PARAQUAT - IN USE AND MISUSE

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ABSTRACT

This thesis sets out to examine the problems that have been associated with paraquat, both in relation to its occupational use as a herbicide and its misuse in cases of accidental or deliberate human poisoning. In order to provide a frame of reference for the later discussion, the general properties of paraquat are reviewed, together with its general toxic effects and possible mode of action in mammalian systems.

The degree of risk associated with paraquat use in normal agricultural practice is examined. The available published literature is reviewed and the results of studies on both formulation workers and spraymen are discussed. It is concluded that the use of paraquat does not constitute a significant risk to health when sprayed at concentrations of up to 0.5% paraquat ion. Studies of situations in which low volume/high concentration application methods have been used would indicate that they are likely to produce an unacceptable level of risk and constitute dangerous agricultural practice.

The problem of paraquat misuse is examined, both in regard to its extent and the effectiveness of treatment in cases of human poisoning. Treatment measures currently advocated are reviewed and their effectiveness discussed in relation to the series of 108 poisoning cases which is presented. On the basis of the data set out it is concluded that the treatment of paraquat poisoning is only likely to be

ABSTRACT (Continued)

effective in those cases who have,

(a) ingested less than 5g of paraquat ion,

(b) had treatment instituted within 2 hours of ingestion, and

(c) show plasma paraquat levels in the order of 1-2mg/litre 2-4 hours after ingestion.

It is also concluded that the only effective form of treatment is the vigorous and rapid removal of paraquat from the gut using Fuller's Earth and purgation or gut lavage. There is little clinical evidence to suggest that measures designed to remove paraquat from the circulation after absorption or block its action in the body have any effect on the clinical course of poisoning.

Some general conclusions are drawn and a select bibliography is appended.

SECTION I

GENERAL INTRODUCTION

1. GENERAL INTRODUCTION

1.1. THE SCOPE OF THE THESIS

The herbicide paraquat is a member of a group of compounds known as quarternary bipyridyls. It was first synthesised in the nineteenth century [1] and has been known to chemists and biochemists for many years on account of its properties as a redox indicator dye, used in the determination of the redox potentials of biological electron carriers [2-5]. In its partially reduced form as a free radical, paraquat possesses a deep blue colour which gives the compound its usefulness in such determinations (hence also the alternative name for paraquat of methyl viologen). It was not, however, until 1959 that its herbicidal properties became apparent which led to its commercial introduction as a weedkiller in the early 1960s [6].

The wide spectrum of herbicidal activity, coupled with a remarkable lack of residual effect as a result of the compound's rapid inactivation on contact with the soil, led to the very wide application of paraquat throughout the world. The output of commercial formulations has been in millions of litres and in some parts of the world it has been responsible for the creation of a situation close to an agricultural revolution.

When paraquat was first marketed, the manufacturers did not apparently anticipate any particular problems with its use, although its general level of toxicity was greater than that of most herbicides being applied in agriculture (table 1.1. provides a comparison of acute oral and dermal LD_{50}s for a number of standard herbicides). It soon became apparent, however, that the compound could be subject to serious misuse by accidental or deliberate ingestion which was seen to be associated with particularly unpleasant consequences. These were highlighted by the first reported cases of human poisoning [7]. It is not surprising, therefore, that considerable disquiet has been expressed about this compound, particularly in view of the high mortality which has followed ingestion of the commercial formulations, the distressing form of death following both accidental and deliberate poisoning, together with the fact that children have at times been the tragic victims of accidental poisoning incidents. Indeed, it was the early accidental deaths, occurring soon after the commercial introduction of paraquat, that occasioned the greatest reaction, especially in the press. The introduction in the United Kingdom of governmental regulation of the sale and purchase of the agricultural concentrates on the one hand, together with an educational programme for the public (more especially farmers and horticulturists) on the other, led to a shift in the nature of the problem. Accidental cases became fewer, as will be discussed later, but (possibly as a result of the widespread publicity) intentional poisonings increased in number.

This thesis is an attempt to set the problems associated with paraquat into a realistic context. Two areas of concern will be reviewed, the occupational use of the compound as a herbicide

TABLE 1.1 COMPARATIVE TABLE OF ACUTE ORAL AND DERMAL LD_{50} VALUES FOR A NUMBER OF STANDARD HERBICIDES

Herbicide	LD_{50} values (mg/kg)	
	Oral	Dermal
Aminotriazole	1100	10 000
Atrazine	1850	7 500
2,4-D	375	-
Dalapon	7570	-
Paraquat	160	236

Oral values are for rat; dermal values for rabbit

Source: WORTHING C R, (Ed), The Pesticide Manual, Croydon, British Crop Protection Council, 1979 and the accidental or deliberate misuse of the compound in cases of human poisoning. The approach will be as follows:

1. The question of whether paraquat poses a signficant risk to spray operators in normal agricultural practice will be examined first. The available literature will be reviewed and the results of the author's studies on formulation workers and on spray workers using both standard and low-volume application methods will be discussed.

2. Secondly, there will be an attempt to examine the extent of the problem of accidental and deliberate human poisoning with paraquat. The various approaches to treatment will be examined and an attempt made to assess the effectiveness of those treatment measures currently advocated, based largely on the author's studies of 108 cases of human poisoning.

1.2. THE PROPERTIES AND MODE OF ACTION OF PARAQUAT

In order to provide a framework for the later consideration of those problems associated with both the normal occupational use of paraquat in agriculture and the misuse of the compound in cases of human poisoning, it is necessary to provide an outline of the main properties of this material. This section will thus set out to describe briefly the physico-chemical properties of paraquat and then go on to describe those aspects of the pharmacokinetics which are relevant to human poisoning, together with a short account of the biochemical mechanism of action and resultant pathological changes in order to relate the toxicity of paraquat to current modes of treatment of poisoning.

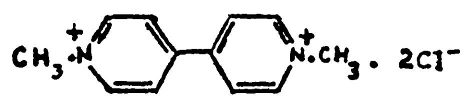
1.2.1 GENERAL PROPERTIES

The physico-chemical properties of paraquat are set out in table 1.2. There are several routes of synthesis of the compound (summarised by Haley [8]), of which the most usual for commercial preparations leads to the production of the dichloride salt and is in two stages. The first involves the coupling of two molecules of pyridine to produce 4,4'-bipyridyl in the presence of sodium in anhydrous ammonia. This is then quarternized with methyl chloride to produce the dichloride salt of paraquat [9]. These reactions are shown graphically in fig 1.1.

The relative insolubility of paraquat in hydrocarbon and other

TABLE 1.2: PHYSICO-CHEMICAL PROPERTIES OF PARAQUAT

Common name:	Paraquat (dichloride)
Chemical name:	1,1'-dimethyl-4,4'-bipyridinium dichloride
Structural formula:	

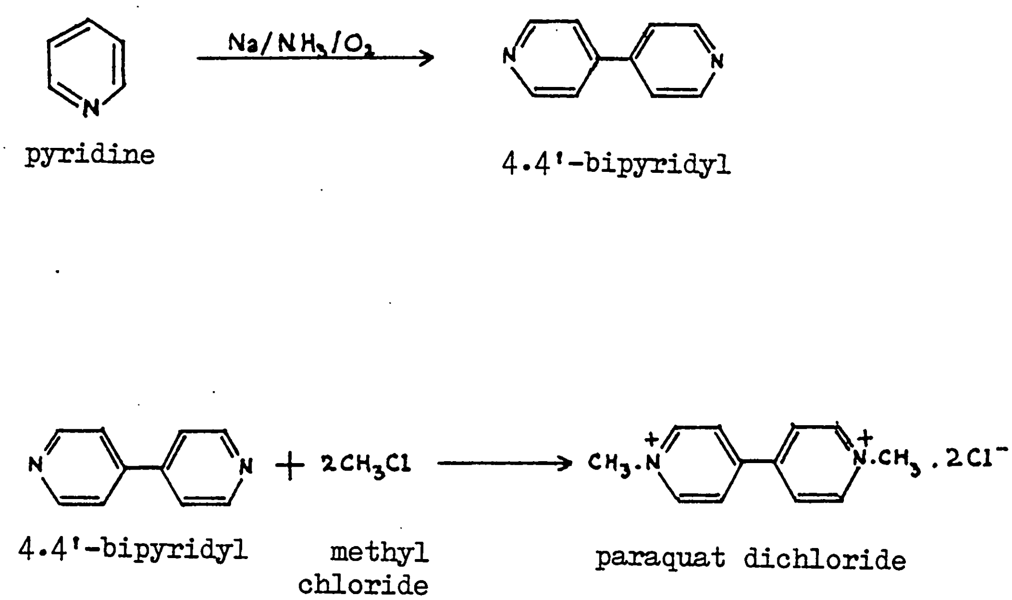


Molecular formula:	$C_{12} H_{14} N_2 Cl_2$
Molecular weight:	257 (as dichloride)
	186 (as cation)
Specific gravity:	1.24-1.26 (20/20)
Melting point:	175-180^{o}C
Decomposition point:	Approximately 300^{o}C
Appearance:	Colourless to yellowish crystalline needles
Solubility:	Highly soluble in water with complete dissociation into paraquat cations and chloride anions. Low solubility in alcohol and insoluble in hydrocarbon-based organic solvents.
Stability:	Stable in acid and neutral aqueous solution. Gradually hydrolizes in alkaline solution.
Vapour pressure:	Below limit of measurement: nonvolatile solid.
Other properties:	Highly corrosive to metals. Non-explosive. Non-flammable.

FIG 1.1: STEPS IN THE SYNTHESIS OF PARAQUAT DICHLORIDE

I

II

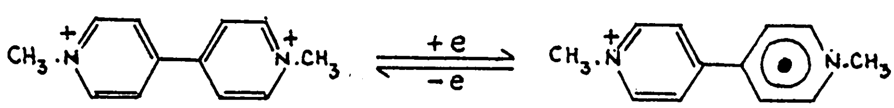


commonly used organic solvents has led to its being marketed as water based formulations, usually with either 10 or 20 percent (w/v) of paraquat ion as the active ingredient. Appendix 1.1 lists the currently available commercial formulations of paraquat marketed by ICI Ltd. In addition to those produced by ICI Ltd there are a large number of other formulations produced principally in Taiwan, some of which are based on the dichloride salt and others on the methyl sulphate. Such commercial preparations are usually maintained at pH 7.0 ($\pm$ 0.5) to ensure the stability of the product, although this is not true of all non-ICI formulations.

In solution, paraquat cation may be readily reduced by the addition of one electron to form a relatively stable, water soluble free radical which is blue/purple in colour. This free radical has a maximum absorption at 396 nm and this fact forms the basis of the spectrophotometric methods of analysis [10]. The reduction step to the free radical is pH independent and consists in the addition of a single electron to the bivalent paraquat ion to produce a partially reduced monovalent cation. The formation of the free radical may be achieved electrochemically, by chemical reducing agents (including biochemical redox systems) and also by a photolytic process in the presence of primary or secondary alcohols. The reaction is readily reversible and is represented in fig 1.2.

A feature of this and similar reactions of the class of radicals

FIG 1.2: REDUCTION OF PARAQUAT TO THE FREE RADICAL



known as 'violenes' is the distribution of an odd number of electrons (in this case one) on an even number of atoms and is known as resonance delocalisation. It is believed to be responsible for the relative stability of the paraquat free radical [11, 12]. The relative ease of free radical formation by single electron reduction is a property of the redox potential of the molecule (in the case of paraquat E_o = 446 mV) and this also is an important determining factor for the phytotoxic properties of the bipyridyl series, especially in regard to the light dependent reduction reactions. Ledwith has recently reviewed these reduction reactions of paraquat [13]. Of particular importance toxicologically are the rapid reactions of the paraquat free radical with molecular oxygen to reform the cation which will be discussed later (see 1.2.2).

Paraquat also undergoes a virtually irreversible base exchange with the cations of the various components of soil, especially the clay constituents. It also undergoes similar reactions with a variety of ion-exchange resins. Such reactions explain the rapid inactivation of paraquat in soil, as a result of its combining with clay particles and as will be discussed later, also point to the usefulness of clay suspensions in the treatment of paraquat poisoning [11, 14,15]. Paraquat is also decomposed by direct sunlight and this photochemical degradation plays an important part in the fate of the herbicide in the environment[9].

1.2.2. ASPECTS OF PARAQUAT PHARMACOKINETICS

There are three aspects of the general pharmacokinetics of paraquat that are of particular relevance to the problem of human poisoning and its treatment. These are: the rate of absorption from the gut after ingestion, the selective uptake of paraquat by the lung and the renal clearance of the compound.

(a) Absorption of paraquat from the gut

It has been generally accepted that paraquat is poorly absorbed from the mammalian gut, over 80 percent being egested in the faeces and only 4 to 11 percent being excreted by the kidneys over the first four days after ingestion [16,17]. Peak concentrations are usually reached in the plasma within six hours of ingestion, depending on the animal species used, and usually the amount of circulating paraquat is at or below the limit of detection by 24 to 48 hours [18]. Although there is little information with regard to the absorption of paraquat by humans, it has been generally assumed that only about 5 percent of the ingested dose is absorbed [18].

It is clear, however, that not all animal work can be directly extrapolated to man. This applies particularly to results from rats and other rodents, although it is on these species that most of the experimental work has been performed. Smith and his co-workers [15] showed an almost linear relationship between gut content of paraquat and plasma levels, with the plasma concentrations remaining remarkably constant for up to 30 hours. In contrast, the plasma levels in dogs [19] (also L.L. Smith 1980, personal communication) and monkeys (L.L. Smith 1980, personal communication) show a rapid and very marked rise after oral dosing, peaking at about 2 to 3 hours after ingestion and falling rapidly thereafter (fig 1.3). Potentially lethal amounts of paraquat thus enter the circulation more rapidly than in the rat and the pattern of human poisoning in those cases in which serial measurements of plasma paraquat have been made [20] suggests that the dog and monkey are better models of events for the human situation than the rat. Fig 1.4 shows serial plasma levels in four recent, and hitherto unpublished, cases of human poisoning. In each case plasma levels were beginning to fall by the time the first blood samples were taken, indicating a peak plasma level within two hours of ingestion and the bulk of absorption taking place within four hours. Proudfoot and his collaborators have shown similar findings in their series [20]. Such a time scale, with most absorption taking place within four hours of ingestion, will clearly have an important bearing on the efficacy of any measures taken to reduce the amount of absorption from the gut in cases of poisoning.

(b) Concentration of paraquat in the lung

It is generally agreed that paraquat is not significantly metabolised in the mammal [16]. The tissue distribution after absorption has been studied by a number of workers and it has

FIG 1.3: COMPARATIVE PARAQUAT PLASMA CONCENTRATIONS IN THREE ANIMAL SPECIES AFTER ORAL DOSING

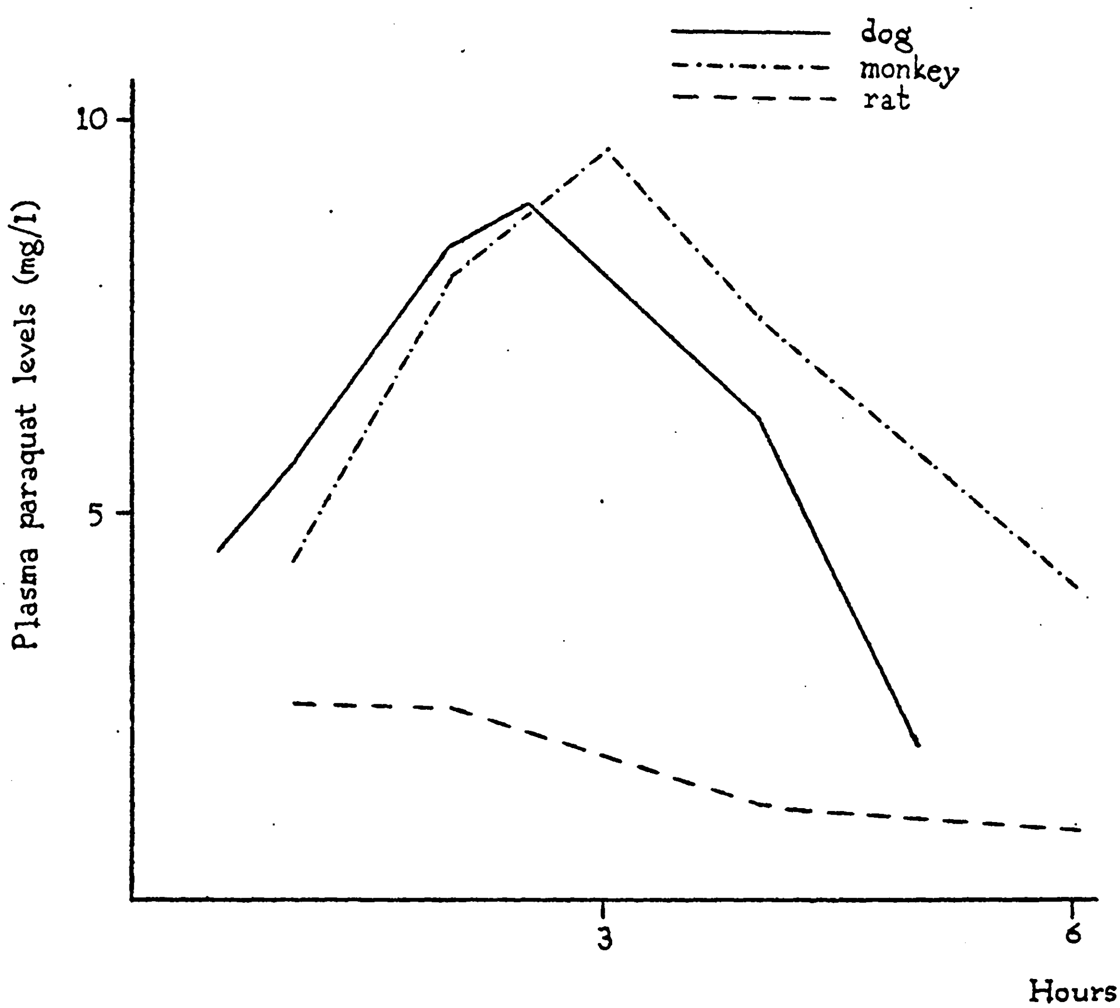
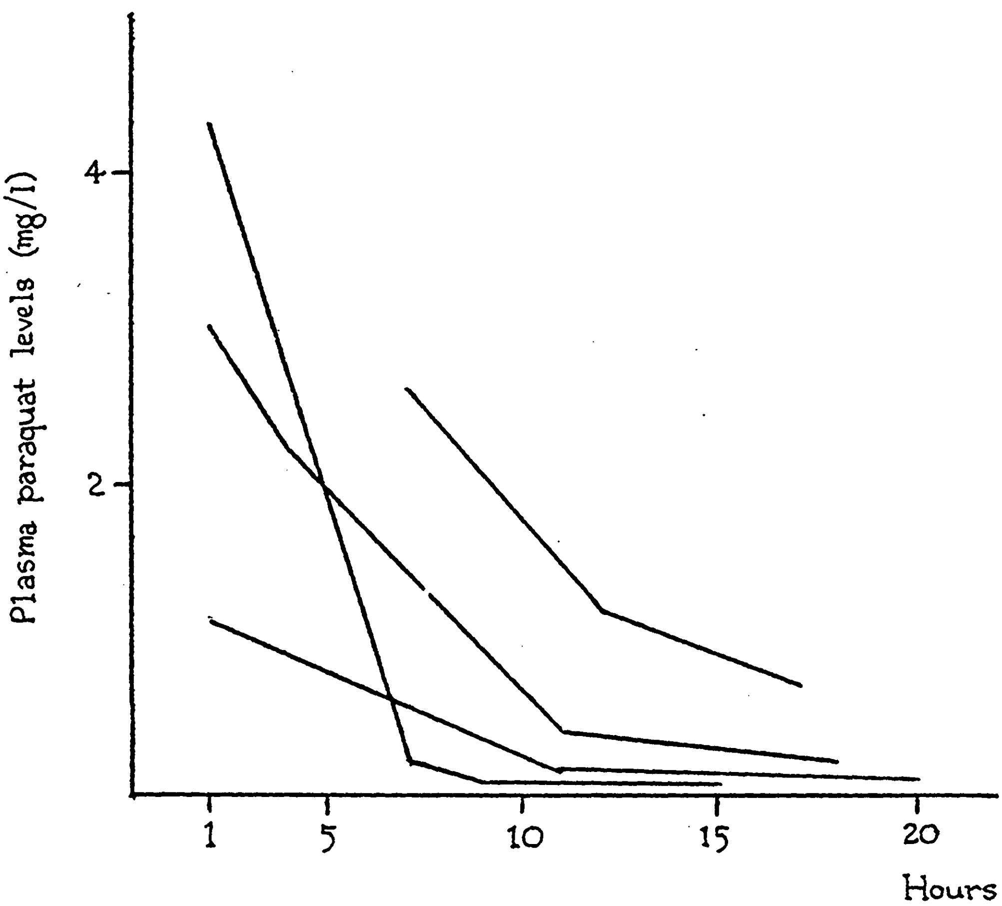


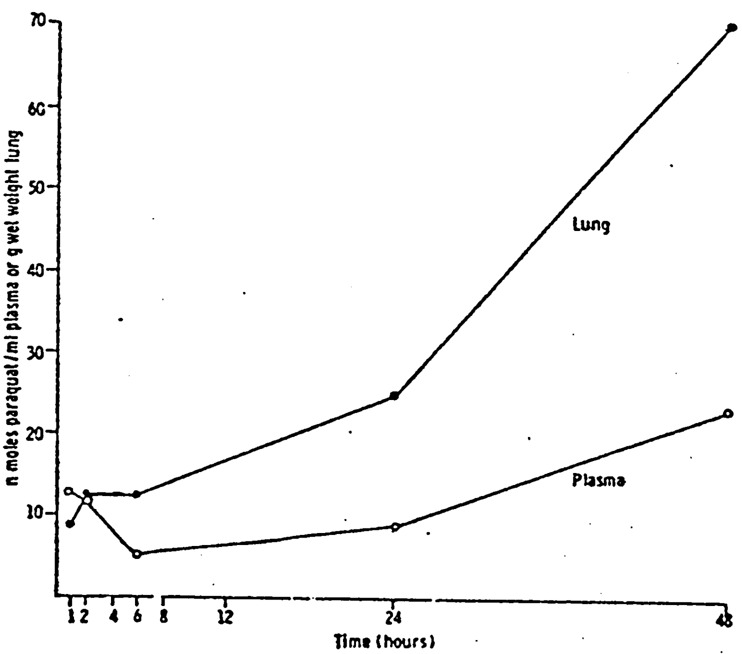
FIG 1.4 SERIAL PLASMA PARAQUAT CONCENTRATIONS IN FOUR PATIENTS FOLLOWING DELIBERATE INGESTION



been effectively demonstrated that paraquat, unlike other members of the bipyridyl family, such as diquat and morfamquat, is selectively concentrated in the lungs of all species, compared with other tissues [21-23]. Rose and his colleagues [24] were able to show that both the plasma and renal levels of paraquat following an initial rise remained very constant after oral dosing in the rat, but that the concentrations in the lung increased with time throughout the duration of the study. By 30 hours after dosing the lung concentrations had reached levels that were some six or seven times higher than those of other tissues (fig 1.5).

The mechanism responsible for this accumulation has not so far been identified, but it has been shown to be energy dependent [25] and unrelated to any binding phenomena [23, 26]. A variety of endogenous amines and amino acids are able to inhibit paraquat accumulation in vitro as are also a number of exogenous compounds including d-propranolol [25, 26]. The sites of accumulation appear to be predominantly the type I and type II alveolar cells. Sykes and his co-workers [27] showed that within 4 hours from intravenous dosing there was evidence of ultra-structural change in these cells which was progressive so that by 16 hours damage was significant. Similar accumulation has been shown to occur in human lungs in vitro [15] and the kinetics of uptake seem to be very similar to those found in the rat. This peculiarity of the lung would explain its ability to take up paraquat over a long period of time from very low plasma concentrations and it would also account for the prominence of lung injury in poisoning cases.

FIG. 1.5. PARAQUAT CONCENTRATIONS IN PLASMA AND LUNG OF RATS AFTER DOSING WITH 680 umol/kg.



(Data provided by L.L. Smith)

(c) Renal excretion of paraquat

A number of clearance studies have been undertaken with paraquat in dogs [19, 28, 29, 30], showing that paraquat clearance was normally in excess of creatinine clearance and that it appeared to be independent of the plasma concentration over a wide range. It seems possible that some passive re-absorption takes place in the proximal half of the nephron, together with active secretion. The latter is indicated by the rapid excretion of low doses at clearance rates above the glomerular filtration rate [30]. It is unlikely, however, that the re-absorption is particularly effective [19] and consequently there is little evidence that forced diuresis would be an effective means of removing paraquat from the circulation.

The effect of paraquat on the kidney appears to be limited to the proximal tubules. Functional damage follows evidence of tubular cell necrosis with induction of both smooth endoplasmic reticulum (SER) and lipidic cytosomes as early changes [31,32]. A similar induction of SER has been noted following administration of cephaloridine, a pyridine containing antibiotic. It is possible that the renal toxicity of paraquat is related to its pyridine-based structure.

In the dog it has been shown that the plasma and renal concentrations closely parallel one another, with the peak being reached at about 90 minutes after ingestion, thus demonstrating an effective quantitative renal clearance provided that no renal damage has occurred [19, 30]. Where such damage has taken place, however, the decline in concentrations in plasma and urine do not run in parallel once the peak has been passed. The plasma concentration lags behind at a higher level, thus allowing the lung to accumulate the material selectively over a long period. The degree of renal damage appears to be dose-related and it has been suggested that early renal failure would increase the uptake in the lung by a factor of five [30]. The evidence suggests that this situation closely parallels that occurring in human poisoning [33]. It has been shown in man that the relationship between paraquat and creatinine clearance remains constant where the kidney is not damaged [34], but that the clearance of paraquat falls rapidly once tubular damage has been induced [19]. Thus the time of onset and the degree of renal damage in such cases must be viewed as an important determinant of the ultimate lung concentrations and subsequent outcome of poisoning.

1.2.3. THE MODE OF ACTION OF PARAQUAT

The phytotoxic actions of paraquat, together with its mammalian toxicity, are to a very large extent functions of the ability of the free radical to react readily with molecular oxygen. In the green plant paraquat appears to function as a catalytic co-factor in the overall photoreduction of molecular oxygen to peroxidic species. The available evidence suggests that it is the superoxide ($O_2^{\cdot-}$) and peroxide($O_2^{=}$) radicals that are responsible for the phytotoxicity of the bipyridyl herbicides [35]. The essentials of the reactions in which the free radical ($PQ^{+\cdot}$)

is oxidised back to the bivalent paraquat cation (PQ^{++}) are as follows [36]:

$$\text{I} \qquad PQ^{+\bullet} + O_2 \xrightarrow{k_1} PQ^{++} + O_2^{\bar{\bullet}}$$

$$\text{II} \qquad PQ^{+\bullet} + O_2^{\bar{\bullet}} \xrightarrow{k_2} PQ^{++} + O_2^{--}$$

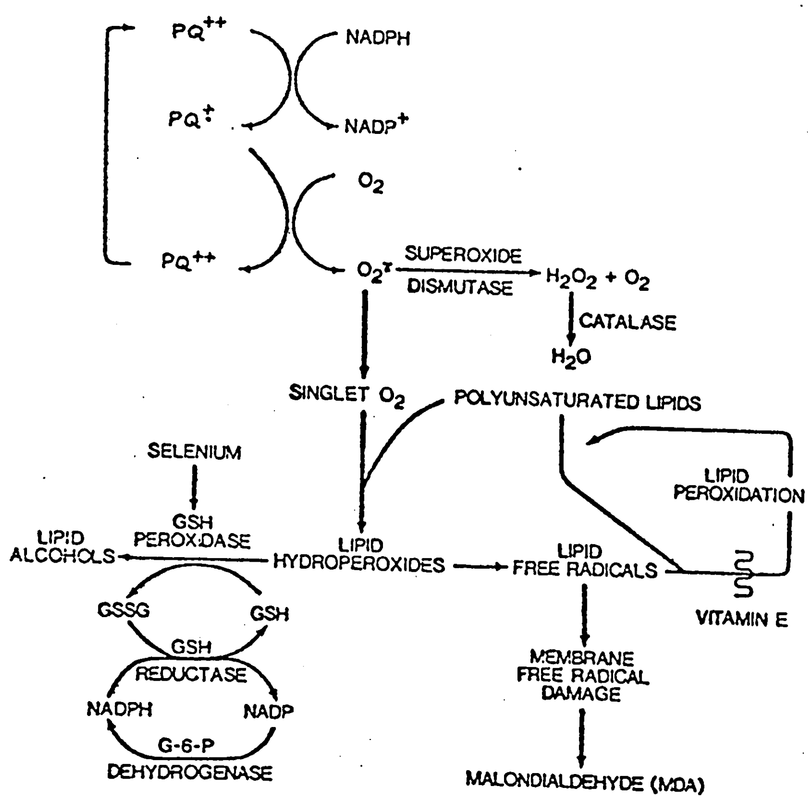
The energy necessary for this process to proceed in plants is derived from photosynthesis, a series of reactions that generates a flow of electrons which are, in turn, transported by a variety of physiological carriers. The end result of the process is the formation of a series of energy-rich compounds such as ATP and reduced $NADP^+$. Because of its redox potential paraquat is able to compete with the natural electron acceptors in the cell and it is probably reduced by the same mechanisms which reduce $NADP^+$ during photosynthesis, such as ferrodoxin.

