; Matthew, 1971; Nienhaus and Ehrenfeld, 1971).

The overall results, therefore, in paraquat poisoning by ingestion or injection are those of a compound causing fairly widespread damage, but having its most severe effect and lethal action on the lung. Animals poisoned by inhalation show a different clinical course (Gage, 1968a). In the form of a respirable aerosol* (mean particle diameter about 5 μm.) paraquat acts similarly to a powerful irritant such as phosgene and the changes in the lung are typical of such effects. Death, at sufficiently high doses, occurs within a short period and animals not dying within this time recover completely; a delayed fibrosis does not occur. It must be emphasized that reported cases of death from paraquat poisoning have been due to swallowing one or other forms of the concentrate. Symptoms following spraying with paraquat have been noted (Guardascione and di Bosco, 1969; Malone *et al.*, 1971), but it should be remembered that paraquat has been used by millions of people, and coincident illness may be expected. The small number of the incidents and their diverse nature lends support to the probability that illness is coincidental with and not caused by paraquat. In a study of Malayan sprayers (Swan, 1969) excretion of very small quantities of paraquat was frequently seen, but over a period of six weeks adverse reactions were limited to minor effects on the skin. Hearn and Keir (1971), investigating 296 sprayers in Trinidad, stated that despite gross exposure of these men no systemic effects were apparent; effects on the finger-nails were, however, reported.

The chemical diagnosis of paraquat poisoning is achieved by analysis of the urine or tissue for paraquat, since paraquat is not metabolized systemically and is excreted unchanged in the urine (Daniel and Gage, 1966). For analysis it can be reduced by dithionite to an intensely coloured free radical which may be estimated colorimetrically by measuring its absorption at 600 nm.

Tompsett and Brown (Matthew *et al.*, 1968) introduced a quick test for paraquat suitable for immediate clinical use. In doubtful cases of poisoning such a test is essential in deciding whether to start intensive therapy since the more accurate laboratory methods are too time-consuming. In this method sodium dithionite and sodium hydroxide are added to urine which is observed for the development of a

*Such aerosols are not produced by agricultural equipment, where the particle size is mostly in excess of 50 μm.

blue colouration; sensitivity is around 1 μg. per ml. A slightly more complicated, but still fast, method has been given by Sharp *et al.* (1972) with detection limits of 0·2 μg. per ml. For small quantities of paraquat, use can be made of ion-exchange resins to concentrate the cation when the sensitivity can be as high as 5 μg. per 100 ml. (Beyer, 1970; Tompsett, 1970). This method is time-consuming, but is quantitative and can detect either those cases where small amounts have been ingested or where analysis is done several days after poisoning.

The excretion of most of the paraquat absorbed systemically is rapid. Daniel and Gage (1966) using ^{14}C-labelled paraquat in rats showed that after subcutaneous injection 90–100 per cent of the dose was recovered in urine within two days. On the basis of this and similar results it was assumed that toxicologically significant amounts of paraquat were not retained and caused paraquat to be called a 'hit and run compound' (Barnes, 1968). Experience of poisoning in man, however, shows that the situation is more complex.

There is very little knowledge of paraquat excretion in human cases in the very early period after paraquat ingestion. In animals Daniel and Gage (1966) showed that about 75 per cent of the compound is not absorbed after oral administration and is excreted in the faeces, and also that 90 per cent of what is absorbed is excreted in the urine within two days. In man, however, it has now been shown that the excretion of paraquat continues for many days. In the first day of analysis the amount of paraquat is comparatively large, and rapidly declines on subsequent days to a lower level, but the 'tail' of excretion is prolonged. The amounts present in this tail are small and represent only a few percent of the total urinary excretion. In the case of Hensel and Durr (1971), of approximately 400 mg. excreted in total, 350 were present in the urine of the first day. The prolonged excretion has now been reported in several cases (Tompsett, 1970; Beebeejaun *et al.*, 1971; Fisher *et al.*, 1971; Grabensee *et al.*, 1971), and must be presumed to be typical. It is of interest that in most cases where the excretion has been followed, a small peak in the amount of paraquat occurs around the ninth day after poisoning. The significance of this is not clear; it may represent the effect of a recovery of kidney function or possibly a release of retained paraquat by the tissues.

