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Cerebral damage in paraquat poisoning

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This is the first report on cerebral changes in eight patients who died of paraquat poisoning. These included generalized oedema, haemorrhages (both subependymal and subarachnoid), glial reactions (microglial activity and astrocytic response) and meningeal inflammation. Oedema and haemorrhage were the most consistent and significant findings: they suggest that paraquat may damage the cerebral blood vessels. The distribution of haemorrhages was unusual and resembled that seen in thiamine deficiency.

Keywords: paraquat, Gramoxone, brain damage

Introduction

The result of paraquat ingestion in man has been the subject of many case reports (Bullivant 1966, Campbell 1968, Fennelly, Gallagher & Carroll 1968, Matthew *et al.* 1968, Oreopoulos *et al.* 1968, Hargreave, Gresham & Karayannopoulos 1969, Toner *et al.* 1970, Ramachandran, Rajapakse & Pereia 1974). Interest has been focussed on the development of pulmonary damage in both man (Smith & Heath 1974a, Smith & Heath 1975, Thurlbeck & Thurlbeck 1976, Rebello & Mason 1978) and experimental animals (Robertson *et al.* 1971, Vijeyaratnam & Corrin 1971, Modée, Ivemark & Robertson 1972, Smith & Heath 1974b, Smith, Heath & Kay 1974, Sykes, Purchase & Smith 1977). Pathological findings in other organs have been reported in human paraquat poisoning, including toxic myocarditis (Bullivant 1966, Nagi 1970), centrilobular hepatic necrosis (Bullivant 1966, Campbell 1968, Ramachandran *et al.* 1974),

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Table 1. Clinicopathological findings

Case no.	Age (yr)	Quantity of Gramoxone ingested (ml)	Predominant clinical features	Ingestion–death interval	Pathological necropsy findings
1	54	800	Coma, respiratory arrest; resuscitated, hypotension	6 h	Pulmonary oedema. Toxic myocarditis. Renal tubular necrosis. Centrilobular liver cell damage
2	52	90	Abdominal pain, diarrhoea, tachycardia, hypotension, anuria, coma	16 h	Pulmonary oedema and congestion
3	67	100	Vomiting, dysphagia, tachycardia, tachypnoea, coma, anuria	23 h	Pulmonary oedema and congestion. Toxic myocarditis. Centrilobular liver cell damage. Kidneys autolysed
4	16	125	Tachypnoea, dyspnoea, oral ulceration, hypotension, anuria, coma, cardiac and respiratory arrests	39 h	Pulmonary oedema and congestion. Toxic myocarditis. Centrilobular liver cell damage. Renal tubular necrosis
5	16	250	Vomiting, dysphagia, jaundice, renal failure—coma	3 days 20 h	Pulmonary congestion and oedema. Toxic myocarditis. Renal tubular necrosis
6	25	20	Vomiting, dysphagia, tachycardia, renal failure, respiratory failure	5 days 13 h	Pulmonary oedema, congestion, early interstitial fibrosis. Toxic myocarditis. Renal tubular necrosis
7	27	20	Haemoptysis, tachypnoea, renal failure, respiratory failure	8 days	Pulmonary oedema, congestion, hyaline membranes, interstitial and intraalveolar fibrosis. Toxic myocarditis. Renal tubular necrosis. Centrilobular liver cell necrosis
8	17	unknown	Oral ulceration, vomiting, diarrhoea, dyspnoea, respiratory failure	23 days	Pulmonary congestion, interstitial and intraalveolar fibrosis, 'honeycombing'. Toxic myocarditis. Centrilobular liver cell necrosis. Renal tubular necrosis

renal tubular necrosis (Bullivant 1966, Campbell 1968, Fennelly *et al.* 1968, Oreopoulos *et al.* 1968, Toner *et al.* 1970, Ramachandran *et al.* 1974) and adrenal cortical necrosis (Nagi 1970). However, in these instances a detailed histological study of the brain was not made, although experimental work has suggested that paraquat might cause cerebral damage (Rose *et al.* 1976, Clark, McElligott & Weston Hurst 1966). The purpose of this paper is to describe cerebral changes in the brains of eight patients who died of paraquat poisoning.