The free radicals thus formed are very rapidly re-oxidised by molecular oxygen back to the parent cation which is thus available for further reduction. This catalytic type reaction shunts the electron flow of photosynthesis or mitochondrial respiration into its own redox cycle, thus depleting cellular energy reserves. At the same time, however, it is also generating a constant flow of superoxide and peroxide radicals which themselves have an immediate toxic action on the plant tissues. These processes have been discussed in detail by Calderbank and Slade [9], Calderbank[11] and Akhavein and Linscott [12].

The biochemical mode of action of paraquat in mammals, including man, appears to be analagous to its mode of action in plants. The detailed mechanisms that have been proposed have been reviewed in depth by Haley [8], Pasi [37] and Smith _et al_ [26]. It is thus only necessary for an outline to be provided here.

The intitial biochemical event is the production of the paraquat free radical ($PQ^{+\bullet}$), a reaction requiring the presence of NADPH as an electron donor and which, _in vitro_ at least, proceeds until equilibrium has been reached [38, 39]. NADPH acts essentially as a co-factor in this series of reactions, passing its two electrons to FAD^+, thus producing FADH. The latter is the prosthetic group of an enzyme from which paraquat in turn takes an electron to form the free radical [38]. Under normal aerobic conditions this process is likely to involve a cyclic oxidation and reduction of the paraquat free radical, involving NADPH and the cytochrome system [40, 41]. It is, however, the stage beyond the formation of the free radical about which there is continuing debate. There are two main hypotheses. One, advocated strongly by Bus and his colleagues [41-45], considers that the major toxic effects are the result of lipid peroxidation, that is, the oxidative deterioration of polyunsaturated lipids. It is postulated that, as cell membranes contain a high proportion of unsaturated lipids and are thus liable to peroxidative damage, the process of lipid peroxidation induces loss of membrane integrity and ultimately cell death. The mechanism that Bus and his co-workers have proposed is shown graphically in fig 1.6.

FIG 1.6: PROPOSED MECHANISM FOR PARAQUAT TOXICITY



(Derived from Bus, et al: ref 44).

The cyclic reduction and oxidation of paraquat, dependent on NADPH, produces the superoxide radical as noted earlier. This rapidly dismutates to singlet oxygen which being a highly reactive molecule attacks the unsaturated lipids of the cell membrane to produce lipid hydroperoxides [46]. These decompose spontaneously in the presence of trace amounts of metal ions to initiate a chain reaction of lipid peroxidation and ultimately cell death, as set out in fig 1.6.

This view is not universally accepted, however. Smith and his co-workers (L.L. Smith 1981, personal communication) believe that a more likely mechanism for lipid peroxidation, if in fact it occurs at all, is as a consequence of hydroxyl ($OH^{\bullet}$) attack on unsaturated lipids (R-H), rather than as an effect of singlet oxygen. The sequence of reactions are taken from Haber-Weiss cycle and is referred to as Fenton toxicity:

1. $O_2^{\bar{\bullet}} + O_2^{\bar{\bullet}} \xrightarrow[\text{spontaneously}]{\text{dismutates}} 2\,H_2O_2$

2. $H_2O_2 + O_2^{\bar{\bullet}} \longrightarrow OH^- + OH^{\bullet} + O_2$

3. $OH^{\bullet} + \underset{\text{(unsaturated lipid)}}{R\text{-}H} \longrightarrow \underset{\text{(lipid hydroperoxide)}}{R\text{-}OOH}$

The scheme proposed by Bus also suggests three possible intracellular defence mechanisms which in theory, might prevent the damaging effects of lipid peroxidation on the cell membrane. Firstly, it is postulated that there would be a rapid conversion of superoxide radicals to molecular oxygen and hydrogen peroxide, a reaction catalysed by the enzyme superoxide dismutase [47]. This enzyme is considered to be of cardinal importance as a defence mechanism against attack by superoxide radicals [48], effectively lowering the $O_2^{\overline{\cdot}}$ concentration so that the reaction

$$2. \quad H_2O_2 + O_2^{\overline{\cdot}} \longrightarrow OH^- + OH^{\cdot} + O_2$$

cannot proceed. The hydrogen peroxide is detoxified by conversion to water by the action of glutathione peroxidase or catalase. The value of this mechanism in real terms is a moot point, however. It has been shown that rats acutely dosed with paraquat die more rapidly in high ambient concentrations of oxygen than they would in normal atmospheric concentrations [49]. Lung microsomes exposed to paraquat show a marked stimulation of the formation of both superoxide radicals and hydrogen peroxide [50] and, although Crapo and Tierney [51] observed an induction of superoxide dismutase in rat lungs after exposure to high oxygen concentrations, Montgomery has demonstrated a marked deficiency of the enzyme in lung microsomes after exposure to paraquat [52]. Such a deficiency might be an additional factor in the pulmonary specificity of paraquat toxicity.

Indeed, the picture that is emerging of paraquat poisoning is one that closely parallels the mechanism and effects of oxygen poisoning. The primary toxic event in this situation is thought to be the generation of $O_2^{\overline{\cdot}}$ from the mitochondria.

As the concentration of oxygen increases so is the likelihood of $O_2^{\cdot -}$ being produced. When paraquat and oxygen act together in high concentrations, as in the study of Fisher and his colleagues [49], then more $O_2^{\cdot -}$ is produced, firstly by the $PQ^{++} \rightleftharpoons PQ^{\cdot +}$ cycling and secondly by mitochondrial generation. In a very real sense paraquat poisoning may be considered as a chemically-induced form of oxygen toxicity.

Secondly, it has been proposed that the various endogenous antioxidants within the cell such as tocopherols (vitamin E) and ascorbic acid which terminate peroxidative chain reactions may well have an important role to play in breaking the cyclic formation of lipid hydroperoxides [53-55]. In addition, the enzyme glutathione peroxidase which reduces unstable lipid hydroperoxides to stable lipid alcohols would be able to break the cyclic production of more free radicals [56]. Selenium has been shown to play a part in glutathione peroxidase activity [57] which may, in part at least, account for the antioxidant properties of this metal. It has been shown that selenium deficient rats are more susceptible to paraquat poisoning than normal animals [58] although the animals in this particular study died from liver lesions rather than from an effect on the lung. The reducing equivalents for the action of glutathione peroxidase in detoxifying the increased levels of tissue lipid hydroperoxides are derived from the cyclic reduction and oxidation of glutathione and NADPH, reactions mediated by the enzymes glutathione reductase and glucose 6-phosphate dehydrogenase [59]. This mechanism probably has a wide role in detoxification mechanisms as the author has demonstrated in respect of heavy metals [60] and recent observations suggest that reduced activity of this enzyme is associated with an increased sensitivity to paraquat toxicity [60a]. These proposed defense mechanisms at the cellular level have led to attempts to improve the outcome in poisoning cases by a variety of innovations in therapy and management. They will be discussed in Section 3 in relation to the problem of human poisoning.

An alternative hypothesis to that of lipid peroxidation has been proposed by Smith, Rose and their co-workers and the main elements of their proposed scheme has been set out in an extended review of the subject [26]. The essential feature of their view is that the basic toxic mechanism of paraquat is a depletion of cellular energy reserves as a result of the oxidation of NADPH [61]. The rate of oxidation is very fast, particularly in those cells in which paraquat is accumulated, as in the lung. If the rate of oxidation outstrips the rate of formation, then the concentration of NADPH will fall below that required to maintain vital processes, resulting in the death of the cell.

Some recent studies have provided confirmation of this hypothesis. The oxidation of NADPH is an early and prominent biochemical event in the lungs of rats after oral dosing with paraquat and the ratio of NADPH to $NADP^+$ is markedly reduced within the cells [62,63]. In mammalian cells the major biochemical process for the reduction of $NADP^+$ to NADPH is considered to be the pentose phosphate pathway. The activity of this pathway has been shown to be markedly stimulated in lung slices incubated with paraquat <u>in vitro</u> and in the lungs of paraquat poisoned rats [61, 61a]. Further evidence for the 'NADPH-depletion' hypothesis is provided by the fact that fatty acid synthesis in the lung is inhibited by paraquat.

The synthesis of fatty acids is dependent on NADPH [64] and may well be of particular importance in the type II alveolar epithelial cells as they are involved in the synthesis of pulmonary surfactant [65]. Incubation of lung slices with paraquat inhibited fatty acid synthesis, but this inhibition could be abolished by the addition of putrescine to the incubation medium, this compound being an effective blocker of paraquat accumulation into the lung [61, 70].

Such a mechanism would also enhance the toxicity of the superoxide radicals formed by the reduction/oxidation cycle of paraquat since it has been postulated that oxygen toxicity itself is mediated through the extreme oxidation of NADPH leading to the formation of lipid peroxides [66]. In such a situation the cellular concentrations of NADPH would first be reduced by the formation of the paraquat free radical and then secondly, they would be further depleted by the defense mechanism against lipid hydroperoxides. The lipid peroxidation would thus be secondary to cellular depletion of NADPH rather than the primary toxic reaction as proposed by Bus and his colleagues. It seems reasonable to assume however, that both mechanisms may be involved in the overall toxic attack of paraquat on the cell.

It should also be noted that as the phosphate pentose cycle is stimulated to regenerate NADPH in response to the action of paraquat [67-70], this co-factor becomes available, not only for the conversion of oxidised glutathione to the reduced form, but also for the further production of paraquat free radicals. It is postulated that in these circumstances the attempts by the cell to replace NADPH in order to enhance the detoxification mechanisms serves only to contribute further to the toxic response. The cellular damage occurring as a result of such metabolic processes is a sufficient cause in itself for the fibroblastic response so prominent in the lung, which has been regarded as no more than the standardepithelial response to injury. Paraquat-induced lung injury thus has two distinct phases and the pathogenesis of the lung effects, together with the effects of paraquat on other organ systems will now be discussed briefly.

1.2.4 THE PATHOGENESIS OF PARAQUAT LUNG INJURY AND OTHER EFFECTS

(a) Lung Injury

The two phases of lung damage to which allusion has already been made, may be categorised as destructive and proliferative. A number of extensive animal studies have been performed, notably by Vijayaratnam and Corrin [71]. They were able to show that, with dose levels close to the LD_{50}, there was evidence of damage to the type I and type II alveolar epithelial cells within the first day after dosing. This process continued rapidly, so that by the end of four days after dosing there was complete destruction of areas of alveolar epithelium. At the same time there was extensive exudation into the alveolar air spaces with haemorrhage. Throughout this destructive phase there was marked infiltration by inflammatory cells into the alveolar interstitial space, the air spaces and the perivascular areas. This inflammatory exudative response grossly reduces the alveolar gaseous exchange and the great majority of animals dying in the early phase as the result of an LD_{50} did so from severe anoxia [72].

The second, proliferative phase, developed in the survivors of the intitial destructive phase. This stage was characterised by an extensive fibroblastic proliferation with attempts to regenerate and restore the normal architecture of the alveolar epithelium [71]. The greatest proliferation of fibroblasts, however, was in the interstitial spaces, which, together with residual oedema and alveolar collapse, resulted in severe anoxia and ultimately death.

Similar changes in the lung have been observed post mortem in cases of human paraquat poisoning [73, 74]. The primary phase has been described as an attack on alveolar capillaries leading to haemorrhage, oedema, the extrusion of pulmonary phagocytes and dilatation of respiratory bronchioles. Deposition of fibrin also occurs in the oedema fluid at this early stage. The phagocytes appear to undertake a scavenging role and there is some evidence that they may be responsible for the removal of surfactant [74]. It is unlikely that they are fibroblastic precursors as suggested by Smith and Heath [73, 75], particularly in view of their abrupt disappearance with time. The proliferative changes of the second phase may occur as early as the eighth day after ingestion, but are more usually found later than 17 days [76]. These changes are a mixture of a diffuse interstitial fibrosis with resultant compression and obliteration of alveolar spaces, together with a variable degree of intra-alveolar fibrosis derived from the reticulum deposition of the first phase.

The evidence from human poisoning cases supports the view outlined previously, that the lung fibrosis, which is such a prominent feature of late surviving cases of paraquat poisoning, is no more than an exaggerated reparative response. Furthermore, the post mortem appearances of the lung, coupled with the evidence for phagocytic scavenging of surfactant [74, 77] is very much the picture found in hyperbaric oxygen poisoning, a condition that has been described as 'lung surfactant deficit syndrome' [78]. This lends weight to the hypothesis, derived initially from a consideration of the biochemical mechanism of toxicity, that paraquat poisoning is to be viewed as essentially a form of chemically induced oxygen poisoning.

The biphasic lung response has implications for treatment which will be discussed in detail later in section 3.

(b) Other Effects

Immediately after the ingestion of the concentrated formulations of paraquat there may be ulceration of the mouth and oesophagus [79, 80] as a result of the caustic/irritant properties of the material. Large doses may lead to proximal tubular renal necrosis [81] and centrilobular hepatocellular necrosis [82, 83]. Large doses may also be associated with adrenal corticonecrosis [84-86] and, less commonly, with oedema and haemorrhage of the brain [87]. Such cases have usually died in the early acute phase after massive doses, often within 48 hours of poisoning, but the adreno-cortical effects have been observed with smaller doses and over a longer period [86]. The implications of the wider organ involvement will be discussed later.

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APPENDIX 1.1

Products Containing Paraquat

Paraquat is sold in 130 countries in various formulations. It is most widely sold under the trade name 'Gramoxone' but may be encountered under any of the following names:—

'Dextrone X' (U.K. 200 g/l.)

'Dexuron' (U.K. 100 g/l. Also contains diuron)

'Duanti' (W. Germany. Granules 25 g/kg. Also contains diquat)

'Esgram' (U.K. 200 g/l.)

'Gramonol' (100 g/l. Also contains monolinuron)

'Gramoxone' (200 g/l.)

'Gramoxone' Plus (Italy. 100 g/l.)

'Gramoxone' S (200 g/l.)

'Gramoxone' ZU (Belgium, Holland. 200 g/l.)

'Gramuron' (South Africa, Mauritius. 100 g/l. Also contains diuron)

'Ortho' paraquat (U.S.A. 2 lb/U.S. gal.)

'Para-Col' (Malaysia, Indonesia. 200 g/l. Also contains diuron)

'Pathclear' (U.K. Granules 25 g/kg. Also contains diquat and simazine)

'Priglone' (France. 120 g/l. Also contains diquat)

'Spray-seed' (Australia. 100 g/l. Also contains diquat)

'Terraklene' (100 g/l. Also contains simazine)

'Tota-Col' (100 g/l. Also contains diuron)

'Weedol' (Granules. 25 g/kg Also contains diquat)

'Weedrite' (Canada. Granules 25 g/kg. Also contains diquat)

'Weedrite' Aerosol (Canada. 0.44% paraquat)

Since this table was compiled Shell Chemicals Ltd have introduced (1981):-

'Cleansweep' (U.K. 100g/l. Also contains diquat)

SECTION 2

THE OCCUPATIONAL USE OF PARAQUAT

AND ASSOCIATED RISKS

2. THE OCCUPATIONAL USE OF PARAQUAT AND ASSOCIATED RISKS [1]

2.1. PATTERNS OF USE AND EXPOSURE

The bipyridyl herbicides are generally available in two forms of commercial preparation, solid (granular) and liquid. The granular formulations* are prepared for the retail market mainly in the U K and are for use in domestic gardens and similar situations. Although of some importance as agents in self-poisoning (see Section 3), they have not been incriminated as posing any hazard in use. The liquid concentrates of paraquat are available only for agricultural or commercial horticultural use and the poisons register should be signed before sale. This is not the case in many other countries, however, and such agricultural concentrates are often widely available to the general public. In the UK, the most widely used is 'Gramoxone' (ICI Ltd), a 20% aqueous formulation of paraquat ion (200 g/l) with various adjuvants such as surfactants. (The equivalent formulation under the trade name 'Dextrone' is available only to local authorities and other official bodies). There is also a variety of other combination formulations (with diuron etc.) in which the paraquat ion is at a strength of 100 g/l. Outside the UK, the ICI Ltd formulations are sold under a number of other trade names in addition to 'Gramoxone' and there is also a large number of 'pirated' formulations made in Taiwan, selling particularly in the Far East.

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* Those commercially available in UK are: 'Weedol' (ICI Ltd.) formulated in sachets containing 1.5 g paraquat ion and 1.5 g diquat ion and 'Pathclear' as sachets containing 1.5 g paraquat ion, 1.5 g diquat ion and the residual herbicide simazine.

The manufacturers recommend a range of dilution for application according to the specific task to be undertaken. The highest concentration obtainable from this range of dilutions is 0.5% paraquat ion in the final spray solution, obtained by diluting 4 pints of 'Gramoxone' in 20 gallons of water. The normal rate of application, however, is considerably less than this, usually in the order of 0.1 to 0.15% paraquat ion, and frequently it may be as low as 0.05% ion in the final spray. Application is either by tractor-mounted boom sprayers (most commonly in UK) or by hand-held spraying lance with hand pump operated knapsack containers (figs. 2.1 and 2.2). Hand held lances are fitted with a variety of nozzles, usually of the flood-jet or 'polijet' type. In some tropical areas (notably Malaysia which has a high volume usage of paraquat) a number of spraymen will use hand-held spraying lances attached by flexible hoses to a tractor mounted feed tank (fig 2.3). This practice allows a much greater area to be sprayed without the necessity of frequent recharging of knapsack reservoirs. Because a single mix will provide sufficient spray solution for at least one full session of spraying, this system is intrinsically safer than standard knapsack methods, but for a variety of reasons it has only a limited application to particular terrains and land usage.

The diluted paraquat is sprayed downwards directly onto foliage. The manufacturers have listed, on the package labels, a series of operating instructions and necessary precautions to ensure safe handling, of both concentrate and spray solution. In the UK these precautions are produced after agreement with the

FIG 2.1: TRACTOR-MOUNTED BOOM SPRAYING

Photo: courtesy ICI Ltd, Plant Protection Division

FIG 2.2: HAND SPRAYING WITH KNAPSACK CONTAINERS

Photo: courtesy ICI Ltd, Plant Protection Division

FIG. 2.3: HAND SPRAYING WITH TRACTOR-MOUNTED FEED TANK

Photo: the author

Ministry of Agriculture Pesticide Safety Precautions Scheme (PSPS). These are set out in table 2.1. Similar controls exist in many other countries. The use of mist blowers and the aerial spraying of paraquat are not sanctioned in the UK.

The manufacturer's recommendations for safe use in the UK do not include any special protective clothing for the actual spraying operation other than a face shield. Rubber gloves and a face shield are recommended when handling the concentrate. Most spray workers, however, do wear rubber boots when spraying and also frequently rubber gloves in addition.

In such spraying operations, the problem that has to be quantified is not the intrinsic hazard of the material, but the degree of risk with which its use may be associated. Considering this on a world scale, skin rashes, eye damage and other local effects are not uncommon and there is a possibility that systemic absorption could occur, either through oral ingestion, percutaneous absorption or inhalation. The published literature relating to these matters will be reviewed and then an account given of the author's investigations of risk in three separate occupational risk situations.

TABLE 2.1: MANUFACTURER'S LABEL INSTRUCTIONS FOR SAFE HANDLING OF 'GRAMOXONE'

Paraquat can kill if swallowed. Do not put in a food or drinks container. Keep out of reach of children.

Directions for use

Application: Apply through a field crop sprayer, in good condition, using a pressure of at least 2 bars (or 30 psi) or through a low pressure spraying device. When using hand held sprayers do not use in concentrations greater than one volume 'Gramoxone' 100 to forty volumes of water. Do not apply 'Gramoxone' from the air, or by means of a mistblower or fogging machine.

Avoid spray drift: Do not spray in windy conditions.

Precautions

The Poisons Act 1972, available from HMSO, applies to this product.
Wear protective gloves and face shield when handling the concentrate.
Wear face shield when handling and applying the diluted formulation.
Take off immediately heavily contaminated clothing and wash underlying skin. Wash clothes before re-use.
When using do not eat, drink or smoke.
Wash splashes from skin or eyes immediately.
Do not breathe spray mist.
Wash hands and exposed skin before meals and after work.

2.2. LOCAL TOXIC EFFECTS

A variety of local effects on eyes, mucous membranes, skin and nails have been recorded. The degree and extent of these lesions depend on the duration of contact with paraquat and the extent of the dilution of the material. These reactions derive from the delayed caustic effect of paraquat and prompt first aid measures are usually effective in preventing the development of any severe tissue response.

2.2.1. CUTANEOUS EFFECTS

Paraquat acts as a delayed caustic and the effects are made worse both by occlusion and by the surfactants and other adjuvants in the commercial formulations. Animal experiments have resulted in a range of effects from mild reddening to superficial epidermal sloughing [2,3]. Reddening is usually associated with the development of some hyperkeratosis followed by desquamation as the lesion heals. This is the response most usually seen in agricultural workers and others who have received either concentrate burns or have been exposed to spray for long periods. In general the burns are superficial and are thus in contrast to concentrated acid and alkali burns. Occasionally bullae have developed after skin damage from the agricultural concentrate [4].

The incidence of skin reactions appears to be relatively high with hand held equipment, especially in workers engaged in extensive or long term spraying programmes. One study suggested that up to half the population of spray operators could develop skin responses to paraquat, chiefly through prolonged contact with spray solutions [5]. Other workers have reported much lower incidences of skin problems [6,7]. Apart from the expected involvement of hands and arms, the groin and genitals are frequently affected, either as a result of spillages [8] or through the use of leaking spray apparatus. The spray solution may leak under pressure from poorly maintained knapsack reservoirs and run down the man's back to set up irritation in the groin area as a result of clothing being soaked. Such problems may be overcome by improving the maintenance of equipment and by the use of simple but efficient protective clothing (fig 2.4). In the writer's experience, the use of a plastic bag as illustrated has reduced the incidence of groin rashes to almost nil on tropical estates.

The presence of skin abrasions frequently worsens the local effects of paraquat. Such effects are more often seen in the tropics where sprayers may work barefooted, although a case has been reported from the UK of a man spraying paraquat with no protection for his legs which were scratched by goose grass (Gallium aparine L) resulting in a vesicular lesion developing on them [9]. Such dermal effects may be avoided altogether by observing the simple precautionary measures laid down on the label, including the rapid washing of concentrate spills from the hands and the appropriate changing and laundering of working clothes. The

FIG. 2.4: PLASTIC BAG WORN AS SIMPLE PROTECTION BY MALAYSIAN SPRAY MAN

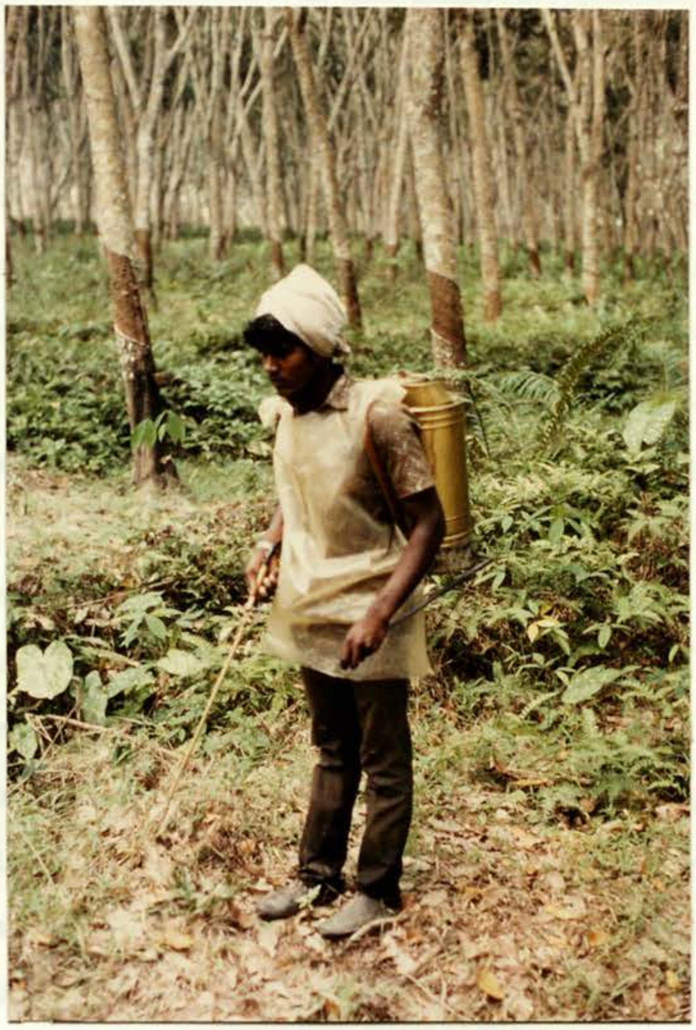

Photo: the author

rapid removal of spillages from the ground would also prevent the sort of accident reported by McDonagh and Martin [10] in which a child was found playing with a pool of spilled 'Gramoxone' and which resulted in a large first degree burn of the thigh and an erythematous rash of the hands taking some four weeks to clear with conservative treatment. The relationship between dermal contamination and possible systemic intoxication is discussed below (Section 2.3.3).

A phenomenon related to the dermal effects of paraquat is the occurrence of delayed healing. This has been observed by the author among spray workers, particularly in the tropics where legs and arms may be unprotected and superficial lacerations from vegetation such as thorns are accordingly common. It has also been observed among formulation workers studied by the author, both in the UK and in Malaysia [4]. The phenomenon manifests itself as a failure of small lacerations and abrasions to heal spontaneously in the usual time. Small wounds tend to remain open for several days with an increased risk of infection. The condition in some cases appears to reflect a lack of personal hygiene, but this is not true of all cases.

2.2.2. EPISTAXIS

Nose bleeds are a relatively infrequent complication of both paraquat spraying and formulation. In the author's experience, this rarely occurs as frank bleeding and the common complaint is one of spotting of the handkerchief after blowing the nose. In formulating plants the problem is most frequently encountered among those working with solid formulations which inevitably give rise to some fine dust which impinges on the nasal mucosa. The phenomenon is usually encountered in the first week or so of working and thereafter the incidence of epistaxis falls rapidly [4]. The effect appears to be the result of the direct irritant/caustic action of paraquat on the nasal mucous membrane resulting in small superficial erosions with capillary bleeding.

Epistaxis is relatively uncommon among spray operators under normal circumstances, although it may occur when spraying is conducted against the wind or when the operator works in the spray mist [5]. Neither situation is to be considered good spraying practice. The use of mist blowers for applying paraquat has resulted in severe nose bleeding, although symptoms have cleared following cessation of exposure [11]. Again, it is worth noting that although frequently used, particularly in Australia, the manufacturers do not recommend the use of this equipment.

2.2.3. NAIL DAMAGE

Nail damage as a result of exposure to paraquat was first reported by Samman and Johnson in 1969 [12]. They described three cases all of which were due to the repeated gross contamination of the hands with agricultural concentrate as a result of careless handling. Although in one case damage was considerable, in all cases there was eventually complete and normal regrowth of the nail. Similar cases among agricultural workers have been reported by others [13, 14] but the most extensive study of this problem was by Hearn and Keir [7] on the Trinidad sugar estates, who reported 55 cases of nail damage as a result of contamination with dilute spray material rather than concentrate.

The workers on the estates all used standard Saval knapsack sprayers with 'flood-jet' nozzles and the final spray strength solution never exceeded 0.02% (1:100 dilution of the 20% concentrate). The earliest lesions to develop consisted of a localized white or yellow discolouration at the base of the finger nail together with a number of transverse white bands on the more commonly affected nails. The nails of the index, middle and ring fingers of the right hand were those most commonly involved, as a result of leakage of dilute paraquat from the junction of the flexible hose and the hand-held lance. Nail deformity, in some cases, developed to a progressive loss of nail surface, leading to deformation and eventual shedding of the nail plate. As in other studies, regrowth of the nails was normal in all cases once further contamination had been prevented.

The mechanism by which nail damage is produced is obscure, although it has been suggested [12] that infection may play a major role. Similar lesions have been observed by the author in those working in formulating plants, handling both solid and liquid formulations of paraquat [4].

2.2.4. EYE INJURY

There have been numerous reports of eye injury following splashes or other accidental contamination with paraquat [15-21]. Although damage may be severe, in general it is only superficial and responds well to therapy. Experimental work with rabbits has shown that the instillation of paraquat into the conjunctival sac is followed after 12 to 14 hours by a severe inflammatory response [2]. This effect has been shown to be dose-related with a range of effect from severe conjunctivitis and occasional slight corneal damage (at strengths from 6.25 to 12.5%) to congestion and swelling of the iris, corneal opacification and the delopment of a pannus reaction (at 25 to 50%) [22]. A typical response showed gross conjunctival injection, with swelling and partially closed lids, a mucopurulent discharge and diffuse corneal opacification. Similar responses are found following human eye contamination with concentrated paraquat solutions. It is likely that the formulating materials play a part in the development of the reaction, as they may be irritant in their own right or potentiate the effects of paraquat.

In the majority of reported cases, recovery has been complete within 24 to 48 hours following injury. Treatment consists of prolonged eye irrigation with water or a buffer solution followed by the topical use of steroids (hydrocortisone) and antibiotics (usually oxytetracycline or neomycin). It has been shown that adequate control of infection and the prevention of adhesions between the denuded bulbar and palpebral surfaces are the mainstays of treatment [23]. Complications have been reported and in one case [15] the onset of eye damage was insidious and not fully apparent until a week after the incident in which a paraquat/diquat mixture had been splashed into the eye*. Damage was extensive with severe keratitis in spite of initial irrigation and atropine was required to control uveitis. Joyce [16] has reported one case in which natural healing was never complete. At four weeks after initial damage there remained a large corneal opacity surrounded by areas of keratitis. This corneal damage was still present five months after exposure and required surgical intervention.