The analysis of blood is of little value since paraquat can seldom be detected after about 24 hours, but paraquat may be found in a variety of tissues after death. Sharp *et al.* (1972) have made a detailed study in the rat and found, after an initial period of four hours, that the highest concentration of paraquat was in the lung, with the kidney and liver containing rather less; the half-life in these tissues was about 56 hours and about 50 hours in the lung. Muscle contained low concentrations of paraquat with a half-life of 4–5 days and could therefore, at a late stage, constitute a major pool of paraquat. In man no obvious accumulation of paraquat in the lung has been shown. At day 4 Hall and Carson (1970) reported kidney to contain 5·8 μg. per g. with 1·6, 1·4, and 0·6 in lung, spleen, and liver respectively; at 8 days Lanzinger *et al.* (1969) found kidney and muscle to contain the greatest concentration (1·76 and 1·52 μg. per g.), whilst liver, lung, and spleen were less (0·9–1·0 μg. per g.). Ten days after ingestion Tompsett (1970) could not detect paraquat in lung tissue whilst finding 0·2–0·9 μg per g. in liver, kidney, and muscle. When death occurred 26 days after poisoning Grabensee *et al.* (1971) found 0·19 and 0·25 μg. per g. in the heart and liver and 0·14 μg. per g. in the lung. Results of analyses in this laboratory in several unreported cases also give similar figures. It is therefore apparent that paraquat can be detected in tissues for a long period after poisoning, and that the distribution is fairly general, with no greater

concentrations in the most severely affected tissues.

The lethal dose of paraquat in man has been the subject of much speculation. Lanzinger *et al.* (1969) quote an 'LD_{50}' of 4 mg. per kg. and speculate that it may be even less; this has been quoted by others as the oral LD_{50} (Hargreave *et al.*, 1969). This figure is, however, based on a single case of poisoning by the injection of 1 ml. of Gramoxone (Herczeg and Reif, 1968). Paraquat is known to be relatively poorly absorbed in rats (Daniel and Gage, 1966) and in our own experiments the disparity between the oral and intraperitoneal LD_{50}'s in other species would tend to show that this is a general phenomenon. In man Grabensee *et al.* (1971) found a high excretion in the faeces, and figures for urinary excretion are far lower than the estimates of the dose taken, so that it is reasonable to suppose that in man also, only a fraction of a swallowed dose is absorbed systemically; our original guess of about 5 per cent (Conning *et al.*, 1969) may still be correct.

The use of animal data to predict a lethal dose for man is not particularly helpful. *Table* 2 shows that the oral LD_{50} in a variety of species is very variable. Some slight correlation with body weight can be seen and this might suggest an LD_{50} for man of around 50 mg. per kg. There are, however, obvious anomalies, perhaps the most striking being the difference in LD_{50} between the rabbit and the hare.

Table 2. Oral LD_{50} of paraquat in various animals

Species	*Body weight (g.)*	*LD_{50} (mg. per kg.)*
Mouse	30	104 (90–120)
Rat	175	130 (110–160)
Guinea pig	400	30 (22–41)
Rabbit	2,500	126 (69–183)
Cat	2,500	35 (27–46)
Hare	3,000	35
Monkey	5,500	75
Dog	12,000	25–50
Sheep	25,000	65
Cow	150,000	35–60

In cases of human poisoning it is seldom that the dose is known with even approximate accuracy, such phrases as 'a mouthful' or 'a sip' being used. The situation is further complicated by the patient spitting out or vomiting some of the material. There are, however, a few cases where a good estimate of dose has been obtained. In the case of Fisher *et al.* (1971) 10 ml. Chevron Dual (equivalent to Gramoxone) was swallowed and the patient recovered, despite the absence of treatment for some six days; similarly Iff *et al.* (1971) reported recovery in a 16-year-old boy after 10–15 ml. of 30 per cent paraquat solution. Two remarkable cases are those of Grundies *et al.* (1971) where the dose was 50 ml., with vomiting, but recovery ensued with treatment, and Malone *et al.* (1971) where a 35-year-old man survived 4 oz. (110 ml.).