Material

The clinicopathological findings in eight patients who drank undiluted 'Gramoxone' (20% paraquat) are shown in Table 1. All the patients were referred to Guy's Hospital during the 3 years 1975–1978; they include seven males and one female with an age range of 16–67 years. In seven instances paraquat was intentionally ingested and in one patient (case 8) an open verdict was returned at inquest. Only three patients (cases 1, 6 and 8) were involved in horticultural or agricultural work and therefore had professional access to Gramoxone (a scheduled poison). In each case the quantity of Gramoxone consumed was estimated from the patient's history and ingestion confirmed by urine analysis (Berry & Grove 1971).

Treatment was aimed at reducing the absorption of paraquat and enhancing excretion. Two patients were subjected to gastric lavage (cases 1 & 4) but all received Fuller's Earth and six were treated by charcoal column haemoperfusion. Steroids were given to two patients (cases 3 & 4); one patient (case 8) received assisted ventilation with oxygen concentrations between 75% and 90% before the diagnosis of paraquat poisoning was made and a second patient (case 6) was ventilated using a nitrogen and oxygen mixture to maintain a pO_2 of 50–70 mmHg.

Early symptoms commonly included oropharyngeal ulceration and signs of gastrointestinal tract irritation. Death within 6 days of paraquat ingestion was associated with pulmonary, cardiac, renal and hepatic failure (cases 1–6).

In those patients who survived for longer than a week (cases 7 & 8) respiratory failure due to pulmonary fibrosis was the dominant clinicopathological finding, although evidence of damage to other organs was seen at necropsy.

Cerebral pathology

Changes found in the brains of patients who died of paraquat poisoning were in order of frequency: oedema, haemorrhages (subependymal and subarachnoid), neuronal damage, microglial activation, astrocytic gliosis, meningeal inflammation and perivascular necrosis (Table 2).

Oedema of the white matter was seen in all but one (case 8) of the cases. It was moderately severe in most instances, but in one brain (case 2) advanced swelling resulted in disruption of tissue. Recent haemorrhages were present in six cases: the subarachnoid space was involved in four patients (cases 1, 3, 6 & 7), while in two

Table 2. Cerebral pathology

Patient	Ingestion-death interval	Oedema of white matter	Subependymal haemorrhages (old or new)	Subarachnoid haemorrhage (old or new)	Neuronal damage	Microglial activity	Gliosis	Meningeal inflammation	Perivascular necrosis
Case 1	6 h	+		+	+				
Case 2	16 h	+ + +	+		+	+		+	
Case 3	23 h	+ +		+	+				
Case 4	39 h	+				+			
Case 5	3 days 20 h	+	+		+	+		+	
Case 6	5 days 13 h	+		+	+		+	+	
Case 7	8 days	+	+	+		+	+	+	+
Case 8	23 days		+	+	+	+	+ +		