Although with rapid treatment, the evolution of most cases of paraquat eye injury follows a benign course resulting in full healing and a restoration of normal function, it should be remembered that delay in treatment may result in permanent damage. That is why the use of a face shield is recommended whenever the agricultural concentrates are handled. It is unlikely that diluted spray solutions would cause actual eye damage, transient irritation being the usual feature after such material has got into the eye. Nonetheless, in the UK, the PSPS requires the recommendation for the use of a face shield when spraying to be added to label precautions (see table 2.1).

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* This mixture ('Preglone' Extra, ICI Ltd.) is now no longer on the market.

2.3. SYSTEMIC TOXICITY FROM USE

2.3.1. GENERAL OBSERVATIONS

There appear to be no adequately documented cases in the world literature of serious systemic absorption of paraquat leading to recognisable toxic effects as a result of proper occupational use of paraquat and with adherence to the recommended precautions. Nonetheless, there have been a number of claims that such poisoning may occur in the course of ordinary usage. Fitzgerald and his colleagues [24] for example, made a detailed study of 13 cases of paraquat poisoning following agricultural use, of which six were fatal. Although it seems likely that all but one of the fatalities in this series arose from ingestion of the concentrate rather than absorption during the course of work, Fitzgerald makes a valid point that there is a widespread tendency among spray workers, and farmers generally, to ignore even elementary safety precautions and it is not realistic to expect workers to maintain consistently high standards of care and avoid carelessness or stupidity without adequate supervision.

An extensive survey of the health hazards associated with paraquat spraying was commissioned by the California Department of Food and Agriculture in the United States [25]. In this document Peoples and his co-workers concluded that paraquat was responsible for between 25 and 40 reported occupational illnesses each year in the period 1965-1976.

The document, however, relied on poorly investigated anecdotal evidence and much of the interpretation of signs and symptoms is confused and is misleading to such an extent that suicidal deaths are reported as deaths 'from exposure'. Nonetheless, in noting the cases of fatal accidental ingestion of paraquat formulations, the necessity for adequate supervision and proper storage is underlined once again. The poor quality of the anecdotal evidence that prompts support for stricter control of paraquat, may be illustrated by the following case reports (quoted from Peoples et al [25]):

1. A gardener was sprayed on the face and arms with paraquat when the hose on a power sprayer separated from the nozzle. He experienced fingertip parathesias and lightheadedness. The diagnosis was inhalation of paraquat spray. Treatment was provided.

2. When driving a weed sprayer in almonds, a worker inhaled paraquat spray. He experienced a tightness and pain in his chest. Some safety equipment was used, but no face protection. A training record indicated that this man was knowledgeable of safety procedures. Inhalation of paraquat was the diagnosis, and 10 cc calcium gluconate I.V was the major treatment provided.

3. An employee was mixing and loading paraquat when a line developed a leak, spraying him in the face with the dilute mixture for 10 to 15 seconds. He then went to a stream of water and washed. The man subsequently became dizzy, nauseated and vomited prior to going to a hospital. He was hospitalized and given the following tests: X-ray; routine blood sampling; EKG; and was treated with intravenous fluids. He missed more than five days of work.

4. While spraying for weeds with a hand sprayer, a worker walked back through the sprayed area. He developed abdominal cramping, diarrhea, and blurred vision. Gloves were the only protective gear worn. He was examined by a physician and conducted the following tests: chest X-rays; CBC; BUN; serum creatinine; electrolytes; liver function; serum alkaline phosphatase; serum bilirubin; and serum trypsin levels. Treatment was administered.

In these and the many others quoted in this report no attempts are made to reach an adequate diagnosis and most, apart from skin and eye effects from direct contact, are examples of what the writer has referred to elsewhere as the 'paraquat fear syndrome' [4] on the one hand, associated with a considerable degree of ignorance of the toxicity of paraquat and its resultant clinical effects on the other. The symptoms and signs described do not relate to what is known of the effects of paraquat poisoning, although it is possible that some of the effects described might have been the result of exposure to insecticides. That the authors of this report were unable to distinguish between two very different types of symptom pattern is almost inconceivable.

Other literature reports of illness have implicated paraquat poisoning in respect of occupational exposure as the cause, but data are clearly insufficient either to support or deny such a causal relationship between exposure and alleged effect. A good example of this is to be seen in the case reported by Mourin [26] in which a peripheral facial palsy was initially attributed to paraquat exposure, although later shown to be much more likely the result of previous geniculate herpes zoster [27]. Another example where cause and effect had little to do with paraquat was reported from Italy [28]. The history was one of chronic hepatitis in a man with heavy wine consumption and extensive exposure to the known hepato-toxic chlorinated hydrocarbons. Nonetheless, the causative agent was considered to be paraquat as he had used this pesticide for spraying (for the first time) a few days before symptoms began.

Under certain conditions, however, systemic poisoning may occur, either by oral ingestion or dermal absorption.

2.3.2 ORAL INGESTION

The oral ingestion of paraquat is only likely to occur in occupational use under the following sets of circumstances. It may occur accidentally, when concentrates such as 'Gramoxone' have been decanted into unlabelled containers, against label instructions and good agricultural practice. The great majority of accidental poisonings have resulted from such malpractice and it is potentially the greatest risk from paraquat. Fortunately, an awareness of the dangers has markedly reduced this problem in Great Britain so that in the past few years cases of accidental poisoning have numbered only one or two per annum.

The following case, investigated by the author, illustrates the type of circumstance which may occur and the tragic results which frequently follow:

> A 47-year old male farm worker was engaged in spraying paraquat using a tractor-mounted spray. In order to facilitate mixing in the field he carried two unlabelled containers mounted on the tractor bumper, one containing the 20% agricultural concentrate of paraquat and the other water. During the course of his work he became thirsty and drank from one of the containers, thinking it held

water. Unfortunately it was the one containing paraquat. Although he spat out what was in his mouth, he had already swallowed sufficient to produce toxic effects and in spite of early medical treatment he died two weeks later from respiratory complications.

Accidental ingestion may also occur when operators suck or blow out blocked pipes or nozzles of spray apparatus. This practice is usually associated with tractor-mounted rather than hand held equipment and in most cases results only in the ingestion of dilute paraquat which, at recommended application rates, is most unlikely to be lethal or even to produce serious symptoms. The report of such an occurrence during spraying operations in Israel [29] however, suggests that even with dilute material some systemic toxicity may occur. In this case a 30-year old healthy male was accidentally sprayed in the face, as a result of which dilute paraquat went into his mouth and was swallowed. The authors reported minor and transient changes of renal and pulmonary function with an uneventful recovery following renal dialysis. Such practices, however, should be strongly discouraged even though it may be estimated that the lethal amount of diluted paraquat would be in the order of two litres at a standard dilution of 0.1% (1:200 dilution of 'Gramoxone'), assuming the fatal adult human dose to be in the order of 2 to 3 g [30].

Oral ingestion may also occur as a result of swallowing the 'run off' caused by droplets impinging on the face should the operator work in the spray mist. Such a practice contravenes the label instructions, but occasionally occurs. At recommended spray strengths of not more than 0.5% paraquat ion (1:40 dilution of the standard 20% concentrate) it would seem to be impossible to ingest sufficient paraquat in this way to produce symptoms of poisoning, although this has been claimed by Malone and his colleagues [31], who erroneously refer to the inhalation of droplets. At higher concentrations of spray solution and under adverse conditions, such as spraying into the wind, local caustic effects from oral contamination have been reported from Eire [24]. Even in these circumstances there is no clear evidence that systemic effects resulted from these conditions alone. Repeated exposure of this nature, although likely to produce local skin effects, would still not produce systemic intoxication. The 'no effect' level for paraquat on dogs, generally the most sensitive species, is quoted by the FAO [32] as 50 ppm in the diet over a two year period. This represents a daily intake in the order of 90 to 100 mg for an adult man, equivalent to 90 ml of spray solution at dilutions of 0.1% paraquat ion.

2.3.3. DERMAL ABSORPTION

Skin contamination is always a risk in field operations with any pesticide. The problem is greater in countries where high ambient temperatures and humidity preclude the extensive use of protective clothing. Paraquat, being a caustic material, has local irritant effects, but it is relatively poorly absorbed through intact skin, particularly at spray strengths [2, 3].

Mention has already been made in respect of local toxic effects seen in the two trials conducted on Malaysian rubber estates reported by Swan [5]. The operators used spray dilutions of 0.05% paraquat (equivalent to 1:400 dilution of 'Gramoxone') and conditions were such that the spray workers were exposed to significant quantities of paraquat ion, demonstrated by the fact that paraquat could be detected in the urine of all the spraymen at some stage of the trial. Under these circumstances, although local effects on skin did occur, as noted earlier, there were no systemic symptoms nor signs, and chest radiographs were normal. Swan was also able to demonstrate that attention to personal hygiene was sufficient to prevent risk from dermal absorption.

These results were largely confirmed by Hearn and Keir [7] who demonstrated the development of local skin and nail effects in workers on Trinidad sugar estates, but found no evidence of systemic absorption. These workers were using higher spray concentrations than those in the Malaysian trial. The dilutions of the 20% concentrate were from 1:100 to 1:200 (i.e. from 0.2 to 0.1% paraquat ion in the final spray solution). Similar results have been recorded in the author's studies of formulation and long-term spray workers, some of which have been published [4, 6]. They will be reported in detail under Section 2.4, but at this stage it should be recorded that these workers showed no evidence of any systemic effects from exposure to paraquat.

McElligott [3] has shown that, to some extent at least, the degree of percutaneous absorption of paraquat is a function of concentration and with proper use exposure will only be to low concentrations in the spray solutions. At the usual spray dilution of 0.1% paraquat ion, for example, and assuming that the lowest published dermal LD_{50} for paraquat of 80 mg/kg is applicable [33], it would require the absorption of all the paraquat contained in 2 litres of spray solution to produce a fatal outcome. In fact, Staiff and his colleagues [34] have shown that the likely dermal dose for a spray operator using the recommended rates of application would not exceed 3 mg/hour, that is a total dose of 24 mg per day, assuming an eight hour working day. Such an exposure represents a dose of approximately 0.4 mg/kg, or no more than 0.5% of the lowest estimate of the dermal LD_{50} per day. This particular study was designed to determine the potential exposure, both dermal and respiratory, of field operators using conventional low pressure power spray equipment at spray strength of 0.15% paraquat ion.

Further evidence for the low level of risk from skin absorption comes from the work of Hogarty and his team [35] as part of a large study to determine the particle size analysis of drops produced by normal agricultural spray nozzles, the concentrations of paraquat likely to occur in the air breathed by a spray operator and the exposure of spray operators under actual working conditions. Exposure pads of lint gauze, approximately 6.25 cm^2 in size, were placed on the neck (open to the air) on the back of the wrist (beneath clothing) and on the groin (beneath clothing). These operators sprayed a total of 4.84 kg paraquat ion over 9 days at dilutions of 1:40 and 1:80 (i.e. 0.5% and 0.25% paraquat ion). Only two out of 87 analyses showed paraquat (one from a neck pad and the other from the wrist of two separate operators on two separate days). The amounts were minute (5 μg per pad: detection limit 5 μg), indicating that the risk associated with skin contamination with proper spraying procedures is negligible. It must be noted, however, that this trial was carefully supervised and a greater level of contamination would be expected under normal spraying conditions in the field. This was the case in field studies undertaken by a team for which the author was responsible and which will be discussed later (Section 2.4.2).

Although not entirely relevant to the problem of paraquat, it is worth noting that a study was undertaken in man of the percutaneous absorption of the very closely related bipyridyl, diquat [36]. A single dose of 4 g of ^{14}C-labelled diquat in aqueous solution was applied to the exterior surface of the forearm of six healthy male volunteers. The material was left for a period of 24 hours and the extent of percutaneous absorption in this time was estimated from the amount of diquat excreted in the urine (recovered as ^{14}C) over a period of five days, since diquat is rapidly excreted in the urine and not retained in the body. The mean value of the total excretion amounted to only 0.3% of the original radio-active dose, half of that amount being recovered in the first 24 hours. This type of study is open to criticism, not least in respect of the very small doses used, but is is nonetheless reasonable to accept the author's conclusion that diquat is only poorly absorbed through intact skin, confirming the results of animal experiments on the bipyridyl family [2, 3].

Nonetheless, two well-documented cases have been reported in which occupational exposure resulted in death from percutaneous absorption. The first was reported by Jaroš [37] from Czechoslovakia, and it is clear that in this case the circumstances were very far from normal spraying practice. The spray was applied at a dilution of 1:4 (equivalent to 5.0% paraquat ion), which is ten times the highest recommended rate and at a concentration which will produce caustic burns of the skin, facilitating absorption. Furthermore, the knapsack sprayer itself leaked and allowed the solution to run down the man's back throughout the spraying operation. In spite of the skin damage the man did not report for any medical attention until six days later, by which time irreversible pathological changes had occurred. The circumstances of this case could be viewed as an example of paraquat gross misuse.

The other case was reported by Levin and his co-workers [38] and was again associated with the use of high spray concentrations. Accoding to Levin <u>et al</u> the spray concentration was 2.8% paraquat ion, but independent information (E. Bougas, 1979 personal communication) would suggest that Levin's figure derives from a miscalculation and the actual spray strength was in the order of 3.5% paraquat ion. There is also some conflict about the type of spraying apparatus used. According to Levin, the sprayer used was a 'Herbi' type applicator, using gravity and an electrically powered spinning disc to distribute the spray. Privately obtained information suggests that the 'Herbi' applicator had been modified to take a knapsack reservoir and the junction between the reservoir and the applicator had a serious leak. In point of fact, the issue is not at stake in either case, since neither are recommended methods of applying paraquat, although the makeshift type of apparatus the author has been given to understand was actually used represented a significantly greater risk to the operator. Furthermore, additional information would indicate that the operator was using a mixture of 1 litre of 'Gramoxone', 1 litre of 'Reglone' (diquat formulation) in 2 litres of oil and 2 litres of water. This represents a 1:6 dilution (3.3%) of paraquat and a similar dilution of diquat, so that the total bipyridyl ionic strength was above 6 per cent.

In view of this evidence of gross malpractice, it is not altogether surprising that lengthy spraying operations were followed by a tragic outcome, and while some of Levin's results and conclusions are open to question, the real issue hinges upon the proper use of an agricultural spray according to the manufacturer's recommendations.

Three other cases of possible occupationally related fatalities have been recorded, but the details are not sufficiently clear to be certain of the route of absorption.

Fitzgerald and his co-workers [24] report a case in which a 50-year old farmer died following use of a leaking spray for a full day of spraying. There is a possible link in this case with the fact that the man apparently suffered from extensive dermatitis which could have facilitated the absorption of paraquat through the damaged skin. There is no information on the spray strength used. Newhouse et al [39] reported a case in Canada where a woman sprayer allegedly died following the spraying of paraquat. This case has so many question marks over it that reaching a final conclusion is almost impossible. It should be noted, however, that the pathological process was very prolonged (end of August to middle of October) and all other documented cases of fatal dermal absorption indicate a relatively short time between exposure and death. Furthermore, the degree of organ involvement described (lung, liver and kidney) is not consistent either with a lengthy absorption of a lethal dose or a short absorption of a 'just lethal' dose. Such organ involvement is usually associated with a single large exposure and in most cases following oral ingestion. This case would suggest that, while there is some circumstantial evidence to suggest that the woman's death was related to exposure to paraquat, for this to have been the result of dermal absorption would indicate a degree of massive exposure that does not seem to have been present and one is left with the possibility that there may have been some (possibly deliberate) oral ingestion.

The third case is of another woman whose death initially appeared to be due to occupational exposure, but which subsequent investigation suggested was not directly related to the application of the hericide. A woman who was involved in spraying was reported by Weston and Dixon [40] to have had extensive contamination of her arms and hands. Additionally she was stated to have 'accidentally' swallowed some material while spraying. It was, thus, not initially clear as to whether the case was one of oral or dermal absorption. However, the author makes the important point that the deceased woman was a chronic alcoholic who tasted various unknown liquids in order to discover whether they contained alcohol. At the time of consuming the herbicide, the evidence suggested that she was intoxicated and thus death in this case must be viewed as a result of 'accidental ingestion' rather than from any other cause, and certainly it was not primarily related to occupational exposure.

It is worth noting two other cases of fatal skin absorption of paraquat, although neither are related to occupational exposure. Both [41, 42] involved the prolonged application of the 20 per cent agricultural concentrate directly to the skin, including the sensitive area of the scrotum, in order to 'control' body lice. Such misguided 'therapeutic' applications can in no way be compared to the situations that arise in normal agricultural practice.

In one case [41] the patient presented with extensive genital corrosion and ulceration which was initially claimed by the patient to have occurred following an accidental spillage of paraquat concentrate at the time of a weed spraying operation three days before. Fortunately, the authors of the report had doubts as to the reliability of this history and further questioning elicited the true facts. The patient 'revealed that he had intentionally applied the chemical to his underwear so that it would remain in close contact with the genitalia as a treatment against phthirus which he claimed to have had at the time'. He died following the development of respiratory complications.

The other case [42] was very similar. Here a man applied the concentrate to his beard and scalp to rid himself of lice. A friend had advised him that 'the medicine (paraquat) was very good for killing insects'. Three days later he was admitted to hospital with his face and scalp covered with infected sores and blisters. He died six days after he had applied the paraquat to his skin.

On the other hand, that a fatal outcome following extensive skin contamination is not inevitable, is illustrated by a case in which a small child who had played with a pool of spilled 'Gramoxone' developed extensive skin damage [43]. Within six to eight hours after the incident, an erythematous rash with blistering developed on one thigh and both hands, but healing took place with no systemic complications. It is likely that prompt action prevented any significant percutaneous absorption.

2.3.4. <u>INHALATION</u>

It is not surprising, in view of the prominence of lung pathology in cases of paraquat poisoning, that concern has been expressed about the possibility of pulmonary damage developing in spray operators exposed to paraquat. Some authors have claimed this to be a genuine risk in spraying operations, but the hard evidence is remarkably slim and, as will be discussed in detail later, technical considerations virtually rule it out as a practical possibility. Malone and his colleagues [31] nonetheless reported a case of a 46-year old man who was spraying paraquat in windy weather, conditions alleged to increase the risk of inhalation. About four hours after the spraying he developed symptoms of nausea and vomiting and six days later there was evidence of minor renal damage with traces of paraquat in the urine five and eight days after spraying. Serial chest X-rays were normal and recovery was uneventful. Malone believed the cause of the symptoms was inhalation of paraquat droplets and absorption through the respiratory tract, but the clinical details suggest that ingestion would be a more likely cause.

Similarly, Peoples, Maddy and Riddle [25] have reported a number of cases of non-fatal and usually transient illness which they associate with 'inhalation experience'. In one case, for example, they report that a driver of a spraying rig 'inhaled' paraquat spray due to the wind blowing it into the cab. Shortly after this incident he began to develop shortness of breath and nausea. He was seen by a physician who diagnosed 'paraquat poisoning' and was given symptomatic treatment only. Symptoms subsided rapidly and he was assigned to other work. As had been indicated earlier, most of the cases described in this report experience symptoms that bear little relation to the toxicity of paraquat, such as paraesthesia, lightheadedness, abdominal cramps, wheezing etc. It is just possible that the various formulation adjuvants could have been responsible for these symptoms, but to report these cases as 'paraquat poisoning' from inhalation can only be viewed as spurious.

Mention should be made, also, of the reports from France [44, 45] in which cases have been reported as '<u>intoxication par voie respiratoire</u>'. Conso [45] reported sixteen such cases, but the grounds for considering them to be cases of poisoning by inhalation are not at all clear. Personal discussions with Mme. F. Conso and her colleagues at the Hôpital Fernand-Widal in Paris failed to elucidate the criteria used for their classification. It would appear, however, that the cases reported were in fact of respiratory symptoms associated with paraquat spraying and without any genuine evidence of cause and effect. Indeed, the circumstances of some of these cases make respiratory uptake most unlikely, although this group of workers continue to express this possibility in spite of the wealth of evidence against it [46]. Nonetheless, these cases have become incorporated into the literature on the subject as poisoning following the inhalation of paraquat.

In this regard, it is worth reporting a fatal case of pesticide poisoning which was claimed to be related to inhalation of paraquat spray, but for which other explanations are equally, if not more, applicable. The writer came to be associated with this case after the death of the patient.

The patient was a middle aged male farmworker who regularly used 'Gramoxone' and an unspecified organo-phosphate insecticide using a standard knapsack sprayer. Such a mixture is most unusual and not in fact suitable for normal use in agriculture or horticulture. The strength of the spray solution was not discovered. A few hours after spraying, the patient developed severe diarrhoea with abdominal cramps and tenesmus. There was also some nausea and vomiting together with dysuria and frequency. He was admitted to the local hospital, but no investigations were undertaken for two days, by which time the patient was markedly dyspnoeic with some cyanosis. On examination, crepitations were heard at both lung bases, and a chest X-ray showed extensive pulmonary oedema. The patient's course was steadily downhill and he died 30 days after admission in cardio-pulmonary failure. At no time were urine or blood estimations for paraquat undertaken nor estimations of erythrocyte or plasma cholinesterase in view of the involvement with organo-phosphates. The post-mortem examination included no tissue paraquat estimations, but the lungs showed 'diffuse fibro-productive interstitial pneumonitis' together with 'extensive areas of bronchiectasis and infiltration compatible with a previous history of chronic bronchitis'. The heart showed moderate right sided hypertrophy. The gastro-intestinal tract showed no evidence of ulceration and there was only mild renal congestion and fatty infiltration of the liver.

The circumstantial evidence could incriminate paraquat as the causative agent in this man's fatal lung disease, but the case raises many questions. Of these the most important relates to the symptomatology. The acute gastro-intestinal upset is most atypical of paraquat poisoning and would in any case be unexpected if the route of entry was via the lung, since paraquat only acts on the gut as a direct irritant and there was, furthermore, no evidence of this at post-mortem. Again, no urinary or blood estimations of paraquat were undertaken, so that there is no evidence that paraquat was actually absorbed. Indeed, the clinical picture, with abdominal cramps, nausea, vomiting, diarrhoea and subsequent pulmonary oedema is more akin to organo-phosphate poisoning than it is to paraquat intoxication. This case has been discussed in detail as a good example of the danger of jumping to conclusions on the basis of insufficient data. Although recorded as a case of occupational paraquat poisoning following inhalation of spray, the actual evidence to support this diagnosis is flimsy indeed.

Recently, two further reports have appeared [47, 48] suggesting that inhalation of nebulised paraquat can occur under normal working conditions and give rise to pulmonary symptoms. Both reports, however, are strictly anecdotal with no supporting data and, as will now be discussed, the weight of evidence militates against the possibility of significant paraquat inhalation in normal agricultural practice.

On the assumption that both systemic poisoning and direct lung damage can occur as the result of inhalation of paraquat in occupational use, some animal experimental work has been carried out. Several hours' exposure to concentrations of paraquat in the order of 1.0 mg/m^3 in aerosols containing more than 80% by weight of droplets between 2.5 and 5.0 micron diameter produced severe bronchial irritation [49]. The effects, however, were all local and it was not found possible to induce a pulmonary fibrosis by exposure to inhaled paraquat. More recently at very high exposure levels (200 mgm in 134 litre chamber over 2 hours for up to 5 exposures per week) localised lung changes were induced in rats [50], but such exposures could not be paralleled by the most extreme working conditions.

The real point at issue, however, is whether there is any real possibility of inhaling material in sufficient quantities to do damage as the result of normal spraying operations. The upper limit of respirable size (i.e. capable of penetrating to the alveoli) is now generally put at 5 microns [51].

Two trials have shown that standard spraying equipment fails to produce significant levels of droplets in this respirable range of less than 5 micron diameter. The first of these trials was a careful characterisation of the droplet spectrum of standard knapsack spray jets of the 'swirljet' and 'polijet' type to which reference has already been made [35]. The results demonstrated that the respirable fraction produced by agricultural sprays of this type is only of the order of 0.001% of the total spray volume and even the volumetric amount of sub 16 micron droplets is very small. It was also shown that the volume of droplets actually reaching the operator's breathing area represented an insignificant fraction of the total spray volume. It was found that under static trial conditions the concentration of paraquat in the air was unlikely to exceed 50 mg/m^3 and on average would be more likely to be of the order of 10 mg/m^3. These conditions were slightly artificial and results obtained from field conditions would give a better picture. Under field conditions the maximum concentration of paraquat to which an operator would be exposed at recommended dilution rates was found to be in the order of 12 mg/m^3. Even if as much as 50% of this amount were in the form of respirable sized droplets, it would still represent an inhalation dose incapable of producing serious effects, particularly when these figures are compared with the levels used for animal experiments quoted above. Similar results were reported by Staiff <u>et al</u> [34] in a trial using spray dilutions of 0.15% paraquat ion, although with different equipment. In neither trial was paraquat detected in the urine of the spray operators with a detection limit of 0.02 ppm. Staiff in fact calculated that based on the dermal LD_{50} of 80 mg/kg quoted by Kimbrough and Gains [33], the combined potential dermal/respiratory exposure obtained would represent only 0.06% of a 'toxic' dose per hour of exposure. Furthermore, the maximum recorded air concentrations of 12 mg/m^3 found by Hogarty [35] under normal field conditions are only a fraction of the currently accepted Threshold Limit Value for airborne paraquat contamination of 100 mg/m^3. It has been shown by Litchfield <u>et al</u> [52] that there is no organ accumulation of paraquat at these low levels of absorption. It may be concluded that the inhalation of droplets in normal agricultural spraying practice does not represent a significant hazard to health and inhalation of toxic chemicals is only likely to be a problem with compounds of high vapour pressure, such as organo-phosphates.

2.4. INVESTIGATIONS OF OCCUPATIONAL EXPOSURE

The foregoing survey of the available evidence in the published data would indicate, as already suggested, that the degree of risk associated with the use of paraquat in normal agricultural practice is negligible. Nonetheless, certain gaps exist in available knowledge and this is especially true in relation to long term exposure, either in formulation or in agriculture, in which special risks might arise through repeated exposure. Furthermore, as the evidence of fatalities through percutaneous absorption would indicate, there appears to be a relationship between the degree of risk and the concentration of paraquat to which an individual is exposed. This is of particular importance in view of the increasing use, especially in developing countries, of low volume-high concentration spray applicators such as the Micron 'Herbi'. Accordingly, three studies were undertaken to look at:

1. the possible problems associated with formulation;
2. the possible problems associated with long term spraying, and
3. the relative risks of high and low volume spraying techniques.

2.4.1. FORMULATION WORKERS

This study was designed to look specifically at workers with significant and continuous exposure to paraquat for several years in order to determine whether such workers developed chronic clinical problems with particular reference to the incidence of chronic skin conditions. This work has already been published [4].

METHODS

(a) Population

Two groups of workers involved in the formulation of paraquat based herbicides were selected for study. It is generally agreed that workers involved in the continuous manufacture and formulation of agricultural chemicals are likely to have a greater degree of exposure than those using them in the field, such as farmers and spray operators, whose exposure in temperate climates is usually intermittent, often infrequent and who also use many types of pesticides making any effects which may occur difficult to interpret. The first group of workers consisted of 18 men at the ICI Plant Protection Division formulation plant at Yalding in Kent. Eight members of the group had worked only with solid formulations of paraquat involving exposure to dust, seven had handled concentrated liquid formulations only and had been faced with problems of spillages and splashes, and three workers had been involved with both types of formulation. The mean age of the group was 44.7 years (range 22-61 years) and the working week was 37½ hours, to which may be added a variable degree of overtime, likely to be about 10 percent. The length of time from first exposure varied from 1 year, 4 months to 12 years, 6 months (mean 5 years, SD 3.0).

Partial protective clothing was worn which consisted of overalls, rubber aprons, rubber gloves, rubber boots and caps and face shield or goggles when handling liquid formulations. Overalls, rubber gloves, rubber boots, caps, goggles and an approved dust mask were used by those handling solid formulations.

The second group of workers also consisted of 18 males from the Chemical Company of Malaysia formulation plant at Kelang, Malaysia. This group of workers was of mixed race, mainly Malay with some Indian and Chinese, with a mean age of 29 years (range 23-39 years). They were involved only with liquid formulations of paraquat and put in a working week of 42 hours with overtime, which was again estimated at about 10 percent. The length of time from first exposure was from 6 months to 6 years 6 months (mean 2 years 4 months, SD 1.6). This group of workers also wore protective clothing of the type outlined above, but with the high ambient temperature and humidity of Malaysia, the use of goggles and rubber aprons was frequently neglected and gloves also were commonly not worn.

The details of these two groups is set out in tables 2.2. and 2.3. and the pattern of exposure in table 2.4. Unfortunately production figures are not available, but it is known that the amount of paraquat handled in the two plants per year is very considerable and may be measured in tonnes of ion.