Against these cases may be set those where death ensued: 30 ml., vomited (Hensel and Durr, 1971), 20 ml. (Matthew, 1971), 10 ml. (Nienhaus and Ehrenfeld, 1971), a teaspoon (?5–10 ml) (Fennelly *et al.*, 1968; Masterson and Roche, 1970).

Cases of poisoning by Weedol have also been reported. In a 32-year-old man 45 g. (equivalent to 2·5 g. paraquat) was survived (Kerr *et al.*, 1968) as was 10 g. (0·5 g. paraquat) in a 2-year-old child (McDonagh and Martin, 1970). Lloyd (1969) reports survival in three children eating 60 g. between them. Death occurred after

160 g. (8 g. paraquat) (Hall and Carson, 1970). We have also been told of a 23-year-old girl dying, after prolonged illness, after taking 20 g. (1 g. paraquat).

If 10 ml. of Gramoxone is taken to be the probable lethal dose this would contain 2 g. of paraquat and in a 60-kg. man would give a lethal amount as just over 30 mg. per kg. paraquat. The total evidence therefore would suggest that the LD_{50} to man of paraquat is about 30 mg. per kg.

The implication, from a history of taking a mouthful and spitting it out, that the lethal dose of Gramoxone is considerably less than indicated above, is difficult to substantiate. Patients giving this account have both died (Bullivant, 1966; Oreopoulos *et al.*, 1968; Heyndrickx *et al.*, 1969; Lanzinger *et al.*, 1969; Tompsett, 1970) and recovered (McKean, 1968; Mracek and Krch, 1969; Grabensee *et al.*, 1971; Malone *et al.*, 1971). It is extremely difficult to avoid swallowing at least some of a liquid which has been taken into the mouth in the mistaken belief that it is innocuous and it is not unreasonable to suppose that in this circumstance 10 ml. can be swallowed; where available, the urinary excretion figures suggest this to be so.

The treatment of paraquat poisoning is at present directed toward the elimination of the material from the body. It has been shown (Clark, 1971) that the mineral adsorbents, Bentonite and Fullers Earth, can remove paraquat very efficiently from the stomach, but this usefulness is confined to the first hour after ingestion. After absorption, treatment is designed to help elimination. Ferguson (1971) has shown that paraquat is freely filtered by the renal glomeruli, but is reabsorbed to some extent in the proximal tubule. Forced diuresis appears to be the treatment of choice, heroic quantities of fluid, up to 30 litres per day being used with success (Grundies *et al.*, 1971). Although these latter authors show that paraquat is freely dialysable, experience with haemodialysis has been disappointing. After 24 hours paraquat is present in blood usually at concentrations undetectable chemically (Sharp *et al.*, 1972) and dialysis will remove little if any. The fact that in these circumstances very appreciable quantities are removed by the kidneys probably reflects the vastly greater rate of blood-flow through these organs.

Immunosuppressive agents and cytotoxic drugs have been used for treatment, but their effectiveness is questionable (Fennelly *et al.*, 1971; Malone *et al.*, 1971). Certainly no consistent response seems to be obtained with their use. Oxygen is quite definitely contraindicated (Matthew, 1971; Nienhaus and Ehrenfeld, 1971; Fisher *et al.*, 1972).

There is at present no substance known to have an antidotal effect in paraquat poisoning. In this laboratory we have examined many compounds for this property, usually on the basis of some hypothesis about the mechanism of toxic action (*Table* 3); without exception these compounds have shown no indication of the required effect. Despite the lack of a specific antidote, an attribute which paraquat shares with the great majority of chemicals in daily use, it is clear that paraquat ingestion is by no means inevitably fatal, even after the appearance of clinical evidence of lung damage. Of the 97 cases recorded in the literature, 29 are of recovery, and in the records kept in this laboratory there are a further 63. (In many of these unreported cases the dose was trivial and would not be expected to lead to symptoms, but on the criteria given above, about half might be classed as serious poisoning.) Recovery seems to be substantially complete, although in one or two cases some residual lung impairment has been reported (Malone *et al.*, 1971; Mracek and Krch, 1969). With a recognition of the problem and the evolution of forms of treatment, the rate of survival would now seem to be higher.