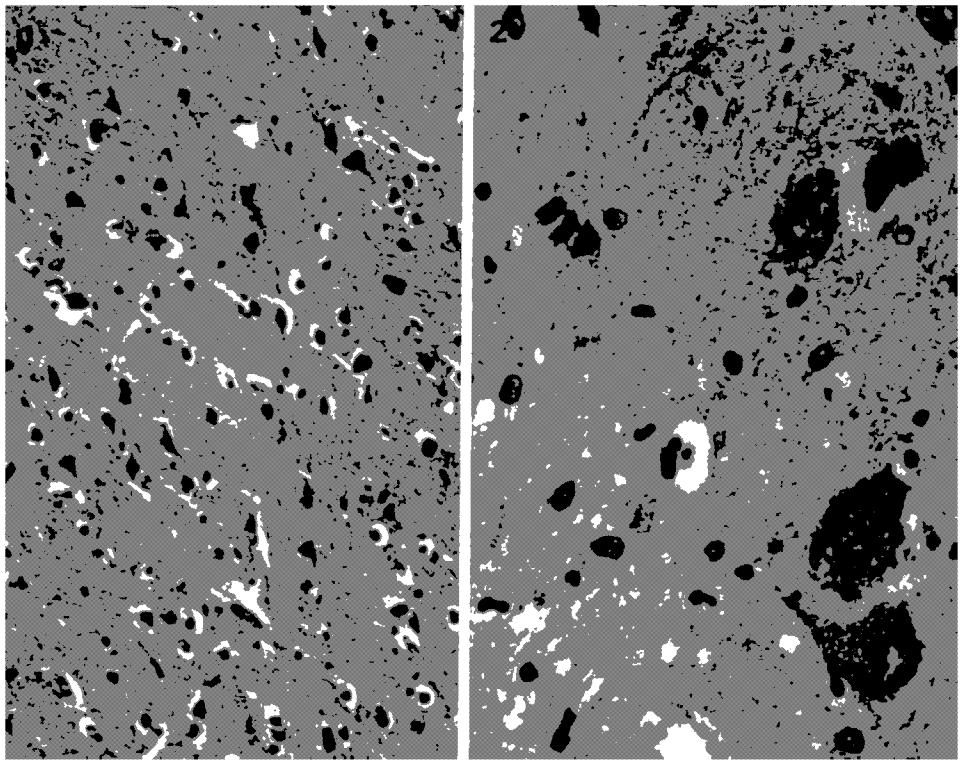

Figure 1. Case 8. Pyknotic neurones in the frontal lobe. H & E. × 180.

Figure 2. Case 7. Neurones (N) in the midbrain, showing central chromatolysis and disintegration and proliferating astrocytes (A). H & E. × 450.

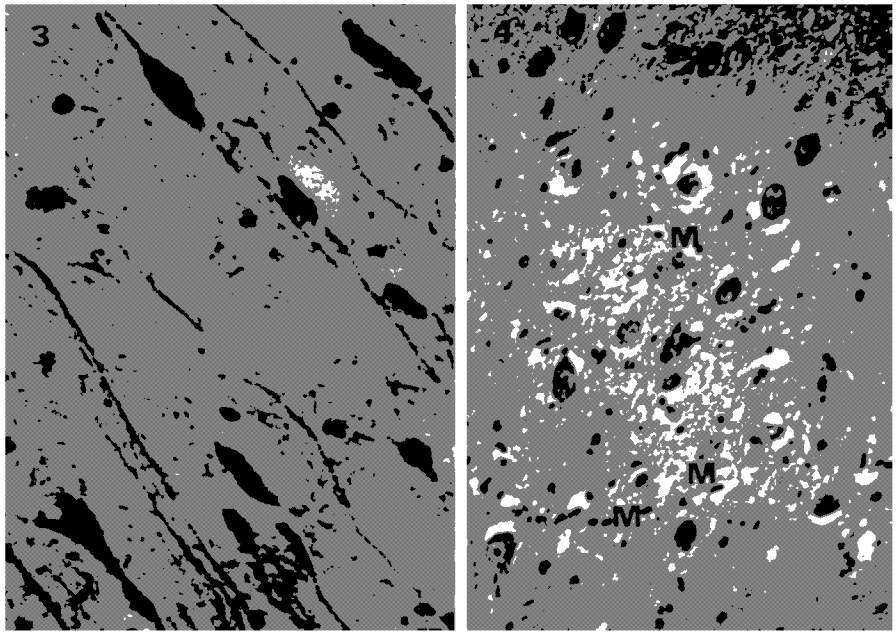

Figure 3. Case 8. Pyknotic neurones in the temporal lobe. Palmgren's silver. × 450.

Figure 4. Case 7. Diffuse proliferation of microglia (M) and central chromatolysis of neurones in the midbrain. H & E. × 180.

(cases 2 & 5) haemorrhages were seen in the subependymal tissue (Figure 10) and one of these patients (case 2) had early necrosis of the mammillary bodies. In addition, evidence of earlier haemorrhage (haemosiderin-laden macrophages) was observed in the subarachnoid and Virchow–Robin spaces in cases 6, 7 & 8. The occurrence of previous bleeding was also betrayed in cases 7 & 8 by the presence of acid haematin as well as haemosiderin in microglia (and even in nearby neurones) in the parenchyma immediately subjacent to the pia and to the ependyma of the third ventricle and aqueduct.

Neuronal abnormalities were seen in six brains: they ranged from central chromatolysis to disintegration (Figures 1–3). Microglial reaction, either diffuse or focal, was noted in five patients (Figure 4) and an astrocytic response in three cases (Figure 2). Gliosis (greatly in excess of normal) was observed around the ventricular system and in some of the subpial areas (Figure 10). This gliosis was particularly severe in the longest survivor (case 8): in this brain a dense feltwork of glial fibres was seen beneath the ependymal lining of the ventricles (Figures 5–7). Mild meningeal