Liquid formulations of paraquat contain either 20 or 10 percent of paraquat ion, together with a variety of wetters and stabilisers. Some formulations also contain other herbicides,

TABLE 2.2 DETAILS OF YALDING (UK) WORKFORCE

Subject	Sex	Age (years)	Ethnic group	Total period of exposure to paraquat	Length of time from first exposure to paraquat	Formulation handled
1	M	22	Cauc.	1 yr 4 mths	1 yr 4 mths	S
2	M	23	Cauc.	2 yrs	2 yrs	S
3	M	43	Cauc.	2 yrs 6 mths	2 yrs 6 mths	S
4	M	24	Cauc.	3 yrs	3 yrs	S,L
5	M	49	Cauc.	3 yrs	3 yrs	S
6	M	43	Cauc.	3 yrs	3 yrs	L
7	M	46	Cauc.	3 yrs	3 yrs	L
8	M	51	Cauc.	4 yrs	4 yrs	S
9	M	55	Cauc.	4 yrs	4 yrs	L
10	M	61	Cauc.	4 yrs	4 yrs	S,L
11	M	49	Cauc.	5 yrs	5 yrs	S
12	M	27	Cauc.	3 yrs 6 mths	5 yrs 6 mths	S
13	M	58	Cauc.	5 yrs	6 yrs	L
14	M	48	Cauc.	7 yrs	7 yrs	L
15	M	55	Cauc.	8 yrs	8 yrs	S,L
16	M	61	Cauc.	8 yrs	8 yrs	L
17	M	29	Cauc.	10 yrs	12 yrs	L
18	M	60	Cauc.	12 yrs 6 mths	12 yrs 6 mths	S

S = Solid formulations of paraquat

L = Liquid formuations of paraquat

TABLE 2.3 DETAILS OF KELANG (MALAYSIAN) WORKFORCE

Subject	Sex	Age (years)	Ethnic group	Total period of exposure to paraquat	Length of time from first exposure to paraquat	Formulation handled
1	M	39	Malay	6 mths	6 mths	L
2	M	30	Chinese	1 yr	1 yr	L
3	M	27	Malay	2 yrs	2 yrs	L
4	M	32	Malay	2 yrs	2 yrs	L
5	M	30	Indian	3 yrs	3 yrs	L
6	M	33	Indian	3 yrs	3 yrs	L
7	M	24	Indian	7 mths	3 yrs	L
8	M	37	Malay	3 yrs	3 yrs	L
9	M	34	Chinese	3 yrs	3 yrs	L
10	M	24	Malay	8 mths	3 yrs 6 mths	L
11	M	23	Malay	3 yrs 6 mths	3 yrs 6 mths	L
12	M	23	Malay	4 yrs	4 yrs	L
13	M	23	Malay	1 yr 3 mths	4 yrs	L
14	M	28	Indian	4 yrs	4 yrs	L
15	M	27	Malay	8 mths	5 yrs	L
16	M	32	Malay	6 mths	6 yrs	L
17	M	31	Malay	2 yrs	6 yrs	L
18	M	26	Malay	6 yrs 6 mths	6 yrs 6 mths	L

L = Liquid formulations of paraquat

TABLE 2.4 WORKER EXPOSURE PATTERNS TO PARAQUAT

Length of time from first exposure to paraquat	YALDING		KELANG		TOTAL	
	No. of workers	% of group	No. of workers	% of group	No. of workers	% of total
More than 10 years	2	11.1	-	-	2	5.5
8-10 years	2	11.1	-	-	2	5.5
5-7 years	4	22.3	4	22.3	8	22.3
Less than 5 years	10	55.5	14	77.7	24	66.7
Totals	18	100	18	100	36	100

including the other commonly use bipyridyl, diquat. Exposure to paraquat is most likely to occur in charging the system or at filling out, or when a blockage in the system is cleared. The solid formulations of paraquat contain 2.5 percent of paraquat ion (plus 2.5% diquat) and exposure was highest when freshly produced granules were removed from the drying trays. Considerable amounts of dust were produced in the drying process and in the early days of formulation the level of housekeeping was not always satisfactory. These problems have now been overcome by total enclosure of the formulation process and the use of extraction ventilation where the sachets are automatically filled and sealed.

(b) Survey

The medical records of both groups of workers were examined. These record all significant episodes of ill health, sickness absence and any accidents or injuries. A questionnaire was applied by the medical staff of the plant which included previous employment history, exposure to other pesticides, past medical history, concentrating particularly on any history of skin, respiratory tract or gastro-intestinal conditions, together with smoking habits and other addictions. The clinical examination was directed particularly towards any evidence of chronic skin conditions. It was not possible at the time this study was undertaken to perform tests of alveolar diffusion, although these were carried out in a subsequent study of spraymen.

RESULTS AND DISCUSSION

The incidence of clinical problems associated with exposure to paraquat is set out in table 2.5. The occurrence of numerous episodes resultant upon direct contact with paraquat indicates a degree of significant exposure in both groups of workers.

There were a number of acute skin rashes, burns and eye injuries at the Kelang plant, and this may reflect the lower level of safety consciousness amongst the Malaysian workers. Skin contact with paraquat usually produced a delayed caustic effect consisting of erythema with occasional formation of bullae. In most cases healing was normal, although in one case with severe scrotal inflammation through careless spillage of paraquat concentrate healing took over two weeks. Eye splashes were followed by intense conjunctivitis with blepharospasm and lacrymation. In none of these cases, however, was there any evidence of permanent damage to skin, conjunctivae or cornea, nor was vision impaired in any case. The particular problem among the workers handling solid formulations was the occurrence of occasional epistaxes. In the majority of cases the phenomenon was encountered within the first week or so of working with the solid formulation and thereafter the incidence of epistaxes fell off rapidly. In no case was there frank bleeding and the invariable complaint was frequent spotting of the handkerchief with blood after blowing the nose.

The only two conditions found in these workers which could be called chronic effects of paraquat exposure were the occasional complaints of blepharitis and the phenomenon of delayed healing. Blepharitis was reported by only three of the thirty six

TABLE 2.5. INCIDENCE OF CLINICAL PROBLEMS ASSOCIATED WITH PARAQUAT EXPOSURE

	YALDING GROUP		KELANG GROUP		TOTAL	
	Number	% of group	Number	% of group	Number	% of total
(a) LIQUID FORMULATIONS ONLY	n = 7		n = 18		n = 25	
Acute skin rashes	0	0	9	50	9	36
Nail damage	2	28.6	1	5.5	3	12
Epistaxis	1	14.3	2	11.1	3	12
Eye injuries	0	0	6	33.3	6	24
Blepharitis	0	0	1	5.5	1	4
Delayed healing	0	0	1	5.5	1	4
No complaints	4	57.1	3	16.6	7	28
(b) SOLID FORMULATIONS ONLY	n = 8				n = 8	
Nail damage	3	37.5			3	37.5
Epistaxis	7	87.5			7	87.5
Blepharitis	1	12.5			1	12.5
Delayed healing	1	12.5			1	12.5
No complaints	0	0			0	0
(c) BOTH LIQUID AND SOLID FORMULATIONS	n = 3				n = 3	
Nail damage	2	66.6			2	66.6
Epistaxis	2	66.6			2	66.6
Blepharitis	1	33.3			1	33.3
Delayed healing	2	66.6			2	66.6
No complaints	0	0			0	0

n = No. of workers

workers and in each case it was very mild. Symptoms subsided rapidly after removal from work. Delayed healing manifested itself as a failure of small lacerations and abrasions to heal spontaneously in the usual time. Small wounds tended to remain open for several days with the increased risk of infection. Only four of the workers complained of this problem, three of whom had handled the solid formulations. The problem resolved as soon as the worker was removed from exposure to paraquat and the condition appears to be a function of skin contamination and, as such, probably reflects lack of hygiene.

Examination of the skin of all workers provided no evidence of the development of chronic skin conditions following exposure to paraquat. Hyperkeratosis has been described following exposure [53], but none of these two groups of workers showed any evidence of this type of lesion, nor did they show any eczematous lesions. No allergic type rashes were found, nor was there any history among these workers of allergic manifestations to paraquat. Although this study did not isolate control groups of workers not exposed to paraquat, the medical records of all workers were available and apart from the usual distribution of various clinical conditions, which appeared common to all workers, especially upper respiratory tract infections at both plants and mild gastro-intestinal upsets at Kelang, there was no other clinical evidence of chronic ill health amongst these men following prolonged exposure to paraquat. Further, none of them attributed any illness, apart from the acute episodes, to their work.

2.4.2. LONG TERM PARAQUAT SPRAYING

In order to investigate the real degree of risk associated with the long term spraying of paraquat a group of workers on Malaysian plantations was studied. The sprayworkers in the study had used large quantities of paraquat for considerable periods of time and the study was designed to estimate the degree of genuine exposure under normal working conditions, and also to determine whether such long-term spraying has any measurable effects. To this end the spraymen were compared with two control groups. One was a group of general workers, some of whom occasionally may work in areas recently sprayed, and the other was a group of latex processing factory workers who had received no known exposure to paraquat in the course of their work. The clinical aspects of this study have been published [6].

METHODS

(a) Population

The workers studied were drawn from six rubber and oil palm estates in Melaka and Negri Sembilan States of Peninsula Malaysia as a result of the ready co-operation of Dunlop Estates Sdn. Bhd. From the standpoint of any epidemiological studies, Malaysia has the advantage over many areas in enjoying tropical rainfall conditions which ensure weed growth throughout the year. Consequently, spraying programmes continue throughout the year so that spraying continues on a daily basis, rather than the intermittent seasonal type of spraying which is characteristic of temperate climates. Furthermore, the rubber and oil palm estates are virtually unique in that there is almost no insecticide spraying and it was thus possible to isolate a group of sprayworkers who had sprayed only herbicides, of which the predominant chemical was paraquat. It is worth noting that paraquat is probably the major herbicide used throughout South East Asia, and particularly in Malaysia. As a result, the sprayworkers not only use considerably larger quantities of paraquat each year than those in temperate climates, but this is used on a continuous basis and the spraymen are also free from the problem of mixed exposure that is usually met in Europe and USA where spraymen will handle a large variety of different types of pesticide (herbicides, insecticides, fungicides, etc.) in the course of a year. No spraymen were included in this study who were from those estates where insecticides and other pesticides (such as fungicides) were used. This excluded estates which were being developed for cocoa bean production on which insecticides are used extensively.

Two control groups were chosen and consisted of general plantation workers and latex factory workers. The original intention had been to use two groups of estate workers as controls, one of rubber tappers and oil palm harvesters and the other of general manual workers. It was discovered, however, that some of the tappers and harvesters had been employed in spraying operations and had, therefore, to be excluded. Because of this and the small number of general workers available, it was decided to consider both tappers and harvesters together with the general manual workers as a single control group (called general workers). The study was limited to male workers as there were very few female spray operators and their data contained too little information for formal statistical analysis.

The following criteria were used in selection. Spraymen were defined as those who had sprayed a minimum of 1,000 hrs. General workers were defined as those plantation workers who had no history of spraying and were employed in a variety of manual duties such as tilling, weeding, tapping and harvesting. Some members of this group had received minimal exposure to paraquat as a result of working in areas of the plantations in which spraying had recently been completed.

The factory workers were those employed on the estate 'factories' where the raw latex is given initial processing to prevent bacterial decomposition and render it fit for travel. Two highly irritant chemicals are used in this process; formic acid and ammonia. Ambient concentrations, however, rarely reach levels that produce irritation of mucuous membranes. Occasional spillages occur, but these rarely produce problems as workers wear rubber aprons, gloves and boots. None of these workers had any known occupational exposure to paraquat. All three groups had similar social backgrounds and resided together in the same estate villages. The workers normally worked an eight hour day for six days per week, with two weeks leave each year and an allowance of two weeks sick leave. As a result of this selection, the three groups finally consisted of 27 spraymen, 25 general workers and 23 factory workers. An analysis of the age and racial structure of the whole group is given in table 2.6.

(b) <u>Exposure to Paraquat at Work</u>

The spraying history of each sprayworker was obtained at a preliminary interview which also recorded the extent of any protective clothing worn during spraying operations, together with any episode of ill health attributable to occupation such as skin rashes. These were later cross-checked with individual medical records. The total amount of paraquat sprayed per year on each estate was obtained from company records, and by combining these figures with the spraying record of each man it was possible to produce an estimate of the amount of paraquat each had used. Paraquat is normally sprayed on the estates at a rate of approximately 0.1% paraquat ion, frequently in a tank mix with diuron and mono-sodium methane arsenate and also one of the phenoxy alkylates to ensure a wide spectrum of weed control. Workers generally did not wear any protective clothing during spraying operations. The normal dress consisted of a shirt, singlet, underpants and cotton trousers. These were usually tucked into the socks when working. Footwear varied from rubber boots to canvas or leather shoes or even open sandals. Table 2.7 shows the amount of protection used. Spraymen regularly showered after work and changed their clothes, but rarely bothered to wash off minor splashes and only infrequently washed before eating when in the field. Work clothing was only infrequently laundered.

TABLE 2.6 AGE AND RACIAL STRUCTURE OF WORKING GROUPS

Age (yrs)	SPRAYMEN				GENERAL WORKERS				FACTORY WORKERS				TOTALS			
	Malay	Indian	Chinese	Total	Malay	Indian	Chinese	Total	Malay	Indian	Chinese	Total	Malay	Indian	Chinese	Total
Less than 25	5	1	1	7	2	2	1	5	11	1	0	12	18	4	2	24
25-34	4	5	0	9	3	4	3	10	4	1	0	5	11	10	3	24
35-44	2	3	0	5	2	1	3	6	2	1	0	3	6	5	3	14
45 and over	3	1	2	6	1	2	0	3	0	1	2	3	4	4	4	12
TOTALS	14	10	3	27	8	9	7	24	17	4	2	23	39	23	12	74

TABLE 2.7 DEGREE OF PERSONAL PROTECTION USED BY SPRAYMEN

TYPE OF PROTECTION	No.	%
Overalls or plastic apron with rubber boots	1	3.7
Rubber gloves with rubber boots	2	7.4
Rubber boots only	8	29.6
Rubber gloves only	1	3.7
No protection used	15	55.6
	27	100

Conditions varied slightly from estate to estate. However, in all cases the terrain consisted of low hill country with gentle undulations. Rubber and palm trees were laid out in uniform contour planting with secondary growth developing between. This consisted of a mixture of grasses, ferns and perrenial broadleaf weeds, which at times could be as high as 120 cm, although usually about 45 to 90 cm in height. This meant that as the spraymen walked forward into the sprayed area there was potential dermal contamination from spray 'run-off' to waist height. Measurements were made of the extent of potential dermal and inhalational exposure in a series of environmental monitoring procedures (see below). Either Saval or Birchmeier knapsack sprayers were used, with standard flowjet, solid cone or 'polijet' nozzles.

A further source of potential exposure came at the first stage of mixing. Mixing procedures varied from estate to estate. In some, all mixing was done centrally at the chemical store in large tractor drawn tankers and the paraquat concentrate was handled under very well controlled conditions. The dilute spray solution was transported around the estate as and when required. On other estates, however, the concentrate was diluted on the field using water dispensed from a transportable tank (fig 2.5). Inevitably, even though it was normal practice for only one member of the spraying team to be responsible for diluting the concentrate, the potential for spillages and other accidents was much greater in the field

FIG. 2.5: FIELD MIXING OF AGRICULTURAL CONCENTRATE

Photo: the author

than under the more easily controlled conditions at a central chemical store.

(c) Clinical Examination*

All the workers were given a full clinical examination with particular attention being paid to respiratory system and skin.

(d) Clinical Measurements

The workers were all examined at a central site, one of the Estate hospitals and at approximately the same time, between 10.00 and 12.00 hours on several succeeding days. Blood was taken for haematological examination, liver and renal function tests, using standard venepuncture technique from the ante-cubital vein. Plain tubes were used for blood for liver function, heparinised tubes for renal function tests and Sodium EDTA was the anti-coagulant for the haematological specimens. All containers were stored in ice and transported to the laboratories in Kuala Lumpur (90 miles away) within three hours of specimens being taken. Measurements were completed by 16.00 hours the same day. The following indices of normal function were used:

(i) Respiratory function Ventilatory function was measured by FVC, FEV_1 and $FEV_1\%$ using the standard 'Vitalograph' Spirometer and digital display meter. Three readings were taken on each subject and the highest value achieved was used. Transfer factor (DCO), as an

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* Clinical examinations were undertaken by Dr. N.N. Sabapathy (Chief Medical Officer, Dunlop Estates, Melaka).

estimate of alveolar diffusion, was measured by a single breath method, using the Hewlett Packard 47404A Single Breath Carbon Monoxide Diffusion System. The higher of two values was used.

(ii) Liver function* This was determined by estimations of the activity of the following enzymes, using the Hycel Super 17 Auto analyser : Serum alanine aminotransferase (ALT) using L-alanine and α-ketoglutarate as the substrate and acidic 2, 4, dinitrophenyl hydrazine as the colour reagent. Serum aspartate aminotransferase (AST), using L-aspartate and α- ketoglutarate as the substrate and Fast Violet B as the colour reagent and alkaline phosphatase (ALKP) using magnesium thymolphthalein monophosphate as the substrate and the addition of alkali to induce the colour reaction.

(iii) Renal function* An estimate of renal function was made by the determination of blood urea nitrogen using the diacetyl/thiosemicarbazide colorimetric method with the Hycel Super 17 auto analyser and the determination of serum creatinine using a manual endpoint colorimetric method with picric acid. Urine albumen tests were also performed simply at the time of the initial clinical examination by the semi-quantitative Ames strip method.

(iv) Haematology* Haemoglobin estimations were made by the colorimetric cyanmethaemoglobin method using the Hycel Model 700 automated counter which also gave red and white

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* Laboratory investigations were undertaken by Dr. H. Kaur (Computer Med Lab, Kuala Lumpur)

cell counts, PCV, MCHC, MCH and MCV. The differential white cell count was performed manually after staining the blood slide with Leishman's stain.

(e) Environmental Measurements*

In order to obtain a measurement of the dermal and respiratory exposure of the spray operators, four groups of male spray operators were randomly selected and measurements were undertaken during a typical working day.

(i) Dermal Exposure This was measured using a modification of the standard WHO protocol [54]. Dermal exposure pads, consisting of polythene backed Whatman grade 542 filter papers with a surface area of 80 cm^2, were applied to the skin (if directly exposed) or clothing at the following sites:

Left arm:	mid-forearm
	mid-upper arm
Left leg:	mid-lower leg (or below knee if boots worn)
	mid-thigh
Trunk:	over sternum
	'V' of neck
	lower back beneath knapsack container
Head:	forehead

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* The actual environmental sampling was carried out by G. Chester and paraquat analysis of samples was undertaken by B.H. Woollen, both of ICI Ltd., Central Toxicology Laboratory, Alderley Park, Cheshire.

The pads were removed at the end of the spraying operation and stored individually in polythene containers for transport to UK for paraquat estimations.

(ii) Respiratory exposure was measured using standard Rotheroe-Mitchell L25F personal air samplers, operating at a flow rate of 2 litres min $^{-1}$. The sampling heads were in the sprayman's breathing zone. Paraquat aerosol was collected onto Whatman Number 1 or 542 filter paper in the sampling head. These filters have collection efficiencies of 100% for particle sizes down to 2 micron diameter. In addition urine samples were collected from each sprayman each day immediately after spraying. Samples were stored on ice in individual polythene containers with azide preservative pending analysis for paraquat.

(iii) Paraquat analysis The radio-immunoassay method developed by Levitt [55] was used for the estimation of paraquat in the urine samples and on the filters from the personal air samplers. The filter papers used for the estimate of dermal contamination were analysed using a modification of the method of Calderbank and Yuen [56]. In this method paraquat is extracted from the sample by shaking in saturated ammonium chloride and the extract mixed with sodium dithionite. The amount of paraquat present is calculated from the absorbance of this solution at 600 nm.

(iv) Method of calculation The dermal exposure data were adjusted to uniform time and extrapolated from mg/paraquat ion per 25 cm^2 filter paper to mg/paraquat ion per body part per hour to calculate the dermal exposure of individual body parts. The body part surface areas given in the WHO Standard Protocol were used for this extrapolation. As these areas have been derived for a 70 kg Caucasian they have been reduced proportionally to take into consideration the lower mean body weight, height and total surface area of South East Asians as indicated from the heights recorded in Appendix 2.2. In order to calculate the latter, a height-area-weight nomogram was used [57]. The mean bodyweights and heights employed (males only) were:

weight: male - 60 kg;

height: male - 162.5 cm;

On this basis, the following body surface area was derived:

for male - 1.65 m^2;

The respiratory exposure data were adjusted to mg paraquat ion per metre ^{3} air using the sampling rate and times, and hence the total volume of air sampled.

RESULTS

(a) Amount of paraquat used

Each estate taking part in this study used between 950 and 2050 litres of 'Gramoxone' (the 20% agricultural concentrate) per annum depending on area and size of the spray team. This represents an average annual quantity of approximately 336 litres of 'Gramoxone' sprayed by each spraymen, equivalent of 67.2 kg paraquat ion. The mean length of time the spraymen in this study had worked was 5.3 years, representing a mean of 8,696 actual spraying hours per man. Some workers, however, had been involved in regular spraying operations with paraquat since 1966 (i.e. for 12 or 13 years at the time of the study).

(b) Adverse responses to paraquat

There were 11 spraymen out of 27 who complained of one or more incidents of skin irritation/rashes associated with spraying. These were commonest on hand, legs or groin. In the case of groin/buttock rashes these were commonly associated with a leaking knapsack sprayer which had allowed material to run down the back and between the legs and buttocks. Medical records indicated that all cases cleared rapidly, usually in a few days, in response to local treatment (usually a steroid cream). Although 12 of the spraymen admitted to having been involved in spillages or splashes of material, only one case of eye injury had been reported and this had responded with no sequelae.

(c) Clinical measurements*

To test the effect of occupational exposure to paraquat, comparisons were made between sprayers, general workers and factory workers for each of the fifteen clinical measurements. The significance of occupation was tested with allowance made for difference in the distributions of race, age, height and smoking history between the three groups. This was achieved by fitting multiple regression equations with race, age, height and smoking history as the independent variables and then by re-fitting the equations with occupation added as a further independent variable. The decrease in the residual sum of squares thus achieved was tested for significance using an F-test. Details of the independent variables used and the regression equations fitted involving all variables are given

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* The statistical calculations were undertaken by P. Anne Whitehead (Statistician, ICI Ltd, Plant Protection Division, Bracknell, Berks)

in Appendix 2.1, and the full results used in the study are set out as Appendices 2.2, 2.3 and 2.4.

Estimates of the effect of occupation on the clinical measurements can be obtained from these regression equations. For example with FVC, then if a sprayer, general worker and factory worker had the same race, age, height and smoking history, then the sprayer would be expected to have an FVC value 0.139 higher than the factory worker, 0.048 lower than the general worker, and the general worker 0.187 higher than the factory worker. Tables 2.8, 2.9 and 2.10 show the estimated values for each of the occupations for Malay, Indian and Chinese males aged 30 years, height 162.5 cm and non-smokers. The tables show the significance of the differences between the occupations (the probability level for the F-test). The standard error (person) is a measure of the deviation of an actual observation from the regression equation. The tables also show the probability level for the test of significance of the occupation. The Lowest Significant Difference (LSD) P = 5% is given when differences between occupations are significant at the 5% probability level. If the estimates for two groups of workers differ by more than the LSD then this suggests a significant occupational effect.

No significant differences could be demonstrated for the respiratory or haematological indices. However, significant differences were found for both liver and renal measurements and in each case it was the factory workers who differed from both spraymen and general workers. Both levels of serum

TABLE 2.8 ESTIMATED CLINICAL VALUES (MALAY)

These values have been estimated using the regression equations in Appendix 2.1 for a Malay non-smoker, male, aged 30, height 162.5 cm

	FVC (litres)	FEV_1 (litres)	FEV_1%	DCO (mmol/ min/kpa)	Hb (g/dl)	PCV	RBC (millions/ ul)	MCV (um^3)	MCH (pg)	$\log_{10}$ WBC	WBC no/ul)
SPRAYMEN	3.28	2.94	90.0	11.6	14.3	41.6	5.31	77.9	27.0	3.916	8250
GENERAL WORKERS	3.33	2.94	88.3	12.4	15.0	43.3	5.54	77.9	27.0	3.858	7200
FACTORY WORKERS	3.14	2.80	89.0	12.2	14.6	43.5	5.57	77.5	26.3	3.935	8600
STANDARD ERROR (PERSON)	0.49	0.44	7.5	1.9	1.3	3.5	0.50	5.2	2.2	0.099	
DIFFERENCES BETWEEN OCCUPATIONS	P= 48%	P= 51%	P= 73%	P= 30%	P= 21%	P= 13%	P= 16%	P= 96%	P= 52%	P=5.3%	
LSD P = 5% S v GW											
S v FW											
GW v FW											

	$\log_{10}$ AST	AST (IU/l)	$\log_{10}$ ALT	ALT (IU/l)	$\log_{10}$ ALKP	ALKP (IU/l)	$\log_{10}$ CREAT	CREAT (mg/dl)	$\log_{10}$ BUN	BUN mg/dl)
SPRAYMEN	1.315	20.7	1.597	39.5	1.510	32.4	-0.013	0.97	1.031	10.7
GENERAL WORKERS	1.286	19.3	1.561	36.4	1.463	29.0	-0.075	0.84	1.023	10.5
FACTORY WORKERS	1.345	22.1	1.167	14.7	1.599	39.7	0.025	1.06	1.107	12.8
STANDARD ERROR (PERSON)	0.153		0.227		0.115		0.113		0.103	
DIFFERENCES BETWEEN OCCUPATIONS	P= 51%		P<0.01%		P= 0.3%		P= 3.4%		P= 2.0%	
LSD P = 5% S v GW			0.134		0.068		0.067		0.060	
S v FW			0.134		0.068		0.067		0.061	
GW v FW			0.144		0.073		0.072		0.065	

TABLE 2.9 ESTIMATED CLINICAL VALUES (INDIANS)

These values have been estimated using the regression equations in Appendix 2.1 for an Indian, non-smoker, aged 30, height 162.5 cm.

	FVC (litres)	FEV_1 (litres)	FEV_1%	DCO (mmol/min/kpa)	Hb (g/dl)	PCV	RBC (millions/ul)	MCV (um^3)	MCH (pg)	log_{10} WBC	WBC (no/ul)
SPRAYMEN	3.12	2.73	88.2	10.2	14.1	40.2	5.21	77.0	27.2	3.954	9000
GENERAL WORKERS	3.17	2.73	86.5	11.0	14.8	41.9	5.44	77.0	27.2	3.895	7850
FACTORY WORKERS	2.98	2.59	87.2	10.8	14.4	42.1	5.47	76.5	26.5	3.973	9400
STANDARD ERROR (PERSON)	0.49	0.44	7.5	1.9	1.3	3.5	0.50	5.2	2.2	0.099	
DIFFERENCES BETWEEN OCCUPATIONS	P= 48%	P= 51%	P= 73%	P= 30%	P=21%	P= 13%	P= 16%	P= 96%	P= 52%	P= 5.3%	
LSD P = Sv GW											
Sv FW											
GW v FW											

	log_{10} AST	AST (IU/1)	log_{10} ALT	ALT (IU/1)	log_{10} ALKP	ALKP (IU/1)	log_{10} CREAT	CREAT (mg/dl)	log_{10} BUN	BUN (mg/dl)
SPRAYMEN	1.362	23.0	1.771	59.0	1.497	30.7	0.055	1.14	1.005	10.1
GENERAL WORKERS	1.333	21.5	1.734	54.2	1.439	27.5	-0.006	0.99	0.997	9.9
FACTORY WORKERS	1.392	24.7	1.341	21.9	1.576	37.7	0.094	1.24	1.031	12.1
STANDARD ERROR (PERSON)	0.153		0.227		0.115		0.113		0.103	
DIFFERENCES BETWEEN OCCUPATION	P= 51%		P<0.01%		P= 0.3%		P=3.4%		P= 2.8%	
LSD P = 5% S v GW			0.134		0.068		0.067		0.060	
S v FW			0.134		0.068		0.067		0.061	
GW v FW			0.144		0.073		0.072		0.065	

TABLE 2.10 ESTIMATED CLINICAL VALUES (CHINESE)

These values have been estimated using the regression equations in Appendix 2.1 for a Chinese, non-smoker, aged 30, height 162.5 cm.

	FVC (litres)	FEV_1 (litres)	FEV_1%	DCO (mmol/min/kpa)	Hb (g/dl)	PCV	RBC (millions/ul)	MCV (um^3)	MCH (pg)	log_{10} WBC	WBC (no/ul)
SPRAYMEN	3.47	3.14	91.9	11.6	13.7	40.4	5.35	75.4	25.9	3.910	8150
GENERAL WORKERS	3.51	3.14	90.2	12.5	14.4	42.1	5.59	75.4	25.9	3.851	7100
FACTORY WORKERS	3.33	3.00	90.9	12.3	14.0	42.3	5.62	75.0	25.2	3.928	8450
STANDARD ERROR (PERSON)	0.49	0.44	7.5	1.9	1.3	3.5	0.50	5.2	2.2	0.099	
DIFFERENCES BETWEEN OCCUPATIONS	P= 48%	P= 51%	P= 73%	P= 30%	P= 21%	P= 13%	P= 16%	P= 96%	P= 52%	P= 5.3%	
LSD P = 5% S v GW											
S v FW											
GW v FW											

	log_{10} SGOT	SGOT (IU/l)	log_{10} SGPT	SGPT (IU/l)	log_{10} ALKP	ALKP (IU/l)	log_{10} CREAT	CREAT (mg/dl)	log_{10} BUN	BUN (mg/dl)
SPRAYMEN	1.276	18.9	1.492	31.0	1.454	28.4	-0.008	0.98	1.019	10.4
GENERAL WORKERS	1.247	17.7	1.456	28.6	1.406	25.5	-0.069	0.85	1.011	10.3
FACTORY WORKERS	1.306	20.2	1.062	11.5	1.543	34.9	0.030	1.07	1.095	12.4
STANDARD ERROR (PERSON)	0.153		0.227		0.115		0.113		0.103	
DIFFERENCES BETWEEN OCCUPATIONS	P= 51%		P<0.01%		P= 0.3%		P= 3.4%		P= 2.6%	
LSD P = 5% S v GW			0.134		0.068		0.067		0.060	
S v FW			0.134		0.068		0.067		0.061	
GW v FW			0.144		0.073		0.072		0.065	

creatinine and blood urea nitrogen were significantly higher in this group, as was also the level of serum ALK activity.