Table 3. Effect of various compounds used as possible antidotes to paraquat poisoning. Groups of 5–10 rats were given a lethal amount of paraquat usually as a single oral dose, but in some instances by incorporation in the diet. The 'antidote' was given by injection. The effectiveness of the antidote was assessed by comparing the group given the antidote with a similar group given paraquat only.

	Compound	*Effect*
Free radical scavengers	2-mercaptoethylamine hydrochloride	Increased mortality
	2-aminoethylisothiouronium bromide	Increased mortality
	Dimethylsulphoxide	Increased mortality
	Cysteamine	No effect
	γ-tocopherol	Some protective action when given before paraquat, none after
Anti-inflammatory	Cortisone	No effect
	Prednisolone	Slight delay in death
	Butazolidine	Slight delay in death
	Chlorpromazine	No effect
Immunosuppressive drugs	Azathiaprine	No effect
	Busulphan	No effect
	Chlorambucil	No effect
Complexing agents	Sodium tetraphenyl borate	Increased mortality
	Sodium amsonate	No effect
Miscellaneous	Trasylol	No effect
	Promethazine hydrochloride	No effect
	Indomethacin	No effect
	Aspirin	No effect
	Calcium EDTA	No effect
	Riboflavin	No effect
	Phenazine	Increased mortality
	100 per cent O_2	Increased mortality
	10 per cent O_2	No effect
	Galactose	No effect
	Theophylline	Increased mortality
	Salbutamol	Increased mortality
	Dibenyline	Increased mortality
	Duramorph	Increased mortality

The biochemical process by which paraquat produces its toxic effects is unknown; possibly the reduction of paraquat to a free radical is involved. Michaelis and Hill (1933) showed many years ago that powerful reducing agents produced a stable free radical and under the name of methyl viologen, paraquat has been used as a redox indicator. The scheme of reactions of *Fig.* 2 can be shown to occur in biological systems. In plants the reduction of paraquat to the radical ion is brought about by photosystem 1, followed by a spontaneous reaction with oxygen to give the O_2^- radical ion and regenerated paraquat. The O_2^- then reacts either spontaneously or enzymatically to give oxygen and hydrogen peroxide, which latter is considered to be the immediate toxic agent in plants (Calderbank, 1968; Dodge, 1971). Similar reactions can occur in animals. Gage (1968b) has shown that flavo-enzymes from rat liver will reduce paraquat to the radical and the subsequent reactions outlined above may be expected to follow. The redox potential of the reduction of paraquat to paraquat radical is −446 mV. and in the isolated enzyme system the amount of radical produced is small. Experiments using pulse radiolysis

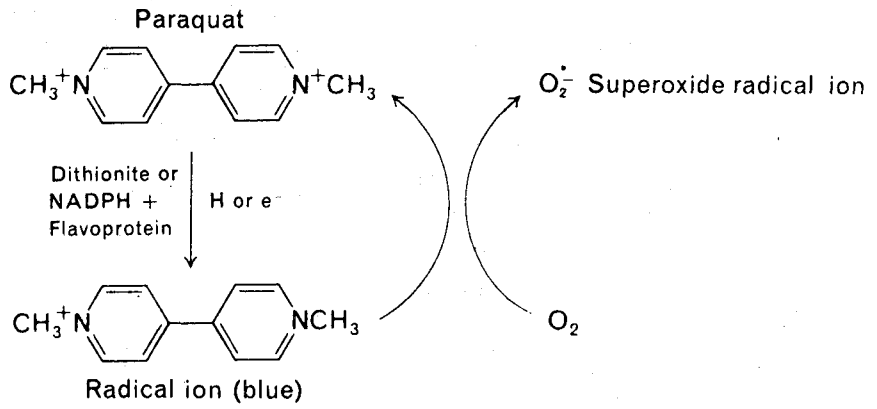

Fig. 2. Reduction and reoxidation of paraquat.