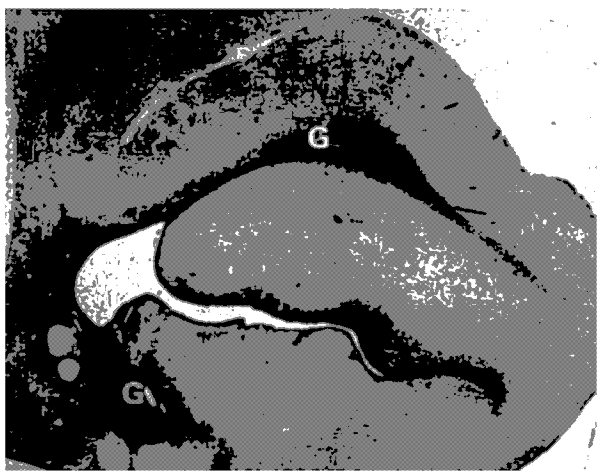

Figure 5. Case 8. Dense gliosis (G) around the temporal horn. Holzer. × 3.

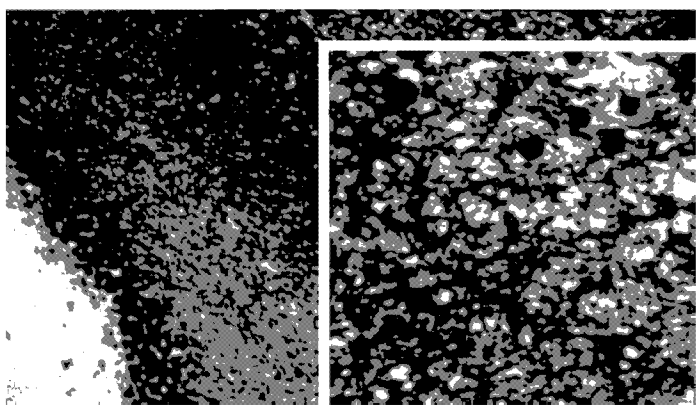

Figure 6. Case 8. A thick feltwork of glial fibres under the ependymal lining of the temporal horn. PTAH. × 180. *Inset:* × 450.

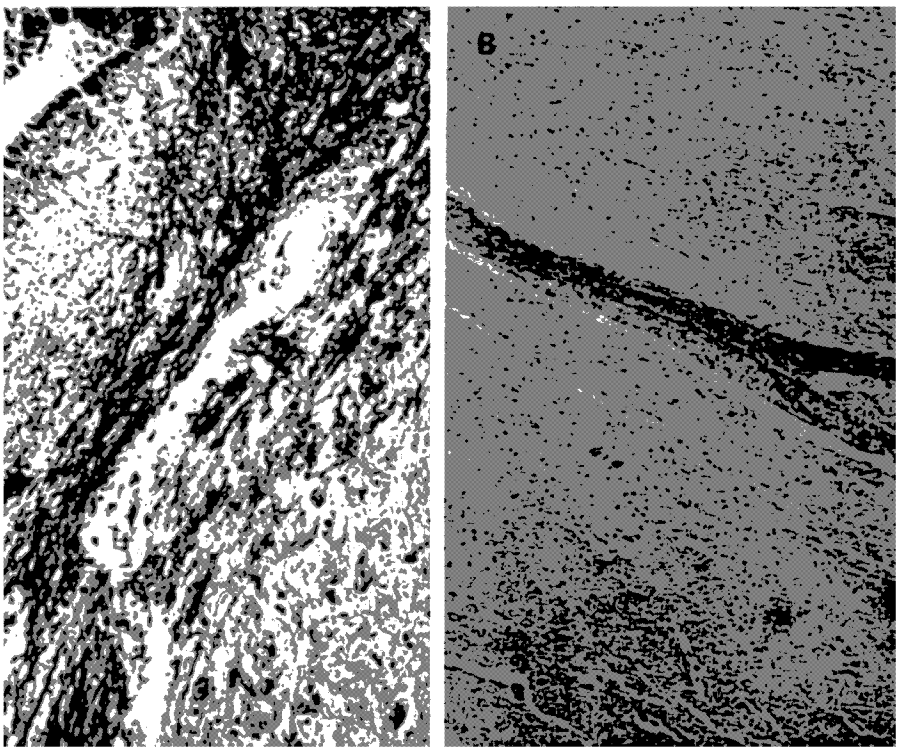

Figure 7. Case 8. Glial fibres under the ependymal lining of the fourth ventricle. PTAH. × 450.

Figure 8. Case 7. Inflammatory cells in the meninges over the occipital lobe. H & E. × 45.