The level of serum ALT activity, however, was significantly lower in factory workers than the other two groups. All group means, however, fell within the levels quoted as normal by the laboratory undertaking the estimations.

Further investigations into the effect of spraying on DCO and Hb estimations were carried out by correlating the residuals of both DCO and Hb from the regression equations in Appendix 2.1 with log total number of spraying hours. In neither case was the correlation statistically significant. All values relating to erythrocytes were lower than corresponding Caucasian values.

Age and height were significant variables with FEV_1, and FVC measurements and age was a significant variable in respect of $FEV_1\%$ and DCO values. A racial trend appeared to exist with DCO values, Indians showing slightly lower values. The mean values and range, however, were comparable with figures obtained from 'normal' Caucasians.

Smoking did not appear as a significant variable in the respiratory measurements, which almost certainly is to be related to the fact that of the 74 subjects only 9 smoked more than 15 per day, and only 2 more than 25 per day. 30 were non-smokers and 22 smoked between 1-10 cigarettes per day.

(d) Environmental measurements

(i) Dermal exposure The calculated dermal exposures for the spray operators are shown in table 2.11. Individual body parts have been separated into two categories according to whether they were clothed or not. Two estimates of total exposure are given. The first is a summation of individual exposures of unclothed areas (i.e. those body parts such as hands and head not normally covered), which is the recommended procedure given in the WHO Standard Protocol. The second is a summation of unclothed and clothed body areas and is recorded as a potential total exposure. Similarly, two estimates of dermal dose are given. The distinction has been drawn because the former interpretation assumes that the clothing worn by a spray worker affords him a measure of protection from dermal contamination with sprayed pesticide, whereas the latter allows estimation of the total potential exposure. The second figure is important in view of the ready permeability of cotton materials worn in South East Asia to water soluble pesticides.

There were large differences between unclothed total and overall total exposures for each spray operator (table 2.11). The mean unclothed exposure was 2.48 mg paraquat ion per hour of spraying with individual variation from zero to 12.3 mg paraquat ion per hour of spraying. The mean value of 2.48 mg/hour is equivalent to a dermal dose of 0.04 mg/kg/hour. The highest individual direct dermal exposure of 12.3 mg/hour is equivalant to 0.2 mg/kg/hour. The mean overall total exposure was 72.04 mg paraquat ion per hour, with individual variation from 12.1 mg/hour to

TABLE 2.11 DERMAL EXPOSURE OF SPRAY OPERATORS

Estate	Worker	Dermal Exposure (mg Paraquat Ion/Hour)													Dermal Dose (mg/kg/hr)	
		Exposed Body Parts					Clothed Body Parts									
		Head	"V" of Neck	Shoulders	Hands	Forearms	Forearms	Upper Arms	Sternum	Buttocks	Thighs	Lower Legs	Direct Exposure of Exposed Body Parts (mg/hr)	Total Exposure (Potential) mg/hr)	Cumulative Exposed	Total Potential
1	1	ND	ND	ND	0.53	0.79		ND	ND	4.4	26.8	55.3	1.32	87.8	0.02	1.5
	2	0.36	ND	0.1	ND		ND	ND	ND	6.0	26.2	19.9	0.46	53.1	$8x10^{-3}$	0.9
	3	0.79	0.04	0.21	0.22		0.33	0.95	ND	9.5	75.8	27.0	1.26	114.8	0.02	1.9
	4	ND	0.05	ND	2.53		3.8	0.45	ND	2.2	72.7	45.2	2.58	126.9	0.04	2.1
2	1	ND	0.13	ND	1.57		2.35	1.09	ND	1.09	17.31	No pad	1.70	23.5	0.03	0.4
	2	ND	ND	ND	0.21		0.31	ND	ND	0.42	16.18	145.29	0.21	162.4	$4x10^{-3}$	2.7
	3	ND	0.04	ND	3.24		4.84	1.23	ND	0.13	49.28	17.82	3.28	76.6	0.05	1.3
	4	ND	ND	ND	ND		ND	4.65	ND	6.20	7.90	39.75	ND	58.5	0	1.0
3	1	ND	0.03	ND	2.24		3.35	0.21	ND	0.24	14.04	21.28	2.27	41.4	0.04	0.7
	2	ND	ND	ND	ND		ND	ND	ND	No pad	3.51	8.54	ND	12.1	0	0.2
	3	ND	ND	ND	0.22	0.33		0.7	ND	6.04	11.79	29.32	0.55	48.4	$9x10^{-3}$	0.8
	4	ND	0.04	ND	0.37	0.56		0.29	ND	0.55	51.41	42.72	0.97	95.9	0.02	1.6
4	1	ND	0.02	ND	1.0	1.50		0.21	ND	0.71	23.40	24.12	2.52	51.0	0.04	0.9
	2	0.63	0.56	0.17	4.4	6.56		5.9	ND	ND	25.41	21.0	12.32	64.6	0.2	1.1
	3	1.77	0.75	0.47	4.74		7.09	5.04	ND	ND	17.05	26.7	7.73	63.6	0.1	1.1
Mean													2.48	72.04	0.04	1.21
SD													3.34	40.0	0.05	0.59

ND - None detected

Lower limit of detection is 10 g/filter

162.4 mg/hour. The mean value is equivalent to a dermal dose of 1.21 mg/kg/hour. The highest individual "total" exposure of 162.4 mg/hour is equivalent to 2.7 mg/kg/hour.

(ii) Respiratory exposure The mean paraquat concentration in the air of the sprayman's breathing zone was calculated to be 1.03 ug paraquat ion / m^3 (table 2.12). This figure represents the total air concentration of paraquat and not that occurring as respirable sized droplets which would be a much lower concentration, although, in view of climatic conditions it is likely that the figure would be higher than Hogarty's [35] estimate of 50% of droplets in the breathing zone as the maximum.

(iii) Urine analysis Paraquat residues were detected in the urine of six out of fifteen spray operators (table 2.13). The levels are remarkably close to those reported by Swan ten years earlier [5].

DISCUSSION

The results of the environmental measurements indicate that the spray worker is exposed to comparitively large amounts of paraquat in the course of his work. Actual dermal exposure may be considered to lie somewhere between the two calculated extremes of 2.1 mg and 63.1 mg paraquat ion per hour. Such figures are significantly higher than those obtained by Staiff [34] in his study of sprayer operators using tractor mounted equipment.

It is apparent from the results recorded in table 2.11 that the greatest potential contamination was on the legs. Hands also represented a significant source of possible absorption and in further studies of this worker population Chester and Woollen [58]

TABLE 2.12 RESPIRATORY EXPOSURE OF SPRAY OPERATORS

Dunlop Estate	Worker	Total Paraquat Ion per Sampler Filter (g)	Sampling Duration (min)	Total Volume of Air Sampled (l)	Air Concentration (g/m^3)
1	3	0.67	60	120	0.67
	4	0.68	135	240	2.8
2	3	0.41	200	400	1.0
	4	0.16	200	400	0.4
3	1	0.28	160	320	0.88
	2	0.27	160	320	0.84
4	1	0.28	225	450	0.62
Mean					1.03
SD					0.8

TABLE 2.13 PARAQUAT RESIDUES IN URINE

Workers	Paraquat Residues mg/litre			
	Dunlop Estate			
	1	2	3	4
Spray Operators				
1	0.05	0.08	0.05	0.05
2	0.05	0.19	0.05	0.05
3	0.05	0.05	0.35	0.09
4	0.05	0.05	0.05	-

Mean value (all spraymen) 0.05 mg/litre (SD 0.1)
Mean value of residues detected 0.14 mg/litre (SD 0.12)
Lower limit of detection is 0.05 g/ml

have shown that hand contamination may exceed that of the legs due to careless work practices. Spray nozzles are frequently handled in order to align them correctly or unblock them, and operators were even observed to wash their hands in the diluted formulation in the spray tank after oiling the knapsack sprayer mechanism.

The fact that such exposure was associated with dermal absorption was reflected in the urinary levels of paraquat. Although these data must be treated with caution as the results are little more than 'spot checks', they do bear comparison with the figures obtained by Swan[5]. His measurements were made on 24 hour specimens, but none the less the figures from both studies are in the same order. It is thus likely that some of the workers studied have been excreting paraquat in their urine for up to 12 years continuously in view of their long spraying history since 1966.

The minor importance of inhalation as a route for absorption was confirmed in this study. The total amount of paraquat in the breathing area was very small, even less than in Hogarty's Irish study [35]. Furthermore, studies on the droplet size distribution have demonstrated that the percentage of droplets within the respirable range is normally less than half the total [35, 56]. Even allowing for a higher percentage as a result of climatic conditions, the total 'inhalable' paraquat is an insignificant amount.

The extent of such a degree of potential exposure over many years has led to concern being expressed about the possibility of systemic poisoning arising as a result of normal spraying operations. This study failed to show any clinical or biochemical evidence of organ malfunction, although claims have been made that the lung in particular may be affected by such operations [9, 10]. The recent study by Levin and his co-workers[7], to which reference was made at an earlier stage of this section, reported reduction in pulmonary function, particularly in the measurement of alveolar diffusion, as a result of spraying with paraquat. This present study of workers exposed daily for long periods, using large quantities of paraquat, and with evidence of paraquat absorption, failed to show any differences in lung function between sprayworkers and the two groups of controls. The range of values for ventilatory function did not differ in the three groups and the mean values were not significantly different. The values were also in close agreement with the 'normal' values obtained in other studies of Asian subjects [60-62], suggesting that the groups under study represented a 'normal' population. In none of the three groups of workers did occupation have any significant effect on ventilatory function, although, in agreement with all previously published work, FEV_1 and FVC values were related to both age and height. As expected, the values were consistently lower than those for Caucasians of equivalent age and height [63].

The assessment of alveolar diffusing capacity by the use of single breath Carbon Monoxide diffusion measurements (DCO) also showed no differences between the three working groups. This study, it is believed, is the first time that alveolar diffusion has been measured in such an Asian population and no comparisons could be made with previously obtained normal values. However, the range of values is very close to those reported from studies of Caucasian subjects [64-66].

Concern has also been expressed that exposure to paraquat may induce blood changes, in that there is a report of isolated instances of blood dyscrasias in cases of clinical paraquat poisoning [67]. However, there has never been any evidence that exposure to paraquat under normal working conditions has had any effects on haematological parameters. In the present study there were no significant differences in the three working groups. Parameters associated with the red cell series were slightly lower than would have been expected in a comparable Caucasian group, but this is a general finding and reflects dietary habits and the effects of helminth infection (Kaur, 1979, unpublished observations), which were indicated by consistently high eosinophil counts in a large proportion of the population studied.

The effects of paraquat on both liver and renal function have been observed in severe poisoning following ingestion from the very first cases reported [68]. Raised BUN and raised levels of serum ALKP and AST are regular features even in non-fatal poisoning cases. No such abnormalities were found in the group of sprayworkers. However, the factory workers did show some variation of both renal and liver function tests. These did not fall outside the range of normal values for the laboratory.

The few instances of local dermal lesions from poor spraying techniques and accidents is indicative both of the high levels of training and supervision on the Dunlop Estates. No cases of nose bleeding were recorded and only one case of eye injury which recovered with no sequelae. The evidence of this study would indicate that paraquat spraying does not give rise to any serious health problems under conditions of proper usage, even with exposure levels considerably higher than those likely to pertain to temperate climates.

2.4.3. COMPARATIVE RISKS FROM HIGH AND LOW VOLUME SPRAYING TECHNIQUES

The studies described, taken in conjunction with the other published data, indicated that at normal spraying strengths (below 0.5% paraquat ion) there was unlikely to be any significant degree of risk for the spray operator, provided that proper agricultural practice was followed. Such studies, however, do not provide any data for assessing the risk associated with the use of higher ionic strength spray solutions. The introduction of spinning disc applicators such as the 'Herbi' (Micron Ltd) which utilise low volume/high concentration spray solutions has raised interest in their applicability over a wide range of herbicides. Such applicators have advantages over conventional spraying methods, especially in developing countries. They are frequently more efficient and because they use a lower volume of spray material to cover equivalent areas, the amount of water requiring to be transported and the amount of mixing that is necessary are greatly reduced when compared with conventional spraying methods. Consequently, there has been widespread (but unauthorised) use of paraquat with such equipment.

In view of the fact that the few fatalities which have occurred through the percutaneous absorption of paraquat have all been related to the use of high strength solutions, together with the fact that stronger spray strengths are likely to increase the risk of dermal irritation, it was considered necessary to investigate the degree of risk which low volume application presents to the spray operator. Accordingly, a risk assessment was linked with an efficacy trial in Thailand. The purpose was to compare the degree of dermal contamination produced by normal high volume knapsack spraying with that produced by low volume spraying techniques. At the same time urinary excretion of paraquat by the sprayworkers could be monitored and any clinical effects noted and comparisons made between the two groups of spraymen.

METHODS

Initial work in the UK, measuring the amount of leg and foot contamination from the 'Herbi' applicator, had suggested that it would be no more than from conventional equipment. Accordingly, the trial was mounted in Thailand using the following methods:

(a) Spraying equipment

Three different types of sprayers were used during the trial:

(i) The Micron 'Herbi' standard model fitted with the yellow feed nozzle and with a guard for the spinning disc. No carrying straps were used initially but in due course the spraymen used strings, wires etc. to facilitate spraying.

(ii) A standard Micron 'Herbi' combined with the 20 litre Allman back pack container instead of the 2.5 litre standard bottle reservoir.

(iii) A Birchmeier Flox 10 knapsack sprayer fitted with the blue polijet nozzle.

In an experiment after the main trial period 3 standard 'Herbi' were compared with 3 modified machines with a 25 cm longer extension tube and fitted carrying strap.

(b) Herbicide

Commercial 'Gramoxone' (20% w/v paraquat ion) was used throughout the trial. For low volume spraying the daily requirement was prepared the previous evening in two 200 litre drums fitted with a tap. For knapsack spraying 'Gramoxone' was added to the water in the knapsack, which is the usual practice in Southern Thailand. The risks of accidental spillage are clearly much higher in this situation than in Malaysia, as described above. The application rates were:

(i) Low volume: 20 litre/ha using 2% solution of paraquat ion (i.e. 2 litres 'Gramoxone'/ha)

(ii) Knapsack: 250 litre/ha using 0.15% solution of paraquat ion (i.e. 1.87 litre 'Gramoxone'/ha)

(c) Spraymen

There were 14 spraymen at the beginning of the trial; 12 spraying low volume with the 'Herbi' and 2 spraying with the knapsack sprayers. However, one man left because of a death in his family and a second one was dismissed because of absenteeism, leaving 12 spraymen only, one of whom used a knapsack sprayer. All men wore a shirt and long trousers. There were 7 who were bare foot except for cheap rubber slippers which gave no protection to the dorsum of the foot. The remaining 5 wore plimsolls.

(d) Clinical*

Each man was given a chest X-ray and a thorough clinical examination before spraying began. Further clinical examinations at the end of each week of spraying and a final examination a week after spraying had been completed were undertaken. A further chest X-ray was also taken one week after spraying had finished. Urine samples were collected into sterile containers containing thymol preservative, for paraquat analysis, at the same time as the medical examinations and sent to Central Toxicology Laboratory in UK for the analysis. Equipment was not available to undertake biochemical, haematological or pulmonary function measurements and such measurements, although desirable, had to be omitted.

(e) Dermal Contamination

Absorbent cellulose pads (3M micro dressings) were fitted with staples on to an impermeable polythene base and then attached to the spraymen's outer clothing according to World Health Organisation protocols [54]. They were applied as follows:

Arm: upper surface of left forearm, midway between elbow and wrist

Thigh: front of left mid thigh.

Leg: front of left leg, above the ankle

Foot: dorsum of left foot, below trouser leg.

Pads were removed at the end of the first period of spraying (at lunchtime after 4 hours' spraying). They were placed in

* Dr. S. Prasan of Pattaya, South Thailand, was responsible for the clinical examinations and X-rays.

labelled plastic bags and sent to the Environmental Sciences Section of Jealott's Hill Research Station in UK for analysis. A total of 6 measurements were made in association with the standard 'Herbi', 4 with the modified 'Herbi' and 4 with the knapsack sprayer.

(f) Spraying

The spraying programme was carried out in fields under cultivation with cassava (grown principally as an animal foodstuff and for the starch content: it is not used as a human nutrient in Thailand). At the time of spraying the cassava was about 100 cm high with undergrowth between the rows varying between 30 and 50 cm high. The terrain was hilly and spraying was carried out with the spraymen walking forward into the sprayed foliage. On the first spraying day the 'Herbi' was briefly explained to the team and demonstrated how it should be carried, but from then on the spraymen were free to hold it in their most convenient position. Spraying was done in a team accompanied by one supervisor. Hence every member of the group sprayed the same amount. The bottles were always filled by the supervisors. There was sufficient water available for the spraymen to wash their hands or other contaminated parts but it was the supervisors' policy not to urge them to do so (except in serious cases of contamination). Spraying began between 08.00 to 08.30 hours and went on until 17.00 hours with a 1 hour lunch break. Occasionally a group had to move to a new field and several times rain interrupted spraying, hence the shorter than expected actual periods of spraying. However, each man worked for two periods of 5 days in the two week spraying programme.

RESULTS

The degree of dermal contamination by paraquat is shown in table 2.14. The amount of paraquat is expressed per 25 cm^2 of exposed surface as in World Health Organisation protocols. It was not considered necessary to extrapolate these figures to a time weighed exposure figure as the study was concerned only to compare two systems of spraying and not obtain absolute figures. The differences between the means of leg and foot contamination produced by the 'Herbi' applicator and by knapsack spraying were statistically significant using the Student 't' test (standard 'Herbi' versus knapsack: leg: $-\ t = 3.17$, df = 8, $P < 0.01$; foot: $-\ t = 3.09$, df = 8, $P < 0.01$; modified 'Herbi versus knapsack: leg: $-\ t = 2.00$, df = 6, $P < 0.05$; foot: $-\ t = 2.98$, df = 6, $P < 0.125$).

The mean values of urinary excretion of paraquat are shown in table 2.15. There is a highly significant difference between the mean value of those using the 'Herbi' applicator without foot protection and those wearing shoes at the end of 14 days spraying, but not apparent at the end of the first week ($t = 5.11$, df = 9, $P < 0.001$).

All 14 spraymen who began the trial were clinically fit and chest X-rays showed no abnormalities. Two spraymen dropped out during the trial and therefore did not have final clinical

TABLE 2.14 SKIN CONTAMINATION: Mean values mg paraquat ion/25 cm^2

	Number of Observations	Arm		Thigh		Leg		Foot	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Standard 'Herbi' applicator	6	0.19	0.38	1.31	0.86	5.29	1.81	10.66	3.26
Modified (long arm) 'Herbi' applicator	4	0.16	0.12	1.05	1.08	5.13	3.15	18.37	9.11
Knapsack sprayer	4	0.22	0.23	0.38	0.16	1.76	1.17	3.37	4.25

TABLE 2.15 URINARY EXCRETION OF PARAQUAT: Mean values mg paraquat ion/litre

	No. of Subjects	PRE-SPRAYING	SPRAYING				POST-SPRAYING	
		Day 0	Day 7		Day 14		Day 21	
			Mean	SD	Mean	SD	Mean	SD
Standard 'Herbi' applicator (wearing shoes)	5	ND	0.13	0.10	0.11	0.07	0.05	0.03
Standard 'Herbi' applicator (with open sandals)	7	ND	0.20	0.14	1.05	0.40	0.08	0.10
Modified 'Herbi' applicator (with open sandals)	1	ND	0.14	-	0.73	-	0.06	-
Knapsack sprayer (with open sandals)	1	ND	0.96	-	0.21	-	0.02	-

ND = None detected

examinations. Only one sprayworker remained trouble free at the end of the 14 days' spraying, although one of the incidents reported (acute diarrhoea) was unlikely to have been related to the spraying. The main problem was severe skin irritation with burns on the feet. There were 5 workers using low volume sprayers who developed skin lesions on the feet, complicated by scratches and other trauma and infection. All showed delayed healing responses. The degree of skin damage was severe in most of the men. The worker using the high volume knapsack sprayer also developed a rash on his feet, around areas of skin trauma. It was reported as mild.

There were three other spraymen who developed severe skin irritation all as a result of poor working practice. Two were involved in spillages and in one of them there was also splashing of concentrate in the eye causing a severe conjunctivitis but no other effects. This subsided with no sequelae. This man also developed a severe erythematous rash of the trunk and groin and later developed what was described as 'weakness' a few days after the incident, associated with a lowered blood pressure. Recovery was rapid and complete. The third worker was soaked with the 2.0% spray and developed a severe groin irritation. All cases of skin rashes cleared in about 10-14 days with the use of local steroids and antibiotics to combat the supervening infection.

The final medical examinations at one week after spraying had ended showed no abnormalities on routine clinical examination. Chest X-rays were normal and urine was negative for albumen in all workers.

At the end of the two week spraying period those using 'Herbi' applicators had sprayed approximately 12.7 hectares, using 25.4 litres of 'Gramoxone'. The knapsack spraymen covered only 7.3 hectares, using 13.7 litres of 'Gramoxone'. Thus while the rate of application/hectare was roughly the same in the two groups, the 'Herbi' operators were able to cover almost twice the area and therefore use almost twice the amount of 'Gramoxone' at a much higher concentration. The economic implications of this form of spraying are thus obvious and it is not surprising that pressure has developed for low volume application to be cleared for use with paraquat.

DISCUSSION

A number of factors made this trial less satisfactory than planned, but sufficient information was forthcoming to enable a preliminary evaluation of the possible hazard in use of low volume applications of paraquat to be made. The most important consideration is the very high degree of skin contamination that occurred using high concentrations. Although both knapsack and low volume spraying applied equivalent amounts of paraquat per hectare, the low volume technique allowed a much greater area to be covered each day. At the end of the trial, those using the 'Herbi' had applied almost twice the volume of 'Gramoxone' that the knapsack sprayer had used and at a much higher concentration (2% paraquat ion against 0.15% paraquat ion). It is not, therefore, altogether surprising that there was a statistically significant difference between the amount of dermal contamination on those using the 'Herbi' applicator, including its modified form, and that on the knapsack sprayman after equivalent periods of application. The level of contamination for low volume sprayers was also much higher than that reported by Hogarty [36] for knapsack sprayers which did not go above 0.2 mg/25 cm^2.

This would almost certainly account for the rapid rise in the level of paraquat excreted in the urine of those using the 'Herbi' sprayer when the feet were unprotected. Although it has never been possible, in following cases of human paraquat poisoning, to show a direct correlation between plasma levels of paraquat and urinary excretion, it is certainly true that the level of urinary excretion among these workers matches that obtained after the oral ingestion of the equivalent of 1-2 gm paraquat ion. The urinary levels of paraquat in the 'Herbi' sprayers without foot protection were much higher than those reported by Swan from knapsack spraying or in the author's study reported above. Unfortunately, it was not possible to obtain plasma paraquat estimations on these workers, which might have provided more significant information.

However, of greater importance is the fact that unlike the urinary excretion of paraquat of the knapsack sprayer and those using the 'Herbi' with foot protection, there was a clear indication of rising urinary levels of paraquat among the unprotected workers as the trial progressed, the differences between the groups being statistically highly significant at the end of the second week. This could be interpreted to indicate that there was a rising body burden of paraquat and that the absorption/excretion equilibrium seen in the other workers and noted in other trials with knapsack spraying at high dilutions, was being overcome.

There seems little doubt that a major contributory factor in the increased absorption of paraquat was the marked degree of skin damage caused by the 2% paraquat solution used. Dr. Prasan noted that 5 of the 6 workers using the 'Herbi' applicator without foot protection developed skin damage on the dorsum of the foot, complicated by scratches and other minor trauma.

It needs to be remembered that these findings relate to a supervised trial. In the unsupervised conditions which frequently prevail in the developing countries, the problems with low volume spraying of paraquat by hand would certainly be much worse. There were two spillages in this trial which produced skin problems and it should be noted that the supervisors discouraged the spraymen from washing themselves. In a situation of prolonged or more intensive spraying, the degree of dermal contamination would be greater and carelessness, lack of hygiene, poor protection and other factors would combine to make the problem even greater.

2.5. CONCLUSIONS

The published data reviewed initially in this study, together with the evidence of the author's three investigations reported here, would indicate that neither the formulation of paraquat as commercial preparations nor high volume spraying at concentrations up to 0.5% (1:40 dilution of 'Gramoxone') are likely to pose any significant risk to worker health. Low volume spraying, using high concentrations of paraquat does, however, present a number of problems which will be discussed later.

The importance of the studies of formulation workers and the Malaysian estate sprayers lies in the fact that both groups of workers had experienced a long period of continuous occupational exposure. As was pointed out earlier, such circumstances are very rare for spraymen in temperate climates where spraying is generally seasonal and intermittent. The mean length of exposure in both formulators and spraymen was 5 years and in a number of cases was very much longer (up to 12 or more years). When this is associated with a lower degree of personal protection worn by the Malaysian spraymen, it is reasonable to assume that the degree of exposure was very much higher for these men than for their British or European counterparts. It is therefore important to note that, in spite of this long exposure period, there were no reports of any symptoms from these two groups of workers handling paraquat under very different circumstances that would point to significant systemic absorption, nor indeed were there any complaints of the nature of what has been termed the 'paraquat-fear syndrome', naively reported by Peoples and his associates [26]. Furthermore, as far as the spraymen were concerned, a wide range of clinical measurement failed to show any significant variation from the values in unexposed control populations.

The studies reported here indicate that the only clinical manifestations resulting from paraquat exposure under normal use conditions are the local effects on skin and mucuous membranes which are well documented and have already been discussed in detail.

The issue of low volume spraying at higher than hitherto recommended concentrations, however, raises very different problems. Exposure to solutions of paraquat at concentrations not much higher than that used in the Thailand trial have since been reported as causing fatalities through percutaneous absorption [38, 39], and other cases of death through dermal absorption have been reported in the literature as discussed earlier [40, 42,43]. In this particular trial the rising urinary levels of paraquat as spraying continued could be interpreted as evidence of an increasing body burden of paraquat in the spraymen and when this is taken in conjunction with the severe skin responses to the higher spray concentrations, the suggestion cannot be escaped that there was a strong possibility that health could have been seriously endangered had the spraying been allowed to continue for any length of time.

In spite of the economic advantages which low volume/high concentration spraying would bring, there can be no question that the practice would increase the level of risk to the sprayman considerably. Indeed, it is the author's opinion that the degree of risk is far too high to offset any other advantages that the practice might afford. Consequently, low volume/high concentration spraying with paraquat should be actively discouraged wherever it is discovered, especially as the equipment itself has often been modified inexpertly, increasing the level of risk even further.

In conclusion, it is perhaps pertinent to note that the types of study which were set up to investigate the various exposure situations have the advantage of being relatively easy to set up and yet are able to provide valuable information from which a realistic assessment of risk may be obtained. It is suggested that such experimental methods could be adapted easily for studying the risks allegedly posed by other pesticides which have become topics of public concern.