(Farrington, 1971) have shown that the reaction between paraquat radical and O_2 is extremely fast (rate constant in free solution $6{\cdot}5 \times 10^8$ litres per mole sec.) so that the life-time of paraquat radical is very short – of the order of one microsecond with a correspondingly limited diffusion range. The O_2^- radical ion is a normal product of biological processes and the enzyme superoxide dismutase specifically catalyses its rapid removal (McCord and Fridovich, 1969). It would appear then that if these radicals are involved in paraquat toxicity they act at very low concentrations close to the site of production, and the hypothesis that it is paraquat itself that is the direct toxic species must still be tenable. From the prolonged urinary excretion in man and the occurrence of tissue residues many days after ingestion, it must be inferred that tissue binding occurs but the significance of this is not known; it may be a non-specific binding to acidic polymers.

The presence of small quantities of bound paraquat may be relevant to the development of fibrotic reactions in the lung. The case of Matthew *et al.* (1968) would tend to support this view and Styles and Conning (1969) have shown not only that the fibroblast, in contrast to the alveolar macrophage, is relatively resistant to paraquat, but is stimulated into division in the presence of low concentrations. Against this, we have shown (unpublished observations) that small quantities of paraquat producing measurable tissue concentrations can be fed to animals for prolonged periods with no adverse effect, and other organs accumulating as high or higher concentrations than the lung show no fibrosis. In view of the massive damage to the lung known to occur soon after ingestion the fibrosis may well be the normal formation of scar tissue after injury.

Manktelow (1967) introduced the idea that paraquat interfered specifically with the formation of pulmonary surfactant and this was taken up by others (Fisher and Clements, 1969; Robertson *et al.*, 1971). Fletcher and Wyatt (1970) disputed these results on the basis of lipid analysis in rat lungs and later (Fletcher and Wyatt, 1972) found no difference in the dipalmitoyl lecithin content of the lung of paraquat-poisoned mice and controls.

Electron microscopic studies of the effects of paraquat have been made both in animals and man. Vijeyaratnam and Corrin (1971) considered that in rats the major effects of paraquat were produced on the alveolar epithelial tissue, the endothelium being relatively little affected. These effects were produced early after an intraperitoneal injection of paraquat, marked changes occurring within 24 hours

leading to complete loss of epithelium after three days. Similar findings were seen by Wasan and McElligott (1972). In the lungs of mice, Fowler and Brooks (1971). found early endothelial cell swelling and damage to alveolar epithelial type A cells, although the type B cells were relatively unaffected, reminiscent of the earlier work reported in rats by Kimbrough and Gaines (1970). Modee *et al.* (1972) showed early capillary engorgement and interstitial oedema followed in 24 hours by mitochondrial degeneration and cytoplasmic vacuolization in various cell types with desquamation of necrotic alveolar epithelial cells at 48 hours. Essentially similar processes were seen in man (Toner *et al.*, 1970) and these authors point out the similarity of the changes to those seen in oxygen poisoning. Fowler and Brooks (1971) studied changes in the proximal convoluted tubules of mice given paraquat and found an increase in the amount of smooth endoplasmic reticulum and the presence of lipid-containing cytosomes. None of these studies has shown paraquat to attack unequivocally a specific cell or cellular constituent, although it would seem that epithelial cells, particularly in the lung, are preferentially damaged. It is not known whether these cells contain higher concentrations of paraquat than others, nor whether their proximity to the high oxygen tensions of the alveoli is significant.

The circumstances surrounding paraquat poisoning are in some respects peculiar. Although there are many agricultural chemicals of greater intrinsic toxicity, the relatively high oral toxicity of paraquat has led to accidental fatal poisoning, because in virtually all cases concentrated solutions have been drunk from apparently innocuous bottles. In most countries of use, solutions of paraquat are recognized as poisons by the authorities and are labelled as such. Nevertheless, perhaps because of the general usefulness and properties of the material, persons requiring small quantities pour it into unlabelled bottles and it is thereafter that accidents occur. Whilst in comparison with other forms of accidental poisonings those from paraquat are relatively few in number, they should be wholly preventable. Suitable labelling and formulation can help towards this, but only by the elimination of the few cases of irresponsible handling will these unnecessary tragedies cease.

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