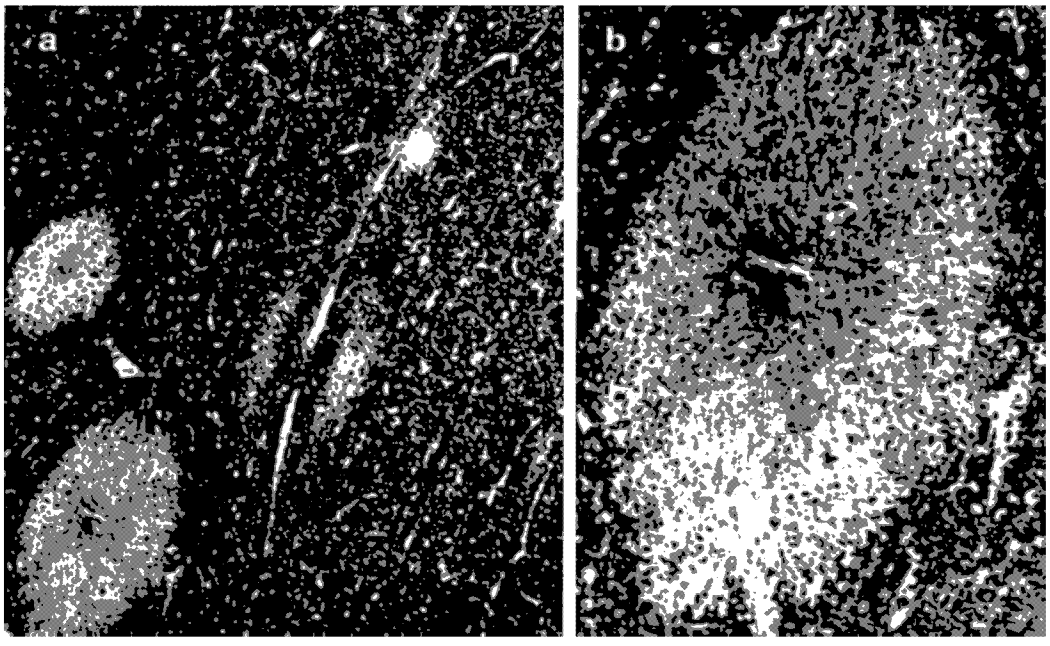

Figure 9. Case 7. Areas of perivascular necrosis in the cingulate gyrus. PTAH. **a** × 65. **b** × 180.

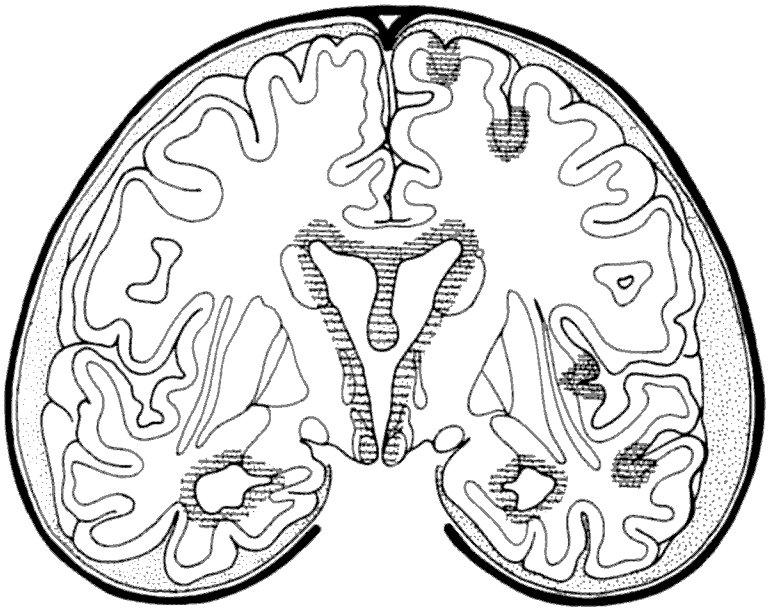

Figure 10. Distribution of brain lesions in paraquat poisoning. □ haemorrhage; ▣ haemorrhage and gliosis.

inflammation composed of mononuclear cells occurred in four cases (Figure 8) and there were several small, disparate areas of perivascular necrosis in the white matter of both cingulate gyri in one patient (case 7) (Figure 9).