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APPENDIX 2.1: REGRESSION EQUATIONS FOR CLINICAL MEASUREMENTS

Regression equations fitted involved eight independent variables denoted by x_1, x_2 . . . . x_8 where;

x_1 = (1 for a sprayer
(0 for a general worker or factory worker

x_2 = (1 for a general worker
(0 for a sprayer or factory worker

x_3 = (1 for Indian
(0 for Malay or Chinese

x_4 = (1 for Malay
(0 for Indian or Chinese

x_5 = (1 for smoker
(0 for non-smoker

x_6 = No of cigarettes smoked a day

x_7 = Age (years)

x_8 = Height (cm)

Derived regression equations are set out as follows:

											% Fit
FVC	=	−4·448	+0·139x_1	+0·187x_2	−0·346x_3	−0·185x_4	+0·434x_5	−0·0115x_6	−0·0156x_7	+0·0507x_8	39
FEV_1	=	−3·837	+0·141x_1	+0·140x_2	−0·413x_3	−0·201x_4	+0·395x_5	−0·0160x_6	−0·0218x_7	+0·0461x_8	47
FEV%	=	88·53	+1·04x_1	−0·70x_2	−3·78x_3	−1·93x_4	+0·23x_5	−0·193x_6	−0·254x_7	+0·062x_8	20
DCO	=	5·16	−0·63x_1	+0·22x_2	−1·44x_3	−0·03x_4	−0·99x_5	+0·030x_6	−0·105x_7	+0·063x_8	44
Hb	=	13·04	−0·34x_1	+0·33x_2	+0·38x_3	+0·57x_4	+0·36x_5	−0·029x_6	−0·003x_7	+0·007x_8	10
PCV	=	37·61	−1·90x_1	−0·18x_2	−0·24x_3	+1·15x_4	+1·18x_5	−0·082x_6	−0·014x_7	+0·032x_8	14
RBC	=	5·599	−0·262x_1	−0·028x_2	−0·148x_3	−0·044x_4	−0·267x_5	+0·0105x_6	−0·0084x_7	+0·016x_8	15
MCV	=	69·85	+0·43x_1	+0·44x_2	+1·59x_3	+2·53x_4	+6·47x_5	−0·322x_6	+0·109x_7	+0·011x_8	24
MCH	=	24·11	+0·71x_1	+0·71x_2	+1·28x_3	+1·09x_4	+2·00x_5	−0·110x_6	+0·039x_7	−0·0003x_8	20
$\log_{10}$ WBC	=	4·2115	−0·0186x_1	−0·0771x_2	+0·0442x_3	+0·0065x_4	+0·0533x_5	−0·00416x_6	−0·00225x_7	−0·00133x_8	27
$\log_{10}$ AST	=	1·9974	−0·0300x_1	−0·0596x_2	+0·0859x_3	+0·0390x_4	−0·0606x_5	+0·00299x_6	−0·00061x_7	−0·00414x_8	9
$\log_{10}$ ALT	=	0·3417	+0·4302x_1	+0·3937x_2	+0·2790x_3	+0·1052x_4	−0·1726x_5	+0·00679x_6	+0·00344x_7	+0·00379x_8	57
$\log_{10}$ ALKP	=	2·0994	−0·0889x_1	−0·1366x_2	+0·0336x_3	+0·0568x_4	−0·1265x_5	+0·00338x_6	−0·00185x_7	−0·00308x_8	34
$\log_{10}$ CREAT	=	0·5176	−0·0383x_1	−0·0994x_2	+0·0632x_3	−0·0057x_4	+0·0479x_5	−0·00163x_6	−0·00031x_7	−0·00294x_8	23
$\log_{10}$ BUN	=	0·6444	−0·0757x_1	−0·0839x_2	−0·0145x_3	+0·0118x_4	+0·0279x_5	+0·00180x_6	+0·00133x_7	+0·00253x_8	23

APPENDIX 2.2: MALAYSIAN SPRAY WORKER STUDY - INDEPENDENT VARIABLES

OBS	x_1 SPRAYER	x_2 GEN_WORK	x_3 INDIAN	x_4 MALAY	x_5 SMOKER	x_6 CIGS	x_7 AGE	x_8 HEIGHT
1	1	0	0	1	1	10	55	61.5
2	1	0	0	1	1	5	25	63.5
3	0	1	1	0	1	7	41	64.5
4	0	1	0	0	1	25	23	68.5
5	1	0	0	1	0	0	43	63.0
6	0	1	1	0	1	10	54	64.0
7	1	0	1	0	1	10	25	67.5
8	1	0	1	0	1	10	28	68.0
9	1	0	1	0	0	0	32	66.0
10	1	0	1	0	1	3	43	61.0
11	1	0	0	1	0	0	19	62.0
12	1	0	1	0	1	10	24	65.0
13	1	0	1	0	1	40	44	64.0
14	1	0	1	0	0	0	28	66.0
15	0	1	1	0	0	0	17	65.0
16	0	1	1	0	1	10	18	62.0
17	1	0	0	1	0	0	19	62.5
18	0	1	0	1	1	6	24	64.5
19	1	0	0	1	1	10	25	61.0
20	1	0	0	0	0	0	47	61.0
21	1	0	0	0	0	0	16	63.5
22	0	1	1	0	0	0	29	60.0
23	0	1	0	1	0	0	53	64.0
24	1	0	1	0	1	20	30	64.0
25	1	0	0	0	1	20	51	67.5
26	1	0	1	0	0	0	38	65.0
27	0	1	0	0	0	0	39	63.0
28	0	1	0	0	0	0	38	65.0
29	0	1	0	1	1	15	37	64.0
30	0	1	1	0	0	0	34	65.0
31	0	1	1	0	1	10	45	63.0
32	0	1	0	1	1	15	34	64.0
33	0	1	0	0	0	0	30	61.5
34	0	1	1	0	0	0	29	59.5
35	0	1	0	0	0	0	29	67.5
36	0	1	1	0	0	0	25	67.0
37	1	0	0	1	1	15	49	66.0
38	1	0	0	1	1	12	32	66.0
39	0	1	0	1	1	15	25	63.0
40	0	1	0	0	0	0	35	66.5
41	1	0	1	0	1	5	45	61.5
42	0	1	0	0	1	20	32	63.0
43	1	0	0	1	0	0	41	61.0
44	0	1	0	1	1	15	28	62.0
45	1	0	0	1	1	12	24	68.0
46	1	0	0	1	1	15	23	66.0
47	1	0	0	1	0	0	18	60.5
48	0	1	0	1	0	0	24	68.0
49	1	0	0	1	1	20	46	62.0
50	1	0	0	1	1	20	30	63.5
51	0	1	0	1	0	0	43	63.0
52	0	0	0	1	0	0	19	67.0
53	0	0	0	1	1	6	22	61.0
54	0	0	0	1	1	12	21	63.0
55	0	0	0	1	1	4	21	60.5
56	0	0	0	0	1	3	45	62.5
57	0	0	[illegible]	0	1	40	53	63.5
58	0	0	1	0	1	7	45	63.0
59	0	0	1	0	1	10	21	65.5
60	0	0	0	1	1	18	19	64.0
61	0	0	0	1	0	0	19	66.0
62	0	0	0	1	1	15	32	62.0
63	0	0	0	1	1	12	19	62.5
64	0	0	0	1	0	0	30	62.5
65	0	0	0	1	1	12	24	64.5
66	0	0	0	1	0	0	19	64.0
67	0	0	0	1	0	0	43	64.0
68	0	0	0	1	1	8	27	61.0
69	0	0	0	1	1	6	23	64.5
70	0	0	0	1	1	15	28	60.5
71	0	0	0	1	1	7	41	63.5
72	0	0	0	1	0	0	18	61.5
73	0	0	1	0	1	8	40	67.0
74	0	0	1	0	0	0	28	61.5

APPENDIX 2.3: MALAYSIAN SPRAY WORKER STUDY - RESPIRATORY FUNCTION VALUES

OBS	FVC	FEV1	FEV1_PC	DCO
1	2.68	2.35	87.6	21.93
2	3.84	3.48	90.6	28.68
3	3.62	3.44	95.0	16.26
4	3.27	3.12	95.4	32.54
5	3.11	2.71	87.1	22.57
6	3.05	2.05	67.2	13.37
7	3.62	3.46	95.5	28.56
8	4.00	3.08	77.0	25.25
9	3.14	2.81	89.4	32.51
10	2.64	2.22	84.0	24.79
11	3.76	3.35	89.0	31.09
12	4.24	3.80	89.6	33.45
13	3.17	2.61	82.3	23.90
14	2.66	2.47	92.8	37.48
15	3.41	2.76	80.9	31.13
16	.	.	.	28.46
17	3.43	3.41	99.4	42.43
18	3.24	3.05	94.1	45.19
19	2.65	2.25	84.9	27.77
20	2.14	1.92	89.7	20.85
21	3.28	3.20	97.5	32.89
22	2.64	2.37	89.7	25.52
23	3.25	2.73	84.0	26.04
24	3.94	3.10	78.6	25.03
25	3.75	2.90	77.3	21.16
26	2.44	2.27	93.0	29.48
27	3.42	2.74	80.1	38.77
28	3.39	3.37	99.4	36.69
29	3.12	2.41	77.2	37.43
30	3.53	2.81	79.6	36.60
31	2.63	2.27	86.3	24.95
32	2.89	2.52	87.1	.
33	3.21	2.69	83.8	28.55
34	2.88	2.26	78.4	26.90
35	4.64	3.84	82.7	35.53
36	3.65	3.27	89.5	36.58
37	2.64	2.44	92.0	.
38	4.91	4.12	83.9	.
39	2.71	2.44	90.0	.
40	4.72	3.63	76.8	.
41	3.80	3.01	79.2	25.30
42	3.85	3.68	95.5	39.71
43	2.81	2.43	86.4	36.50
44	4.09	3.30	80.6	33.41
45	4.40	3.80	86.3	27.38
46	.	.	.	36.61
47	2.89	2.70	93.4	34.72
48	4.30	4.59	95.6	41.18
49	3.00	2.20	73.3	22.84
50	3.74	3.15	84.2	32.22
51	2.56	2.49	97.2	23.42
52	2.86	2.31	80.7	43.55
53	3.45	3.22	93.3	27.65
54	3.20	3.04	95.0	28.91
55	3.44	3.18	92.4	31.36
56	3.23	2.99	92.5	29.80
57	3.11	2.49	80.0	34.13
58	3.02	2.21	73.1	22.44
59	3.87	3.12	80.6	32.54
60	3.80	3.22	84.7	37.50
61	3.43	3.38	98.5	42.68
62	2.61	1.56	59.7	26.78
63	3.54	3.29	92.9	30.29
64	3.54	3.10	87.5	34.91
65	4.00	3.83	95.7	28.26
66	3.51	3.24	92.3	29.76
67	3.01	2.38	79.0	23.51
68	3.34	2.80	83.8	41.17
69	3.38	3.18	94.0	36.59
70	2.80	2.57	91.7	38.46
71	3.75	3.08	82.1	32.68
72	2.50	2.36	94.4	33.58
73	3.51	3.35	95.1	29.80
74	2.26	2.23	98.6	28.23

APPENDIX 2.4: MALAYSIAN SPRAY WORKER STUDY - HAEMATOLOGY VALUES

OBS	HB	PCV	RBC	MCV	MCH	WBC
1	15.5	44.7	5.69	78	27.2	5500
2	14.2	43.2	5.28	81	26.8	7100
3	14.7	41.4	4.79	86	30.6	9000
4	14.5	41.5	5.12	81	28.3	8300
5	14.3	42.2	5.10	82	28.0	9400
6	.	.	.	.	.	.
7	14.4	42.3	6.05	69	23.8	7200
8	16.6	45.6	5.56	82	29.8	12000
9	14.0	43.2	5.64	76	24.8	7400
10	12.7	37.5	4.10	91	30.9	8600
11	15.0	41.4	5.04	82	29.7	7500
12	13.1	37.6	4.89	76	26.7	9600
13	13.4	38.0	5.25	72	25.5	5200
14	16.1	43.3	5.62	77	28.6	6200
15	13.8	39.7	5.25	75	26.2	8000
16	.	.	.	.	.	.
17	14.3	42.1	5.47	76	26.1	14800
18	13.9	39.5	4.81	82	28.8	7800
19	13.0	38.4	4.55	84	28.5	10900
20	13.7	38.5	4.81	80	28.4	10000
21	13.0	36.9	5.14	71	25.2	7200
22	16.2	41.9	5.36	78	30.2	5400
23	16.3	48.2	5.74	83	28.3	5400
24	16.5	45.7	5.51	82	29.9	10400
25	12.3	34.8	4.33	80	28.4	7500
26	13.4	37.7	4.88	77	27.4	6700
27	14.0	42.3	5.27	80	26.5	7700
28	13.8	40.4	4.94	81	27.9	5900
29	15.5	45.0	5.75	78	26.9	4700
30	13.1	37.6	5.10	73	25.6	8100
31	15.0	40.7	5.29	80	28.3	8700
32	14.3	40.3	5.54	73	25.8	7800
33	13.4	41.7	6.89	60	19.4	6900
34	14.1	40.7	5.24	77	26.9	13300
35	15.0	45.4	6.08	74	24.6	7000
36	14.1	40.8	5.55	73	25.4	7600
37	13.4	42.3	4.97	85	26.9	6400
38	14.3	46.3	6.39	72	22.3	6200
39	16.7	48.2	6.00	80	27.8	6800
40	14.9	43.3	5.61	77	26.5	6500
41	14.0	40.4	5.01	80	27.9	14900
42	14.6	43.8	5.73	76	25.4	5800
43	15.5	40.7	5.31	76	29.1	6400
44	14.5	43.0	5.22	82	27.1	5600
45	.	.	.	.	.	.
46	12.3	35.8	4.39	81	28.0	8800
47	13.7	41.8	5.41	77	25.4	8200
48	16.9	47.8	5.84	81	28.9	8900
49	12.7	37.5	4.34	86	29.2	9000
50	15.6	44.3	5.69	77	27.4	11300
51	14.2	41.1	4.94	83	28.7	8000
52	14.0	42.0	5.08	82	27.5	9800
53	14.3	41.8	5.40	77	26.4	7900
54	14.5	43.2	5.31	81	27.3	10000
55	14.2	41.3	5.37	76	26.4	10200
56	17.9	52.5	6.00	87	29.8	7500
57	11.6	36.2	5.66	63	20.4	5300
58	13.6	39.9	4.74	84	28.6	10700
59	14.9	44.8	5.64	79	26.4	11600
60	14.3	41.8	5.65	73	25.3	3200
61	15.6	45.7	5.79	78	26.9	8600
62	15.8	46.7	5.83	80	27.1	10500
63	14.3	43.1	5.02	85	28.4	7300
64	12.2	39.1	6.41	61	19.0	11600
65	.	.	.	.	.	.
66	.	.	.	.	.	.
67	15.0	41.3	5.22	79	28.7	9600
68	.	.	.	.	.	.
69	14.5	42.1	5.19	81	27.9	10500
70	16.7	51.5	5.90	87	28.3	8400
71	14.0	40.1	5.10	78	27.4	7500
72	14.7	43.7	5.51	79	26.6	9600
73	13.5	39.5	4.72	83	28.6	8500
74	15.3	47.4	5.60	84	27.3	7700

APPENDIX 2.5: MALAYSIAN SPRAY WORKER STUDY - LIVER FUNCTION VALUES

OBS	AST	ALT	ALKP	CREAT	BUN
1	20	31	22	0.9	10
2	22	25	33	0.9	10
3	25	31	23	0.9	11
4	13	15	20	1.0	11
5	22	36	40	0.7	8
6	.	.	.	.	.
7	16	41	20	1.1	9
8	20	78	23	1.3	13
9	18	72	23	1.2	10
10	27	16	18	1.2	7
11	20	35	41	1.2	8
12	18	53	72	1.0	10
13	30	141	32	1.2	15
14	39	196	33	1.1	11
15	24	92	19	1.2	11
16	.	.	.	.	.
17	23	47	29	2.2	11
18	17	25	20	1.4	14
19	21	66	30	1.1	15
20	15	23	32	1.0	15
21	15	18	26	0.8	7
22	37	91	29	1.0	7
23	24	35	48	1.3	9
24	32	78	35	1.2	12
25	15	27	23	0.8	13
26	10	32	26	1.0	12
27	21	61	19	1.0	13
28	10	23	25	1.1	13
29	18	51	31	1.0	10
30	16	46	28	0.9	15
31	24	72	23	1.1	13
32	6	23	31	0.9	12
33	30	52	25	0.7	9
34	24	25	21	0.8	12
35	36	41	27	0.9	11
36	19	25	30	0.9	7
37	15	33	21	1.0	15
38	24	41	21	0.6	10
39	21	36	27	0.5	15
40	9	31	25	0.6	11
41	17	26	16	2.4	19
42	21	25	22	0.8	9
43	13	18	31	1.1	10
44	14	22	20	1.3	11
45	28	28	20	1.2	19
46	30	54	20	1.2	13
47	15	20	33	1.0	12
48	24	41	27	0.7	13
49	31	92	33	1.2	19
50	31	41	30	0.6	8
51	19	36	25	0.6	8
52	21	13	41	0.9	14
53	21	6	33	1.3	16
54	14	7	39	1.1	20
55	17	5	30	1.3	13
56	31	27	39	1.3	14
57	21	9	26	1.3	18
58	24	15	33	1.6	10
59	21	14	44	1.3	14
60	19	8	33	0.9	14
61	19	6	48	1.4	12
62	24	10	25	1.1	14
63	19	13	36	1.1	12
64	29	16	39	1.3	12
65	.	.	.	.	.
66	.	.	.	.	.
67	31	35	31	0.7	14
68	.	.	.	.	.
69	24	13	28	1.2	13
70	24	12	41	1.1	9
71	19	26	23	1.4	18
72	31	19	65	1.1	12
73	13	19	16	1.0	13
74	29	30	45	1.2	12

SECTION 3

THE MISUSE OF PARAQUAT: THE PROBLEM OF ACCIDENTAL AND INTENTIONAL POISONING

3 THE MISUSE OF PARAQUAT: THE PROBLEM OF ACCIDENTAL AND INTENTIONAL POISONING

3.1 THE EXTENT OF THE PROBLEM

It is not possible to gain an accurate picture of the size of the problem of paraquat poisoning on a world-wide basis. Few countries keep sufficiently accurate statistics and even where good recording systems exist they are often not sufficiently detailed to allow deaths from paraquat poisoning to be isolated from those caused by other agricultural chemicals. The general literature is also of little help in this respect as, although there have been a large number of reports of single fatal cases or small groups of cases, there have been remarkably few attempts to collate data from several sources or publish large series. Further, cases of survival from paraquat poisoning have been poorly documented and consequently the overall incidence of poisoning is difficult to define accurately.

The problem is compounded by the fact that frequently authors fail to make any distinction between accidental and deliberate poisoning in their reporting of cases and on other occasions purposive self-poisoning is reported as 'accidental', thus giving a very distorted picture. The following discussion, although limited by the quantity and quality of the data, will endeavour to provide some idea of the situation world-wide and also the relative importance of accidental and deliberate poisoning with paraquat.

Park and his colleagues [1] published a series of 31 cases treated in

Edinburgh and more recently Fitzgerald and his colleagues[2] have reviewed 136 cases of poisoning occurring in Ireland, between 1967 and 1977. This is the largest published series so far in the world literature and probably accounts for virtually all of the paraquat poisoning cases in the Irish Republic in this period. He and his colleagues have also published a short series of 13 cases of long-term follow-up after recovery from paraquat poisoning[3]. Carson and Carson have analysed 26 fatal and 7 non-fatal cases occurring in Northern Ireland between 1967 and 1975 [3a] and note that the incidence of paraquat poisoning has been proportionately higher in Ireland than elsewhere. The present author has published a series of 68 cases of poisoning occurring in Britain between 1975 and 1977 [4], but these were selected cases and the series is certainly incomplete as far as the total number of poisonings is concerned in these years. Wright and his co-workers [5] have also published a series of seventy cases from the Birmingham area relating the severity of poisoning to urinary paraquat excretion. From France Mme Conso has reviewed the experience of the French Poison Control Centres between 1970 and 1977[6], but again her series is admittedly incomplete as not all cases were reported to the Poison Centres. Fletcher [7] attempted to record all the published cases to 1974, but while giving some evidence of geographical distribution and the relative incidence of accidental and deliberate poisonings, such a review does not provide any real idea of the actual incidence of poisoning. There have been a number of other reports and reviews, but most of these collected cases have only examined one aspect of the problem, namely intentional poisoning, and have not addressed themselves to the parallel problem of accidental poisoning.

3.1.1 ACCIDENTAL POISONING

There are very few accurate statistics from which a picture can be built up of the world-wide incidence of accidental paraquat poisoning. The United Kingdom probably has the most complete figures currently available, derived from both official statistics and the record of paraquat 'incidents' maintained by ICI Ltd. The total number of accidental deaths from paraquat is small (table 3.1) and it is worth noting that since the introduction of better labelling in 1972, together with an eduction programme designed to warn farmers and others of the dangers of decanting agricultural concentrates into other containers (frequently soft drinks bottles) and the restriction of the sale of such concentrates to farmers and professional horticulturists, the number of deaths from accidental ingestion of paraquat has fallen quite dramatically. Further, the problem of accidental poisoning is restricted to the agricultural concentrates (Gramoxone, etc) and there are no records of any fatalities from accidents with the granular retail products. The difference between the pre-and post-1972 figures are just outside the limits of statistical significance ($t = 1.86$; $df = 4$; $P < 0.1$), but both the total sample and the annual figures are very small.

It is encouraging, however, to note the relatively small number of children involved in such accidents, a fact to which Fraser has recently drawn attention [8]. The four cases of fatal childhood poisonings between 1968 and 1972 represent 2.7 per cent of the total of 148 cases of fatal accidental child poisonings occurring in that period from all causes. The two cases that

TABLE 3.1 ACCIDENTAL POISONING DEATHS FROM PARAQUAT IN UK: 1968-1977

	Adults	Children*	Total	Mean/Year
1968-72	19	4	23	4.6
1973-77	12	2	14	2.8
Totals	31	6	37	3.7

* Source: Fraser N C, Brit Med J 1980; 280 : 1595-98

occurred between 1973 and 1977 are 1.9 per cent of the 105 fatal accidental poisonings of children in these years. However, the problem of distinguishing accidents from attempts at self-harm is difficult even in children and it is highly probable that some reported childhood 'accidents' are misrepresentations.

Evidence of the size of the problem elsewhere is hard to obtain. The author has examined the detailed figures for Japan collected by ICI (Japan) Ltd for the years 1975 and 1976 and in this period only three cases of paraquat poisoning were reported as accidental, all others being deliberate. The official Government statistics, however, differ from these, being considerably higher. The figures are set out in table 3.2. Total pesticide accidents are set alongside for comparison. It is possible that these figures represent under-reporting, but there are factors in the Japanese situation that, while tending to make intentional poisoning easier, militate against accidents. Of these undoubtedly the most important is the size of container used for the agricultural concentrate 'Gramoxone'. Because the great majority of Japanese farmers cultivate a very small area (generally no more than a small holding) there has been little demand for large quantities of concentrate, merely sufficient for a single application at the beginning of the growing season. 'Gramoxone' was thus marketed for commercial use, until very recently, in 100 ml plastic bottles and there was thus little likelihood of material being decanted into smaller unlabelled containers (the main cause of accidental poisoning). The small size of pack did, however, make ingestion with suicidal intent much easier. The recent change to a 1 litre container as part of a campaign to reduce suicidal use of paraquat may alter the situation.

TABLE 3.2 ACCIDENTAL PARAQUAT POISONING

IN JAPAN: 1971-1977

	Accidental Paraquat Poisoning			All Accidental Pesticide Poisonings		
	Fatal	Non-Fatal	Total	Fatal	Non-Fatal	Total
1971	6	1	7	28	9	37
1972	3	-	3	23	37	60
1973	2	1	3	12	8	20
1974	1	1	2	10	8	18
1975	6	1	7	14	28	42
1976	2	2	4	12	19	31
1977	6	-	6	22	11	33

Source: Annual Report of Japanese Ministry of Agriculture, Food and Fisheries, Tokyo 1978.

Accidental deaths have been reported from many other countries[9,10], but occasional incident reports do not provide any real indication of overall frequency. Furthermore, the looseness of terminology in many instances makes it difficult to decide whether a particular incident was genuinely accidental or deliberate. The general impression, however, is that accidental paraquat poisoning does not present a major problem and that on this ground alone, there is no reason for banning the product as too dangerous as some have proposed [11].

5.1.2 DELIBERATE SELF-POISONING

Once again, it is not possible to estimate the size of the problem throughout the world. It is known that a number of countries, such as the United States, do not have a problem with paraquat poisoning even though large amounts may be used in agriculture. The reasons for this probably relate to the patterns of use and general availability of the product as well as possible cultural preferences in suicide methods. On the other hand, a number of countries such as the United Kingdom, Eire and Japan do have significant numbers of deliberate self-poisonings each year.

The most accurate figures for the annual incidence of deliberate paraquat deaths probably come from Japan. The incidence of suicide from all causes is high in Japan, which reflects the fact that suicide has been rooted in Japanese culture from the days of ritual seppuku by the samurai as a face-saving and honourable form of death. According to Japanese government statistics, the annual suicide rate in Japan is about 15,000 to 20,000 in a population of approximately 114 million.

The great majority of suicides are caused by mechanical means (jumping from tall buildings, falling in front of trains etc.) and self-poisoning accounts for a relatively small percentage of the total deaths. Table 3.3 indicates the number of deliberate self-poisonings with pesticides in Japan between 1970 and 1977, the last year for which the author has been able to obtain complete figures for all pesticides. Total numbers have shown a steady decline, but both the real numbers and the proportion of paraquat poisonings show a marked increase. This trend has continued beyond 1977 through the years 1978 and 1979, by which time the number of paraquat poisonings had reached 110 per annum.

The equivalent figures for two other commonly used pesticides, parathion and malathion (both organo-phosphorus insecticides) are included to provide a comparison. It is worth noting that the dramatic decline in deliberate parathion self-poisoning was the direct result of government action. This insecticide was re-classified in 1972 as <u>tokutei dokubutsu</u>, that is 'special poison', which resulted in the very stringent regulations associated with this class of compounds being applied to parathion. As a result the possession and use of this pesticide was so severely restricted that it was effectively removed from the market and from general use within a very short time.

The other important point which emerges from these figures is the very high mortality associated with paraquat poisoning. Table 3.4

TABLE 3.3 DELIBERATE SELF-POISONING WITH PESTICIDES IN JAPAN: 1970-1977

	POISONING CASES							
	Paraquat		Parathion		Malathion		All Pesticides	
	Fatal	Non-Fatal	Fatal	Non-Fatal	Fatal	Non-Fatal	Fatal	Non-Fatal
1970	-	-	113	4	62	13	725	94
1971	40	2	83	3	66	9	574	110
1972	50	4	54	1	50	16	545	123
1973	36	6	41	3	47	10	423	118
1974	48	3	30	5	30	12	396	108
1975	82	1	6	-	30	13	423	103
1976	82	6	21	1	nr	nr	405	108
1977	101	8	11	-	nr	nr	410	103

nr : not reported separately

Source: Annual Report of Japanese Ministry of Agriculture Food and Fisheries, Tokyo 1978.

TABLE 3.4 MORTALITY FROM DELIBERATE SELF-POISONING WITH PESTICIDES IN JAPAN: 1971-1977

Year	Mortality (%)	
	Paraquat	All Other Pesticides
1971	95.2	83.2
1972	92.6	80.6
1973	85.7	77.6
1974	94.1	76.8
1975	98.8	76.9
1976	93.2	68.4
1977	92.7	69.3

The differences in mortality rates are highly significant

($t = 6.93$; $df = 6$; $P < 0.0005$)

compares the mortality from paraquat ingestion with that for all other pesticide poisoning in Japan for the years 1971-1977. All pesticide poisonings are associated with a high mortality, no doubt to be associated with the large amounts ingested, but the mortality from paraquat poisoning is significantly higher than that for all other pesticides ($t = 6.93$; $df = 6$; $P < 0.0005$). As will be discussed later, this high mortality is almost certainly linked to the fact that only the 20% agricultural concentrate ('Gramoxone') is available in Japan and also that it is relatively easy to obtain. Consequently, a large amount of paraquat may be ingested easily with fatal results.

High mortalities are also to be found in other countries where only 'Gramoxone' and similar high concentration formulations are available and where suicide rates are higher. Eastern Malaysia and Western Samoa have shown similar patterns of mortality to Japan (J. K. Howard 1977, unpublished ICI Internal Report). In Western Samoa there are about 25 or more cases of paraquat self-poisoning every year in a population of only 153,000. The mortality approaches 90 per cent and what is particularly tragic about many of these cases is that they involve young people as the result of relatively minor domestic upsets. What set off as a mere gesture or a 'cry for help' turns into an irreversible tragedy (J. K. Howard, unpublished observations).

The size of the problem in the United Kingdom in absolute terms is much smaller than Japan, although the total number of both fatal and non-fatal poisonings is not known. It is, however, possible to provide a reasonable estimate of numbers. It is known that the National Poisons Information Service deals with approximately 300 calls per year relating to paraquat poisoning (J. A. Vale 1979, personal communication). A large proportion of these are 'false alarms', but is is estimated that about 70-80 of these do represent genuine paraquat self-poisonings. Many of them will be trivial, little more than 'gestures', using very small amounts of retail granular formulations such as 'Weedol'. The mortality from these attempts may be estimated approximately from the Registrar General's statistics, although changes in classification make it difficult to compare year with year. In 1979, however, there were 31 deaths from self-administration of 'farming and gardening preparations, not plant foods or fertilizers' (Class E863) and it is likely that most, if not all, these deaths were due to paraquat. The total suicide deaths for 1979 were 4195, so that paraquat deaths account for well under 1 per cent of the total. According to ICI Ltd records, the number of paraquat fatalities for 1980 was about 37 (L.L. Smith 1981, personal communication).

It will be apparent that the mortality in the United Kingdom appears to be very much lower than in other countries. An estimate from the combination of the Registrar General's figures and the total cases reported both to ICI Ltd and the National Poisons Information Service would suggest a mortality of about 40 to 50 per cent. This is in broad agreement with other estimates that put mortality in the region of 60 per cent [1,2,4,9,12]. There would appear to be two main factors which probably account for this lower mortality compared with Japan. The first is that the liquid agricultural concentrates containing 20% paraquat ion (e.g. 'Gramoxone') are less easily obtained by the general public in the UK than they are, say, in Japan. They are properly only available to bona fide farmers and horticulturists and the 'poisons book' should be signed on purchase. Secondly, there is an increasing tendency by would be suicides to use the retail granular preparations such as 'Weedol' for deliberate self-poisoning. These have a low concentration of paraquat ion which means that a large quantity of a highly unpalatable material must be ingested before it would prove fatal. The past few years have seen a marked shift to the use of such easily obtained formulations with a consequent reduction in mortality (J. A. Vale 1979, personal communication). The problem of deliberate self-poisoning thus does not appear to be a major problem in the United Kingdom in terms of total numbers.

Small series of cases from a number of other countries have been published. The Swiss Poison Control Centre dealt with 14 cases of paraquat ingestion in the period 1966-1975 [13]; the Dutch Poison Control Centre has reported on 15 cases of deliberate ingestion from 1964 to 1974 [14] and the French Poison Control Centre on 45 cases of poisoning by ingestion, of which 20 cases were deliberate [6]. Suicides in Malaysia have only been analysed up to 1972 [15], but between 1968 and 1972 there had been 82 cases of deliberate self-poisoning with herbicides of which 56 were due to paraquat. There were 61 deaths, most of which may be presumed to have been from paraquat ingestion although this is not stated. It is recorded, however, that mortality was very high. The total recorded cases of intentional poisonings using all agrochemicals including insecticides was 604, with 395 deaths, in a population of 12.6 million and with 1749 total recorded suicides. Two things need to be said about these figures. Firstly, they are obviously incomplete as many suicides are not investigated nor even reported in Malaysia, particularly in rural areas. The problem is thus most likely to be larger than reported. Secondly, there appears to be some confusion between accidents and suicides, both categories being reported together as suicides. Paraquat poisoning in Eire has been extensively reviewed by Fitzgerald [2,16]. The general religious ethos of the country, however, almost certainly has led to reporting errors and it is not easy to set Fitzgerald's 136 cases into a context of all deaths from poisoning, nor of suicides generally. It is likely, however, that in terms of total cases per unit of population the Irish Republic has the greatest problem; as Fitzgerald remarks[16], it is 'an unenviable record'.

3.2 APPROACHES TO THERAPY

A consideration of the pharmacokinetics of paraquat, as discussed in Section 1, with especial reference to the rapid peaking of plasma levels after ingestion, underlines the necessity of therapeutic measures to be introduced at the earliest possible moment in all cases of significant poisoning if there is to be any chance that treatment will be effective. As with all cases of poisoning, irrespective of the agent, treatment may be directed towards,

(a) the prevention of significant absorption of the material from the gut by rapid removal/elimination or neutralisation,

(b) the rapid removal of absorbed material from the circulation and,

(c) the introduction of specific therapeutic measures designed to inhibit or block the action of the poison in the body or neutralise its toxic affect on body processes.

All three of these approaches have been tried in cases of paraquat poisoning with very varying degrees of success. Before going on to discuss the various forms of treatment that have been advocated it is necessary to consider briefly the indications for starting active treatment in cases of paraquat poisoning.

3.2.1 INDICATIONS FOR ACTIVE TREATMENT

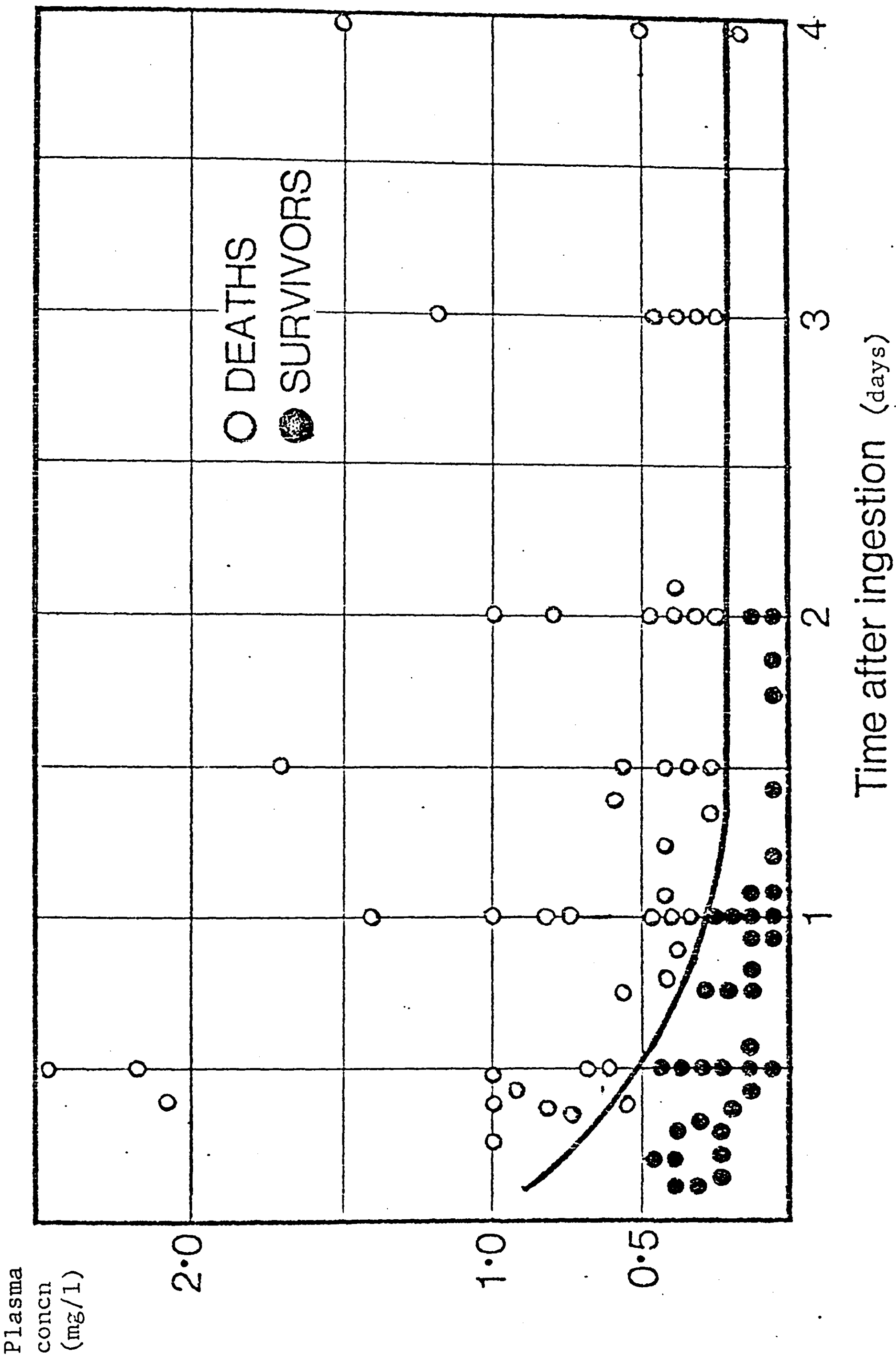
The onset of serious symptoms may be delayed in cases of paraquat poisoning. Clinical symptoms are therefore not a good indication of the severity of poisoning. Treatment should be based in the first instance on the history provided by the patient or by a relative or friend. This should be coupled with the simple qualitative test that may be applied to the urine to determine whether or not paraquat is being excreted. As a stomach wash-out should also be performed as a routine emergency measure in all cases of suspected paraquat poisoning, the same qualitative test may be applied to the stomach contents (or vomitus). It must be emphasized, however, that while such qualitative tests will confirm whether or not paraquat has been ingested, they are of little value in prognosis and may, at times, give misleading results. It has been suggested [5] that an urinary excretion of paraquat of more than 1 mg per hour after eight hours have elapsed from ingestion is indicative of a poor prognosis. It should be noted, however, that if therapy is to be effective, it is essential that it is begun long before eight hours after ingestion.

The value of the history from the patient is related principally to two matters: the time at which the paraquat was ingested and the approximate amount taken. In those cases in which one of the granular formulations has been used, it is usually possible to obtain an accurate estimate of the amount ingested, but in cases in which the liquid concentrates have been used, this is often more difficult to determine and it may only be possible to make an approximate estimate of the quantity taken. The importance of these factors will be discussed later.

The history, taken in conjunction with the qualitative tests of urine or gastric contents for paraquat, may be used as indications to start treatment and a good history is likely to provide some guidance on the likely outcome and effectiveness of that treatment. Further objective guidance may be obtained from the results of plasma paraquat estimations. Relatively simple colorimetric [17] or the more recently introduced radio-immunoassay methods [18] may be used to provide rapid estimations of the plasma paraquat concentration. Proudfoot and his colleagues [19], in a two centre survey have been able to demonstrate the prognostic value of such measurements, showing that there is a good prognosis in those patients whose plasma paraquat concentrations do not exceed 2.0, 0.6, 0.3, 0.16 and 0.1 mg per litre at 4,6,10,16 and 24 hours respectively after ingestion. This conclusion is borne out by hitherto unpublished data from cases for whom plasma paraquat estimations were performed at ICI Ltd, Central Toxicology Laboratory (fig 3.1).

The patient's history taken in conjunction with the plasma paraquat concentration determined on blood taken at the time of hospital admission, will provide a rational basis for the physician to decide whether treatment should be vigorously pursued or whether it should be merely palliative.

FIG. 3.1: PLASMA PARAQUAT CONCENTRATIONS RELATED TO TIME FROM INGESTION



3.2.2 TREATMENT METHODS

THE PREVENTION OF ABSORPTION

The first approach in the prevention of absorption of any ingested material is its removal from the stomach. Because of the rapidity of absorption, evidenced by early peak plasma paraquat levels, it is essential that vomiting should be induced as a first aid measure (one of the few occasions when the induction of vomiting should be recommended). The further aspiration of stomach contents or gastric lavage should be undertaken as soon as the patient arrives at hospital. By themselves, such measures are unlikely to be life saving and fatalities have followed effective gastric lavage even when performed within one hour of ingestion [20-22]. Moreover, since the undiluted commercial formulations of paraquat are highly irritant and corrosive, great care is necessary in the passing of stomach tubes to prevent perforation of the oesophagus or stomach [10].

The work of Smith and his colleagues[23], following on the studies of Clark [24], has provided a rational basis for the use of clay-based absorbent materials in order to bind the paraquat lying in the gut and prevent any further absorption into the body. Their work demonstrated that the administration of Fuller's Earth to paraquat-dosed rats dramatically increased their survival and it was suggested that the use of this material should form the basis of the treatment of human poisoning.

A variety of other adsorbent materials have been evaluated [25], but the naturally occurring aluminium silicate-based minerals (Fuller's Earth, bentonite, etc) are undoubtedly the most efficient, which accords with what is known of the inactivation of paraquat by the soil [26] (see also Section 1.2). There are differences, however, in the adsorbent qualities of these minerals and Fuller's Earth is the most efficient binder of paraquat. Table 3.5 sets out the differences in adsorbing capacity between Fuller's Earth (Surrey finest grade) and another naturally occurring aluminium silicate used for therapeutic purposes ('Adsorbin', Sankyo Ltd). This latter material will be seen to have about 70 per cent of the capacity of Fuller's Earth, weight for weight. The adsorbent should be administered as a 10 per cent suspension, the volume required will be discussed later.

The administration of the adsorbent material should be associated with vigorous purgation in order to flush the gut as quickly as possible. Mannitol solution (20%) is probably the best purgative available and a satisfactory faecuresis will usually be obtained with doses in the range of 200 to 400 ml, although this may need to be repeated for several doses. The dose required, in fact, is simply that necessary to produce rapid and as near complete as possible purging of the gut, which should be continued until there is evidence of the adsorbent material being passed in the faeces. This should be achieved as rapidly as possible, certainly within four hours of instituting therapy [27].

TABLE 3.5 ADSORPTION CAPACITIES FOR PARAQUAT OF TWO NATURALLY OCCURRING ALUMINIUM SILICATES

	Mg paraquat adsorbed/g dry weight clay	
	Maximum adsorption capacity	Tightly bound capacity
Fuller's Earth (Surrey finest)	63	30
Adsorbin (Sankyo Ltd)	50	20

Data from Prashad S, 1979 (personal communication)

Two considerations will affect the success of this form of therapy. The first is the volume of adsorbent material administered. If a dose of 5 g of paraquat ion has been ingested (equivalent to only 25 ml of 'Gramoxone') then, on the basis of the data in table 3.5, something in the order of 100 g of adsorbent clay will be required to bind this paraquat in the gut, that is 1 litre of a 10 per cent suspension. In cases in which commercial concentrates have been used the amount ingested will frequently be in excess of 5 g paraquat ion, thus requiring the administration of very large volumes of Fuller's Earth suspension over a very short time span.

It seems highly probable that in the past there has been serious undertreatment of paraquat poisoning, both in respect of the amount of adsorbent material administered and the period of time over which it has been given. There seems little doubt that the earlier use of the rat as a model for human poisoning seriously misled many workers and it was too readily assumed that paraquat absorption was relatively slow allowing a long time span for the administration of adsorbents. The early editions of the ICI Ltd Treatment Booklet issued to hospitals and treating physicians in the United Kingdom and elsewhere, for example, suggested that Fuller's Earth could be effectively administered for as long as 48 hours after paraquat ingestion. Such treatment regimes are no longer tenable and, in the light of present knowledge, should be considered virtual malpractice.

The clinical problems associated with the administration of such large volumes of fluid over such a short time period are considerable. Such suspensions are highly unpalatable and it is not uncommon for patients to be unable to swallow these large quantities of unpleasant fluid, particularly if there is associated oral or bucco-pharyngeal ulceration. Higher concentration suspensions (up to 30 per cent) were previously advocated, but these are more unpalatable than the weaker suspensions, more difficult to swallow and, in addition, there is the likelihood of the material impacting at the pylorus.

The use of gastric or duodenal intubation may help to overcome this problem, but, although not widely used in the United Kingdom, the best means of both administering adsorbent and clearing the gut is by the use of gut lavage as advocated by Okonek and his co-workers [28, 29]. The technique involves the rapid passage of a large volume of fluid (14 to 18 litres) through the gut at a rate of about 75 ml per minute using a stomach tube and peristaltic pump. The irrigation fluid is normally a physiological solution such as Ringer's solution and 250 to 500 ml of a 10 per cent suspension of an adsorbent clay is fed into the gut each hour through a by-pass. The whole procedure is completed in less than 4 hours. Such therapy is not without its complications, however. Perforation of the gut wall may occur (particularly oesophagus or stomach) and fluid and electrolyte balance may be seriously disturbed and will require careful maintenance and continuous monitoring.

The second limiting factor that will reduce the effectiveness of adsorbent/purgative therapy has already been alluded to briefly, namely the speed at which paraquat is absorbed from the gut into the circulation. Recent animal work (discussed in Section 1.2) together with observations such as those of Proudfoot [18], indicate that most absorption will have taken place within four hours from ingestion. Unless vigorous therapy can be instituted within this time, it is unlikely to be effective in those patients who have taken potentially lethal amounts. The importance of the time factor in treatment will be demonstrated later in the discussion of the author's series of cases. Delayed treatment together with under-treating may be responsible for the failure of Fitzgerald and his colleagues [30] to demonstrate any improvement in survival after paraquat poisoning when comparing mortality before and after the introduction of the Fuller's Earth regime in an extensive survey of Irish experience.

THE REMOVAL OF PARAQUAT FROM THE CIRCULATION

Paraquat does not bind to plasma macromolecules (Rose M S, 1976, unpublished data) and may thus be removed readily from the circulation by both haemodialysis and haemoperfusion. The latter, using charcoal columns, is much the more efficient and effective down to very low plasma concentrations of paraquat [28, 29, 31-39]. Clearance values of approximately 90 ml/minute may be obtained with some columns at plasma concentrations in the range of 1.0 to 20.0 mg/litre. At plasma concentrations below 1.0 mg/litre, although the efficiency is markedly reduced, it is still effective (Widdop B, 1978, personal communication).

It is important to distinguish clearly between two very distinct possible indications for the use of haemoperfusion or haemodialysis. These measures may be used to remove paraquat from the circulation or they may be used to support the kidney through a period of transient or incipient failure* resulting from the toxic effect of paraquat. Both the indications and the likely effectiveness in these separate situations are very different, but this is not always made clear in the numerous literature references. Kidney support in renal failure is of great clinical value, but although there is no doubt about the effectiveness of haemoperfusion in removing paraquat from the circulation, there is more doubt about its real therapeutic value when used for this purpose.

The most important factor limiting the therapeutic effectiveness of these measures as a treatment for paraquat poisoning is, once again, that of time from ingestion. Haemoperfusion is only indicated in those situations where the plasma paraquat levels are approaching or exceeding the critical concentrations at given times[18]. In the great majority of cases in which such treatment would be of value, the peak plasma levels and the bulk of absorption has taken place before haemoperfusion could be started. By that time the target organs will have already received a substantial (and possibly lethal) dose of paraquat and the reduction of circulating levels will have little effect in preventing the vicious cycle of pathological change.

Even when it has been possible to set up haemoperfusion within three hours of poisoning, it has not prevented fatalities [28,31,32,39] and, as will be discussed later, these measures failed to show any clear evidence of benefit in the author's series. However, note should be taken of the two cases reported by Okonek and his colleagues [37,38] in which plasma paraquat levels were greatly in excess of the critical values indicated by Proudfoot [18] or reported here (fig 3.1). The presumed dose was in the order of 15 to 20 g paraquat ion (3 to 4 mouthsfull of 'Gramoxone'), a dose at which there have been no survivors in the author's series, previously reported [4] or discussed later, nor in the extensive survey of Fitzgerald [2]. Haemoperfusion was maintained for two to three weeks for 8 hours per day suggesting that if it is begun early enough and pursued with vigour, it may be possible to remove paraquat from the circulation at a rate faster than the lung is able to accumulate it. Further clinical experience is required before Okonek's claims for haemoperfusion can be generally substantiated. The fact that it is now possible to make quite accurate predictions of the likely outcome of poisoning on the basis of plasma paraquat estimations makes the evaluation of the actual effectiveness of such newer methods of treatment a real possibility.

Forced diuresis has been advocated by some workers [40-42], but it has no real place in the treatment of paraquat poisoning. As noted earlier (Section 1.2) paraquat is excreted by glomerular filtration coupled with active tubular transport. Neither of these excretion mechanisms is affected by forced diuresis and in consequence the use of this procedure will not increase the renal excretion of paraquat. Further, it is a potentially highly dangerous technique, particularly in paraquat poisoning in which there is likely to be early renal damage. Even if this is transient, the administration of large volumes of fluid with diuretics is likely to be an embarrassment to the kidney and will lead to the patient becoming rapidly waterlogged. Such a situation will dramatically, even fatally, increase the pulmonary oedema.

THE USE OF 'ANTI-PARAQUAT' THERAPY

There have been a number of approaches to the treatment of paraquat poisoning which have been designed either to prevent or to reverse the effects of paraquat on the end organs. Some of the more important of these will be discussed briefly.

(a) Superoxide dismatase (SOD) and d-propranolol

The endogenous enzyme SOD, which dismutates the superoxide radical to form hydrogen peroxide (see Section 1.2.3), prevents the formation of other free radical species (especially the hydroxyl radical). The fact that the superoxide radical is produced as a result of the cyclic reduction and oxidation of paraquat in the cell has led a number of workers to advocate the use of SOD to 'mop up', the excess superoxide ions. The measure was given some support from the in vitro effectiveness of SOD in rat liver microsomal systems[43]. To this was linked the use of β-adrenergic blocking agents such as d-propranolol which were thought to displace either or inhibit the uptake of paraquat by the lung as demonstrated by in-vitro studies[44]. Although some success was claimed by a number of workers for this approach to treatment [45-49], these claims have not been borne out by further experience, either experimental or clinical [50-52]. Further, considerations of the biochemical mechanisms in paraquat poisoning (see Section 1.2) make it unlikely that the application of exogenous materials would affect sub-cellular events. This form of therapy was not used in any of the 108 cases collected by the author and to be discussed later.

(b) <u>Anti-inflammatory agents and immunosuppressants</u>

The use of anti-inflammatory agents, particularly steroids and a variety of immunosuppressants, such as bleomycin, azathioprine or cyclophosphamide, have been used separately or in various combinations in the treatment of paraquat poisoning [32,47,53-56]. The approach is purely empirical. Because there is an inflammatory component in the toxic response and because fibrosis is the dominant pulmonary effect, these agents were used in an attempt to reduce inflammation and reverse the fibroblastic response. While there may be some palliative value in the use of steroids, these agents have no effect on the development of the toxic tissue damage and the ultimate fibrosis.

It has been argued that steroids have a place in those cases in which there has been severe adreno-cortical damage [57]. The use of steroids in such cases, however, while of value in reversing the effects of adrenal shock, is unlikely to prove of lasting effect since doses sufficiently high to cause adrenal insufficiency will be invariably fatal.

(c) Hypoxic regimes and PEEP ventilation

The enhancement of paraquat toxicity by high ambient oxygen tension is a direct corollary of the consideration of the theoretical aspects of paraquat poisoning and has been demonstrated in animal experiments [58-61]. For this reason it is important to withhold the administration of oxygen to those suffering from paraquat poisoning until as late a stage as possible. On the other hand, the administration of hypoxic breathing mixtures is of very limited value in cases of human poisoning [32,50], and has not protected the lung against the toxicity of paraquat in experimental animals [62,63], in spite of some early claims to this effect [64].

A variant approach to low oxygen therapy has been pursued by Douze and his co-workers in Holland [65-67]. The principle of the method is to reduce arterial oxygen tension to between 50 and 70 mm of mercury by the administration of nitrogen, together with positive end-expiratory pressure ventilation (PEEP). The patient is sedated with the use of diazepam and muscular paralysis is achieved with tubocurarine. At the same time as artificial ventilation is applied, there is a programme of vigorous haemoperfusion. It is very difficult, however, to judge the real effectiveness of this form of therapy. It is certain that treating physicians would agree that the use of PEEP is valuable in the terminal care of paraquat poisoning, allowing easier nursing and preventing the gross dysproea which is distressing to patients, relatives and staff (Vale J A, 1978, personal communication). Claims for the success of this form of treatment in paraquat poisoning are much less certain. In theory PEEP ventilation should help to prevent atelectasis and reduce pulmonary oedema, but clinical evidence for this is sadly wanting and the relatively small reduction of arterial oxygen tension would have no effect on tissue concentrations. As an active therapy, PEEP ventilation with low oxygen therapy has not been satisfactorily demonstrated to have any significant effect on the course of poisoning. On the other hand, PEEP ventilation certainly has a place in general supportive therapy.

One point should be added: although low oxygen therapy has not been shown to have any clinical benefit, it is well established that the administration of oxygen at concentrations greater than ambient is contraindicated, except as a last resort in terminal cases. In all cases of paraquat poisoning, the use of oxygen should be delayed for as long as possible.

3.3 THE EFFECTIVENESS OF THERAPY

There have been a large number of reports of recovery after paraquat poisoning, sometimes claimed to be as a result of the use of one or another form of therapy. Some reports frequently fail to provide details of the dose of paraquat ingested, or the length of time that had elapsed before therapy was started. Any investigation of the effectiveness of therapy must take both these basic considerations into account. The obvious measure of success is the number of patients surviving after a potentially lethal dose, but an additional measure is the length of survival time in fatal cases indicating whether treatment increased the period of survival in fatal cases. Both these indicators of effective therapy will be examined in turn.

3.3.1 LENGTH OF SURVIVAL IN FATAL POISONING

The effectiveness of therapy will be shown primarily in improvements of overall survival rates, but the length of survival after ingestion of fatal doses will also give some indication of whether newer forms of therapy are having an effect on the clinical course. In order to determine whether there was any objective evidence for a change in survival time as the result of changes in treatment, it was decided to examine the data existing in the 'Incident File' of ICI Ltd from 1970 to the end of 1978. The records are not complete, but numbers are sufficient for comparative purposes. The use of Fuller's Earth with purgatives, together with haemodialysis and haemoperfusion became generally established in treatment from the beginning of 1975. The cases were therefore divided into those occurring up to December 1974 and those occurring thereafter. Only those cases for which there was a reasonable estimate of dosage were used in the comparison and it was also decided to omit those cases in which dosage was sufficiently high that the outcome of poisoning was unlikely to have been affected by therapy (on the basis of published evidence [52], this was set at 10g paraquat ion). A large number of cases in the files were excluded on this criterion as doses were too high or not recorded. It must be recognised, also, that in most cases of poisoning with liquid concentrates, the estimates of dosage are likely to be no more than approximations.

The results of this comparative study are set out in table 3.5. It is apparent that there is a very marked difference between the mean survival times in the two group, although mean doses are very comparable. A Student's 't' test applied to the two sets of survival times indicates a difference between them of such high mathematical significance that some factor or factors appear to be operating in one group and not the other ($t = 3.1$; $df = 42$; $P < 0.0025$).

While it may reasonably be concluded from this data that the introduction of newer treatment methods has done nothing to increase the survival time in fatal cases, it is not so easy to account for the highly significant reduction in survival time from a mean of nearly 11 days to less than half that time at equivalent dose levels. It could be that over-heroic therapy has hastened the patient's death in the past by some upset in electrolyte and fluid balance. Further, it is known that a number of cases certainly have occurred in which there has been fatal perforation of a friable oesophagus by a stomach tube and in which there has been fatal inhalation of Fuller's Earth. It is difficult however to

TABLE 3.5. COMPARISON OF SURVIVAL TIMES IN FATAL CASES OF PARAQUAT POISONING AT INGESTED DOSES BELOW 10g PARAQUAT ION, BEFORE AND AFTER DECEMBER 1974

Period	No. of Cases	Mean dose (g) (below 10g)		Mean Survival time (days)	
		Mean	SD	Mean	SD
Jan 1970 - Dec 1974	17	6.0	3.0	10.7	10.8
Jan 1975 - Dec 1978	27	6.7	3.3	3.8	3.4

(Differences between survival time are highly significant : $t = 3.1$; $df = 42$; $P < 0.0025$)

to account for such a marked reduction in survival time by iatrogenic causes alone.

It is possible, however, that with the increasing recognition that intensive supporting therapy is of little value in those cases where a downhill course is apparent, there has been less willingness to submit patients to heroic measures which, while maintaining life for a period, have no influence on the eventual outcome and could very well be uncomfortable or even distressing to the patient. The reduction in survival time may thus reflect a reduction in the use of life support systems in recognisably fatal cases, but this is no more than a surmise. What may be said, however, is that the available evidence indicates that newer treatment methods have not increased this period of survival from ingestion to death in fatal cases.

3.3 RECOVERY RELATED TO THE TIME TREATMENT WAS INSTITUTED, TREATMENT METHOD AND INGESTED DOSE

A total of 108 cases were followed-up by the author in the period 1976-1979 as a result of the co-operation of treating physicians. The data collected included the age, sex and as far as possible the occupations of the patients, together with details of therapy, clinical and laboratory measurements and the eventual outcome. The time that had lapsed between ingestion and the institution of therapy was noted in all but twelve of the cases. Urine and plasma levels of paraquat were recorded where these were available. The actual number of deliberate paraquat poisonings was greater than the 108 reviewed, but for the purpose of this study it was decided to include only those cases in which there was a clear statement of the amount ingested. Cases in which the statement of dosage was in such terms as 'a mouthful' were rejected as not being sufficiently precise.

The approach to treatment in all cases reviewed comprised the standard recommended treatment: the initial induction of vomiting and/or gastric lavage, followed by the oral administration of repeated doses of Fuller's Earth suspension and saline purgatives or mannitol. Additional therapeutic measures included the use of forced diuresis, haemodialysis and haemoperfusion, together with corticosteroids and immunosuppressive agents.

RESULT AND DISCUSSION

The age and sex distribution of the 108 cases is shown in Figure 3.2. There were 84 males (77.8%) and 24 females (22.2%). The age distribution in both sexes is skewed, but two peaks appear among the males (between 20 and 30 years and 50 and 60 years of age) whereas only a single peak occurs in the case of females (between 30 and 40 years of age).