Discussion

Paraquat (1,1'dimethyl-4, 4'bipyridylium) was introduced as a herbicide in 1962 and is commonly encountered in the United Kingdom as Gramoxone (a 20% solution of paraquat) or Weedol (granules containing 2.5% paraquat). It has been postulated (Fairshter & Wilson 1975) that the mechanism of paraquat toxicity in animals is related to its ability to act as an electron acceptor. Reduced paraquat radicals are reoxidized to molecular paraquat by oxygen with the reduction of molecular oxygen to super-oxide ions which are thought to be capable of direct tissue damage. The apparently selective nature of pulmonary damage following paraquat poisoning has been attributed to its selective and energy-dependent uptake by animal lung slices *in vitro* (Rose, Smith & Wyatt 1974). Within 2 hours lung slices were able to accumulate paraquat in a concentration exceeding by 10 times that of the medium. Brain was found to be the only other tissue exhibiting this property, although to a lesser degree (Rose *et al.* 1976). However after oral administration of paraquat to rats the chemical accumulated in the lung and not in the brain: the concentration in the brain was lower than that detected in the plasma. This was thought to imply poor penetration of paraquat through the blood-brain barrier (Rose *et al.* 1976). That the poison can reach the brain was suggested by the finding of central nervous system signs in rats after a single large intraperitoneal dose of paraquat (Clark *et al.* 1966).

The changes found in the brains of these eight patients who died of paraquat poisoning are related to the length of their survival after its ingestion. In the four cases with short ingestion–death intervals (6–39 hours) generalized cerebral oedema was the most significant and ubiquitous finding, although it was also present in patients with longer survival times (3 days 20 h–8 days). The microglial activity seen in most instances is thought to be a consequence of the persistent oedema. Cerebral oedema has been classified on the basis of pathogenesis into vasogenic, cytotoxic and hydrocephalic types (Klatzo 1967). Vasogenic oedema is caused by major endothelial damage resulting in increased vascular permeability and consequent leakage of plasma protein: it involves chiefly the white matter. Cytotoxic oedema develops either in the grey or white matter depending on the agent, and the excess fluid is accommodated by swelling of cells and their processes: vascular permeability remains unchanged. Hydrocephalic oedema is a consequence of increased hydrodynamic intraventricular pressure: the cerebrospinal fluid floods the periventricular white matter through the disrupted ependymal lining.

The mechanism by which paraquat causes oedema is not known, but it may bring about direct damage to vascular endothelia rendering them pathologically permeable and resulting in vasogenic oedema. The pulmonary oedema produced in experimental animals was attributed to an increase in the permeability of endothelial cell junctions (Vijeyaratnam *et al.* 1971), although ultrastructural damage was almost entirely confined to the alveolar epithelial cells (Smith *et al.* 1975, Thurlbeck & Thurlbeck 1976, Robertson *et al.* 1971, Vijeyaratnam & Corrin 1971, Smith & Heath 1974b, Sykes *et al.* 1977). Experiments have shown that brain tissue *in vitro* has an affinity for paraquat (Rose *et al.* 1976), but there is no convincing evidence to support the contention that paraquat actually crosses the blood–brain barrier. Therefore cytotoxic oedema is an unlikely consequence of paraquat poisoning. The possibility that therapeutic manipulations could have played a part in the production of oedema cannot be excluded. Intravenous infusions and haemodialysis with hypotonic solutions resulting in alteration of the osmotic balance across the capillary wall can cause cerebral oedema (Manz 1974).

Haemorrhages (subependymal and subarachnoid) were present in six patients who died within 9 days of paraquat ingestion; evidence of previous haemorrhages in these areas was seen in the remaining two. Gliosis was present in a similar periventricular location and was also seen in the subpial region in patients who survived more than 5 days. These findings strongly suggest that the gliotic scarring was caused by the haemorrhages.

Changes in the vascular permeability may thus account both for the oedema and the haemorrhages; they do not however alone explain this restricted distribution (see Figure 10). The periventricular pattern together with the mammillary body necrosis (case 2) is reminiscent of acute vitamin B_1 deficiency (Wernicke's encephalopathy). Although it is tempting to postulate substrate competition as a possible pathogenesis we are not able to suggest a biochemical mechanism.

In all cases there was some evidence of neuronal damage, mainly pyknosis; this change however is very likely to be artefactual. It is known that inadequate fixation of the brain results in two types of artefact: hyperchromatic neurones or 'dark cells'

and swollen cells due to 'hydropic cell changes' (Brown 1977). Both changes, particularly dark neurones, were seen in all cases.

Thus paraquat has been shown to cause cerebral damage. Since abnormalities have also been reported in other organs, it must be considered a multisystem poison.

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