As will be seen from the figures, these two age groups in males (ie from 20 to 30 and 50 to 59 years of age) account for 50% of all the male paraquat poisoning cases. The reasons for these age peaks is not clear although unemployment may have been a factor in some suicides. Similarly, the female peak between 30 and 39 years of age accounts for approximately 30% of cases and over 50% fell in the age group 30-49 years. Menopausal depression may have been a factor in some of these cases. Virtually half the episodes (46.7%) occurred in the summer months

FIG 3.2: AGE AND SEX DISTRIBUTION OF PARAQUAT POISONING

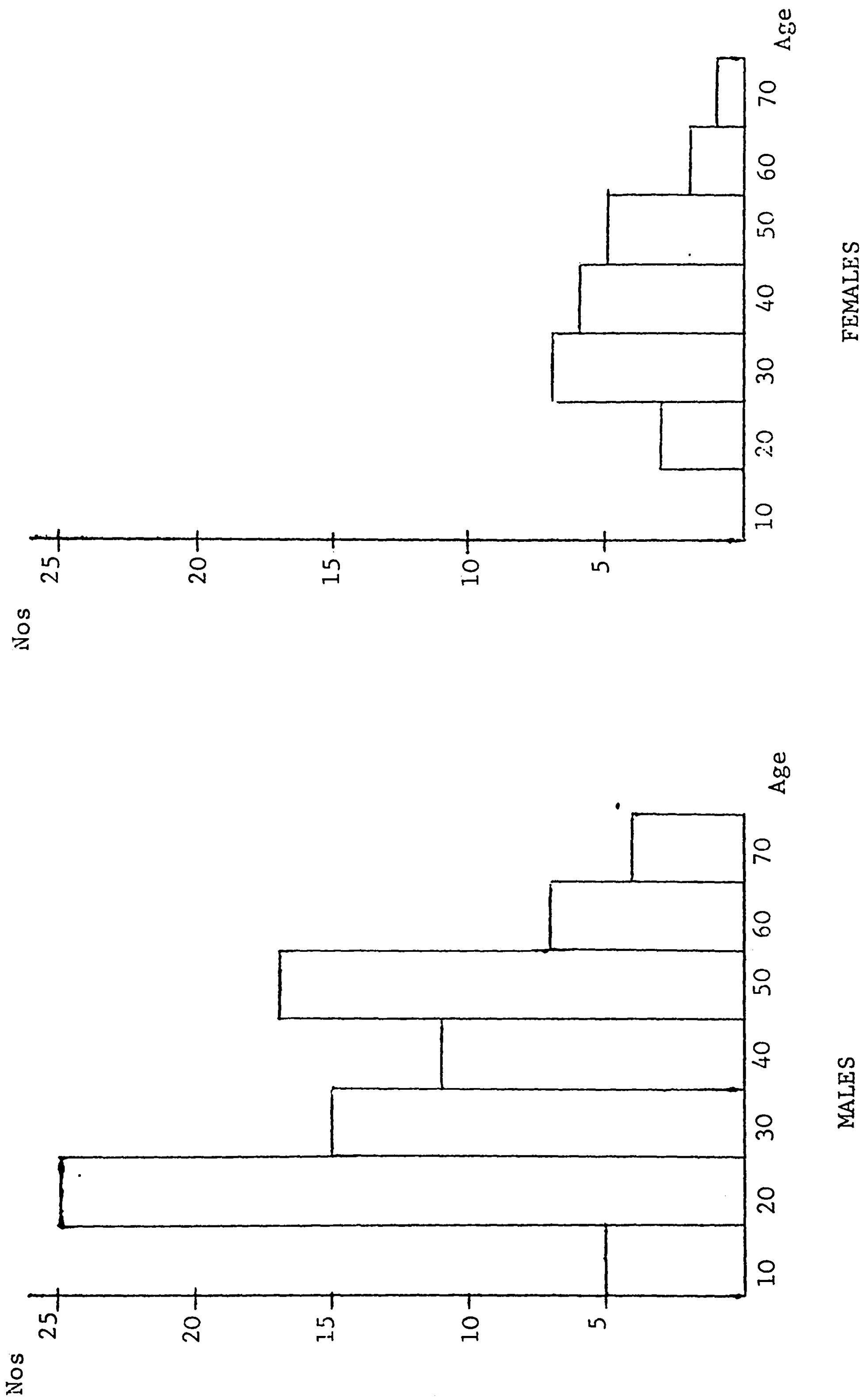
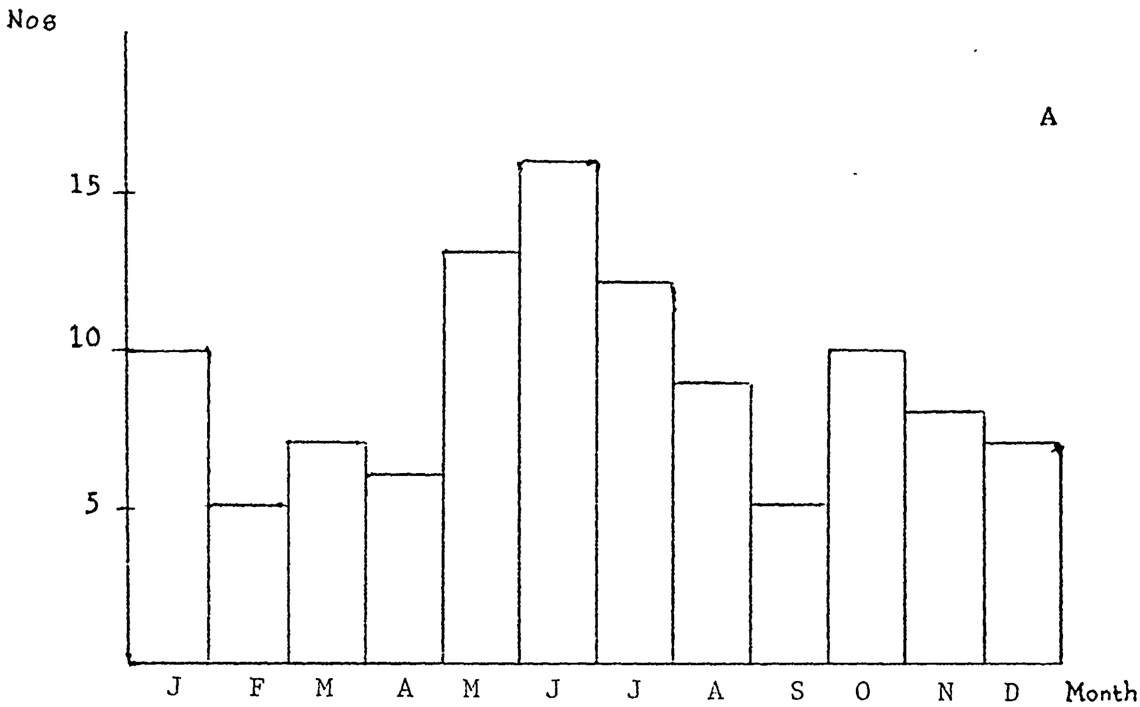
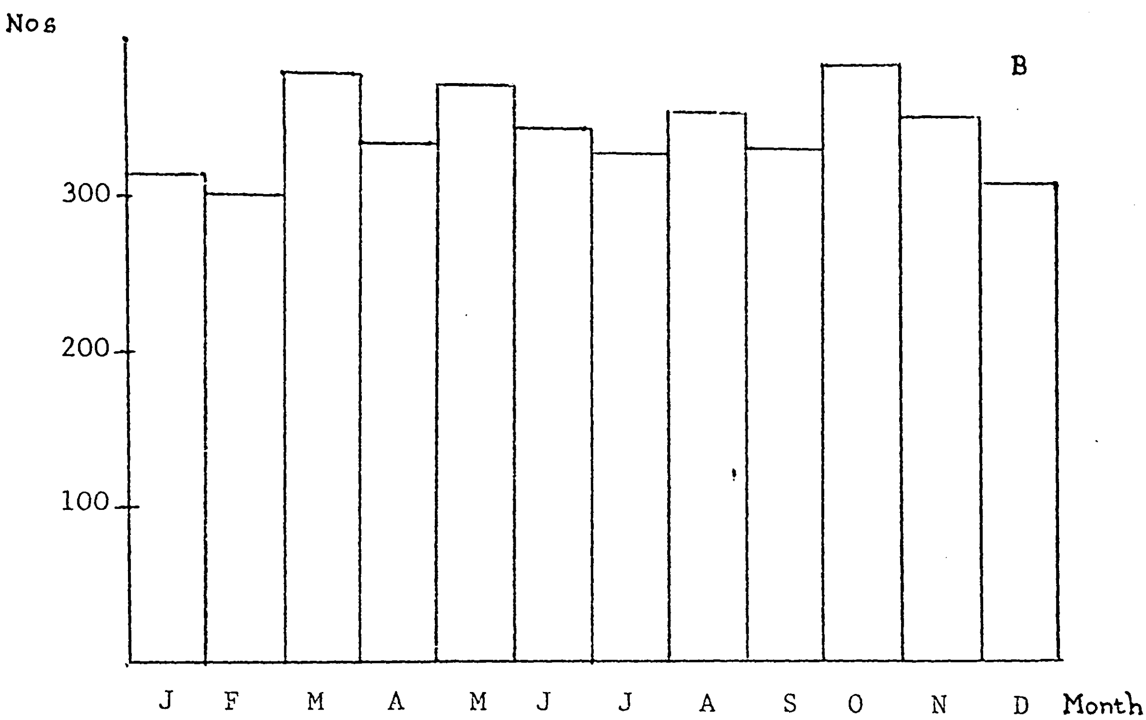


FIG 3.3: SEASON INCIDENCE OF PARAQUAT SELF POISONING (A) COMPARED WITH SEASONAL INCIDENCE OF ALL SUICIDES (B)





May to August with a peak in June, which corresponds very largely to the period of the year when paraquat would be in use as a herbicide in domestic situations (fig.3.3), thus differing from the relatively even distribution of self-poisoning throughout the year as a whole in the UK.

It was not possible to elicit psychiatric histories from all the cases, but table 3.6 provides evidence that previous mental illness is a significant factor in such poisoning cases. In most cases this had been severe endogenous depression. Alcoholism was a feature of only four cases. Ten patients had histories of previous attempts at suicide. Three cases were known to have been suicidal gestures following domestic rows, sadly two of these were fatal.

The social background of the patients reviewed was not easy to elicit, especially in females who were described mainly in case notes as housewives. However, job classification suggested that at least half of the male cases came from social classes IV and V (unskilled workers) and very few from the professional and skilled social groups.

Where possible, the source of paraquat was noted in cases where agricultural concentrates were used for self-poisoning. The results are shown in table 3.7. Approximately half the cases had no entitlement to access to agricultural concentrates such as 'Gramoxone'. In one case a young man admitted to stealing the material from a nearby farm. Another 12 cases obtained the concentrates from relatives and friends, decanted into other containers. In each case it was the farmers who were prepared

TABLE 3.6 PSYCHIATRIC BACKGROUND TO PARAQUAT POISONING CASES

	Males		Females		Total	
	No.	%	No.	%	No.	%
Previous history of mental illness	18	21.4	9	37.5	27	25.0
Previous history of personality disorder	1	1.2	0	-	1	0.9
History of alcoholism	3	3.6	1	4.2	4	3.7
History of previous suicidal attempts	9	10.7	1	4.2	10	9.3
No previous history of mental illness obtained	3	3.6	0	-	3	2.8
Not known	50	59.5	13	54.1	63	58.3
Total	84	100.0	24	100.0	108	100.0

TABLE 3.7 : SOURCE OF PARAQUAT IN SELF-POISONINGS USING AGRICULTURAL CONCENTRATES

	Numbers		%
	Male	Female	
Entitled to possess concentrate, or easy access through work	17	1	36
Obtained through relatives, friends etc. Stored in unauthorised containers	10	2	24
Bought openly from merchants, stores etc, by unauthorised purchasers	8	3	22
Stolen (admitted)	1	-	2
Source not known	6	2	16
	42	8	100

to undertake such a dangerous and illicit practice who are most to blame. In addition, a further 11 cases, according to their own stories, bought 'Gramoxone' openly 'across the counter' from agricultural merchants or similar stores with apparently no questions asked and no signing of the poisons register. The occupations of these purchasers ranged from ordinary housewives to a mechanic, bus driver and a builder, none being even remotely concerned with agriculture. Such apparent ease in obtaining highly toxic material in an illicit fashion must give cause for concern.

The overall mortality in the series was 50.0 per cent (54 deaths in 108 cases). Mortality was much higher in cases of poisoning with liquid concentrate formulations (mainly 'Gramoxone') where there were 42 deaths from 50 cases (a mortality of 84.0%), but there were only 12 deaths from 58 cases of poisoning with the retail granular formations (20.7%) (tables 3.8 and 3.9). These differences are largely a reflection of the size of dose ingested: larger quantities of paraquat are usually taken when liquid formulations are used. This cannot be the whole story, however, as a comparison of mortality at equivalent doses (table 3.10) indicates a higher mortality following the ingestion of liquid concentrates than from the retail formulations. It is possible that this variation may be due to the differences in concentration in the ingested material. The concentrates are normally ingested neat, at a concentration of 20% paraquat ion, but the granular material must first be dissolved in water. The stories obtained from patients would suggest that the concentration of this material is usually well below 10 per cent. The differences in the

TABLE 3.8 DEATHS FROM PARAQUAT POISONING

Formulation	No. of Deaths	No. at Risk	Mortality %
Concentrates (liquid)	42	50	84.0
Granular (solid)	12	58	20.7
Totals	54	108	50.0

TABLE 3.9 OUTCOME OF PARAQUAT POISONING RELATED TO FORMULATION INGESTED

	Deaths		Recoveries		Total
	No.	%	No.	%	
LIQUID					
Gramoxone	38	84.4	7	15.6	45
Gramonol	2	66.7	1	33.3	3
Dextrone	2	100.0	0	-	2
GRANULAR					
Weedol	11	21.6	40	78.4	51
Pathclear	1	14.3	6	85.7	7
TOTALS	54		54		108

TABLE 3.10 COMPARISON OF MORTALITY FROM PARAQUAT POISONING WITH DIFFERING FORMULATIONS AT EQUIVALENT DOSES (2-10g PARAQUAT ION)

Formulation	No. of Cases	Deaths	Mortality %
Liquid concentrates	19	15	78.9
Granular	13	6	46.2
TOTAL	32	21	65.6

formulations (stabilizers, wetters, etc.) may also play a part in accounting for the differing mortality rates.

The relationship between the dose of paraquat ingested (in grams of paraquat ion), the time elapsed between ingestion and the institution of treatment and the ultimate outcome is shown in table 3.11. There were no survivors in this series among the 23 who had ingested more than 10 gm of paraquat ion (equivalent to 50 ml 'Gramoxone' or 6-7 sachets of 'Weedol') irrespective of the time at which treatment was instituted, and there was only one survivor from 16 cases who had ingested more than 5.0g of paraquat ion (equivalent to 25 ml 'Gramoxone' or 3-4 sachets of 'Weedol') but less than 10g. Such a dose of 'Gramoxone' represents no more than a single mouthful. Taking both these higher dose groups together, there were 39 patients of whom 13 were given proper treatment within two hours of ingesting paraquat and in only 8 cases was the institution of therapy delayed beyond 10 hours from ingestion. Nonetheless, there was only one survivor out of these 39 cases, suggesting strongly that doses in the area of 5g represent the maximum treatable ingested amount, particularly if there is any delay in instituting treatment beyond 2 hours after ingestion. The importance of the time factor in treatment is shown in table 3.12 in relation to the 'treatable' dose range of 2 to 10g paraquat ion. This correlates closely with the data on plasma paraquat levels indicating the rapidity of absorption.

The pattern of major organ damage in this series is shown in table 3.13. These figures are based on clinical observations and investigations and not on post mortem findings. The two

TABLE 3.11 OUTCOME OF PARAQUAT POISONING RELATED TO THE INTERVAL BETWEEN INGESTION & TREATMENT AT DIFFERENT DOSE

Time interval before treatment	up to 2.0g		over 2.0 to 5.0g		over 5.0 to 10.0g		over 10.0g	
	Recovery	Death	Recovery	Death	Recovery	Death	Recovery	Death
Less than 2 hours	6	2	5	0	1	4	0	8
From 2 to 5 hours	12	2	3	3	0	4	0	7
From 5 to 10 hours	5	1	1	1	0	4	0	3
Over 10 hours	13	0	1	2	0	3	0	5
* Totals	36	5	10	6	1	15	0	23
Mortality (%)	12.2		37.5		93.7		100.0	

* In 12 cases it was not possible to estimate either the time of treatment or the actual dosage ingested.

TABLE 3.12 INGESTION/TREATMENT INTERVAL AND OUTCOME OF POISONING AT DOSES BETWEEN 2.0g AND 10.0g PARAQUAT ION

	No. of recoveries	No. of Deaths	Total Cases	Mortality %
Up to 2 hours	6	4	10	40.0
From 2 to 5 hours	3	7	10	70.0
Over 5 hours	2	10	12	83.3
Totals	11	21	32	65.6

TABLE 3.13 THE PATTERN OF MAJOR ORGAN DAMAGE IN PARAQUAT POISONING

	Fatal	Non-Fatal
Kidneys	5	7
Kidneys + Lung	22	3
Lung	2	4
Liver + Lung	1	2
Liver + Kidneys	2	1
Kidneys + Lung + Liver	21	1
Liver	1	2
Totals	54	20

fatal cases in which lung damage only was seen, were both treated with forced diuresis, and it is more than probable that the fatal pulmonary oedema was a result of over-energetic treatment rather than the paraquat itself. Hepatic damage alone was seen in only three patients, and there were 3 cases in which lung effects were seen in association with hepatic damage. The normal pattern, however, was for lung damage to follow evidence of renal failure. Renal damage in many cases was severe, judged from biochemical indices. The relatively high numbers showing renal involvement following 'Weedol' ingestion may reflect the additive effect of the diquat also included in this formulation. Two of these cases showed marked central nervous system involvement with convulsions and another two cases showed methaemoglobinaemia, a phenomenon that is difficult to explain. It is worth noting that among the deaths there were two who died from the inhalation of Fuller's Earth, both of whom had taken less than 2g paraquat ion and three who apparently died from myocardial infarction during therapy, although this may have been a toxic myocarditis which has been observed in a number of cases (Vale, J A, 1978, personal communication). There was a further case who died with extensive intravascular clotting.

The introduction of Fuller's Earth as the basis of therapy, designed to prevent the initial absorption of paraquat from the gut, was widely welcomed with cautious optimism as a possible answer to a hitherto insoluble problem. However, as discussed earlier (Section 3.2) the only large scale review of poisoning undertaken so far has failed to show any significant improvement in mortality following the introduction of Fuller's Earth [30]. Fitzgerald's conclusion in that study was that the only patients likely to have benefited from therapy were those treated within six hours of ingestion and who had taken between 5 and 30 ml of 'Gramoxone' (equivalent to 1 to 6 gm of paraquat ion). The French review of poisoning with paraquat would lower the upper level of treatable dose to 4 gm paraquat ion [6]. The indications of the present study would put the upper limit of treatable ingested dose at just above 5g paraquat ion (table 3.11), in close agreement with the conclusion of Fitzgerald.

The mortality pattern in the present series of 108 cases is very similar to that of Fitzgerald's series. The overall mortality rate is similar and the great majority of survivors had taken less than 2 gm of paraquat ion, a dose level at which only minimal therapy is probably necessary. On the other hand, there were no survivors at doses above 10 gm paraquat ion, irrespective of the time at which therapy was instituted or the vigour with which it was applied. An important intermediate group is thus disclosed who have taken more than 2 gm, but less than 10 gm of paraquat ion and in whom treatment may be shown to be of value. The critical factor in this group, however, is the time at which treatment is started. Table 3.12 shows that the chances of survival are very much poorer if the start of treatment is delayed beyond 5 hours, whereas there were 6 survivors out of 10 cases treated within 2 hours of ingestion in the same dose range. Time thus appears to be the critical factor and this is to be related to the rapid absorption of paraquat demonstrated by the early peaking of plasma paraquat levels (section 3.2.1 and fig 3.1). The practical success of therapy thus closely mirrors the picture obtained from considerations of absorption patterns. It is thus possible to set out the three minimum criteria for possible successful therapy:

1. an ingested dose less than 10 g paraquat ion (equivalent to 50 ml 'Gramoxone'; 6 sachets of 'Weedol'). In reality, as already suggested, it is likely that the really 'treatable' dose is not more than 6 g paraquat ion, equivalent to 30 ml of 'Gramoxone' or 4 sachets of 'Weedol' (see table 3.11). The setting of too rigid a dose criterion could lead to the exclusion of cases that might benefit from early and vigorous treatment and, accordingly, an upper limit of 10g is suggested. This also allows for variations in the amount of paraquat available for absorption as a result of vomiting, existing stomach contents etc.

2. active therapy instituted within 5 hours of ingestion, (ideally within 2 hours)

3. plasma paraquat levels below 2.0 mg/litre at 4 hours after ingestion or 0.6 mg/litre at 6 hours after ingestion.

The 'window' for introducing effective therapy is thus very small and while small treatable doses are the rule with the retail granular formulations ('Weedol' and 'Pathclear'), a single mouthful of the agricultural concentrate is potentially lethal.

The problem in assessing the value of treatment is to decide which aspect is the most important. Slightly more than half the patients in this series vomited spontaneously and frequently profusely, but this did not appear to influence the final outcome as there were as many who vomited among fatalities as survivors. However, there is a variety of factors such as time to vomiting and the volume distribution of paraquat in the stomach which would affect this situation. All patients received gastric lavage on admission to hospital followed by the administration of Fuller's Earth and purgatives. The importance of the time factor in treatment, related to what is known of gastric emptying, would suggest that gastric lavage is equally as important as the use of Fuller's Earth. This raises the whole question of the oral administration of this adsorbent. Two cases in this series died through the inhalation of orally administered Fuller's Earth. Furthermore, patients are generally intolerant of these suspensions especially when concentrated (eg 30%) and the problem is made worse in the presence of inflamed or ulcerated mouth and fauces with dysphagia or intractable vomiting. There is also some unpublished post-mortem evidence which suggests that the passage of Fuller's Earth across the pylorus into the duodenum is not as complete or as rapid as usually thought if the suspension is concentrated. For these reasons the regime of

Okonek and Hofmann [28,29] using gut lavage with Fuller's Earth in saline is likely to be more effective in ensuring that the adsorbent reaches the small gut in sufficient quantities. However, unless this regime can be introduced rapidly it is not likely to be much more effective than present methods.

The use of a variety of adjuvant forms of therapy has been advocated, both to remove paraquat from circulation and to protect the lung. There was no evidence from this study that the use of such adjuvant therapy plays any part in increasing survival after poisoning. Table 3.14 indicates the apparent effectiveness of the most common forms of adjuvant therapy at various dose levels. It is not easy to separate the effects of individual forms of additional therapy, since all were combined with the basic form of treatment using Fuller's Earth and were also frequently used in combination together. It will be seen from the table that the mortality rates in the dose range 2.0 to 10.0g paraquat ion compare very closely with those shown in table 3.12, which sets out the overall mortality in this dose range. It would probably be argued by Okonek on the basis of his successful use of haemoperfusion [36,38] that this regime was not pursued with sufficient vigour nor for a sufficient length of time to produce an effect in the cases in this series. The results following forced diuresis are markedly poorer, however, than those associated with other forms of therapy. This is likely to be related to the secondary effects of pulmonary oedema which, according to the case histories, developed in at least half the cases treated by this method. Such therapy is likely to be hazardous when the patient is developing oliguric renal failure.

TABLE 3.14 EFFECTIVENESS OF ADJUVANT THERAPY

IN PARAQUAT POISONING

Form of Therapy	Dose Range								Mortality % (2-10g range)
	Less than 2g		Over 2g to 5g		Over 5g to 10g		Over 10g		
	No. of Cases	Deaths	No. of Cases	Deaths	No. of Cases	Deaths	No. of Cases	Deaths	
Haemodialysis and/or haemoperfusion	9	1	5	2	7	6	9	9	66.7
Forced diuresis	10	1	9	5	7	7	5	5	75.0
Anti-inflammatory agents and/or immunosuppressants	1	0	4	1	8	7	9	9	66.7

* Death from inhalation of Fuller's Earth

Furthermore, as noted earlier, it is a form of therapy contraindicated on theoretical grounds. None of the patients in this series received d-propranolol, nor was PEEP ventilation used. Neither form of therapy will prevent the progress of the lung lesion, although the latter is certainly of benefit in the terminal management of fatal cases.

Perhaps the most important aspect of this analysis of 108 cases of paraquat poisoning is the way in which it serves to emphasize both the very small dose range for which treatment is likely to be effective and the narrow time band available to institute such therapy once ingestion has taken place. The author's experience would suggest that neither of these issues is sufficiently understood, particularly in accident and emergency units to which the majority of patients are taken in the first place.

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SECTION 4

CONCLUDING OBSERVATIONS

4 CONCLUDING OBSERVATIONS

It is always easy to be wise after the event and it seems clear that the manufacturers of paraquat as a herbicide did not anticipate any exceptional problems with this compound when it was first introduced onto the market during the mid-1960s. In retrospect, however, it should perhaps have been expected that some serious accidents would occur with a herbicide of relatively high toxicity and in particular one with the type of toxic properties that pre-registration animal studies would have uncovered. It has to be remembered that farm workers are notoriously careless and often exhibit little safety consciousness. In general, however, the incidence of serious accidents in occupational use appears to have been very low, as has been discussed earlier. On the other hand there have been a large number of deaths as a result of accidental or deliberate ingestion of paraquat formulations.

This short section will attempt to draw some conclusions from the data provided in the earlier parts of this thesis in relation to the two situations of paraquat use in agriculture and paraquat misuse in accidental and, more particularly, deliberate poisoning.

4.1 PARAQUAT IN USE

The main conclusions to be drawn from the available published data, together with the results of the author's three studies of paraquat occupational use situations, have been discussed broadly in Section 2.5. The data would indicate that neither the formulation of paraquat as commercial preparations, nor the standard higher volume spraying at concentrations of up to 0.5% paraquat ion (1:40 dilution of 'Gramoxone') are likely to pose any significant risk to worker health.

The importance of these studies lies, in part at least, in the long period of occupational exposure which the formulation workers and Malaysian spray operators had experienced. It is thus worth re-emphasising that in spite of such long and continuous occupational exposure associated with significant dermal contamination, there were no reports of any symptoms that would point to significant absorption of paraquat. More importantly, as far as the group of spray workers was concerned, a wide range of clinical measurements failed to show any variation from the values that were found in the unexposed control populations. It may therefore be reasonably affirmed that paraquat does not constitute a significant risk to health under proper conditions of manufacture and use.

It was noted earlier, however, that the use of low volume/ high concentration spraying raised very real problems. Exposure to concentrations not greatly in excess of those used in the Thailand trial have since been reported as causing fatalities through percutaneous absorption [1,2]. The results of that particular study would strongly indicate that the practice of low volume spraying, using hand-held equipment, is a dangerous practice which increases the level of risk to the sprayman to totally unacceptable degrees.

Unfortunately, the label instructions on ICI Ltd formulations did not, in the past, make it clear that there was any consideration of safety to be taken into account in deciding on the dilution for spraying. A range of dilutions was set out, but these related to herbicidal efficacy not to matters of safety. Partly as a result of the Thailand work reported in this thesis, ICI Ltd have now clarified their label instructions and have placed a clear limit for the upper spray strength to be used with hand-held sprayers (1:40 dilution of the 20% agricultural concentrate) (see table 2.1, p 49). Considerable amounts of the older formulations, however, are still likely to be in use around the world.

4.2 PARAQUAT IN MISUSE

The real problem with regard to paraquat relates to its misuse in cases of accidental or deliberate poisoning. The existing controls on the sale of the agricultural concentrate in the United Kingdom have done much to reduce the incidence of accidental poisonings. On the other hand, the evidence for 'illicit' sales and the apparent ease with which commercial formulations were obtained by those not entitled to them, as discussed earlier in the thesis (Section 3.3.2), must raise considerable concern. It seems likely that the voluntary registration scheme devised by the British Agrochemicals Association for distributors will go a long way towards reducing the sale of scheduled materials to the general public (Major C S, 1981, personal communication), but clearly if such voluntary means fail, there will be a need for a tighter statutory control and inspection system to ensure the proper regulation of the sale of scheduled pesticides.

The evidence from the author's series of cases reported here and from the only published data dealing specifically with retail granular formulations [3], would indicate that these preparations present no significant risk of fatal accidental poisoning, although they are being increasingly used for deliberate self-poisoning. The mortality, however, is low in such cases and the actual dose of paraquat taken is frequently very small indeed. In view of this situation it would seem to be a gross over-reaction to ban the use of paraquat in those garden and retail formulations specifically designed for domestic use. On the other hand, in those countries (such as Eire, Japan and Western Samoa) where liquid agricultural concentrates are more freely available than they are in the United Kingdom and where self-poisoning is a significant problem, then there is a strong case for the manufacturer to introduce measures which may help in reducing fatalities from self-poisoning. In total numbers, 20 or 30 deaths each year from paraquat self-poisoning in Western Samoa may appear small, especially in the world-wide terms in which large companies think, but in terms of a population only the size of Oxford, the problem changes in significance considerably.

The very small range of dose for which any treatment is likely to be effective has not always been sufficiently recognised. The great weight of evidence, discussed earlier, would indicate that the only cases likely to be saved with any degree of probability are those who have:

(a) ingested less than 5g of paraquat ion,

(b) had treatment instituted within 2 hours of ingestion, and

(c) show plasma paraquat levels not exceeding 2mg/litre at four hours after ingestion.

The dose of 5g paraquat ion represents but 25ml of 'Gramoxone', literally 'a mouthful'. There are very few other compounds in general use where there is such a sharp 'cut off' between treatable and fatal doses and any measure which can be introduced which will extend that boundary should be given careful consideration, especially in view of the 'cry for help' cases whose self-poisoning is no more than a suicidal gesture. This is an important group of poisoning cases who often take what they believe to be a 'small' dose (a mouthful, for example), but which in the case of paraquat turns out to be inevitably fatal. One recent estimate suggests that as many as three quarters of self-poisonings are 'impulse' cases of this type [4].

The benefits of paraquat in agricultural practice have been demonstrated over the past twenty years, but in common with most benefits there are associated risks and dangers. It may be used with safety, but it may also be misused with dire results. Good and evil are rarely far apart in this world and it requires vigilance and a willingness to act to ensure the continuing good. It was, after all, but a league between Mount Gerizim and Mount Ebal [5].

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5 DEUTERONOMY 11:29

SECTION 5

SELECT BIBLIOGRAPHY

5 SELECT BIBLIOGRAPHY

The literature on paraquat is immense with something in the order of 1200 publications relating to the matters discussed in this thesis. The accompanying bibliography is thus in no sense complete, being merely a supplement to the specific references for each section of the thesis. The bibliography lists only papers, review articles etc related to the human toxicity and treatment, general toxicology, biochemistry (including toxic mechanisms) and the ecotoxicology of paraquat. The references are set out by year of publication and in alphabetical order of authors. Foreign language papers are included and the language of the publication is noted. Where English abstracts of foreign papers are available, these are noted in relation to the original paper. There are a great many publications of individual cases of poisoning, autopsy results etc. Only a representative sample of these is included in the bibliography.

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