

Paraquat lung: a reappraisal

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Smith, P. and Heath, D. (1974). *Thorax*, 29, 643–653. **Paraquat lung: a reappraisal.** The histopathology of the lungs from four human cases of paraquat poisoning is described. In two of them there was a dense mass of fibroblastic tissue which obliterated the lung architecture, and one of these showed an extensive deposit of collagen with honeycomb change. In a third case pulmonary fibrosis was less severe and could be demonstrated exclusively within the alveolar spaces. The fourth showed earlier lesions of capillary congestion, alveolar oedema, and hyaline membrane formation. We suggest that paraquat produces the same effect on the lung in man as in the rat, namely a diffuse, cellular, *intra-alveolar* fibrosis. The *intra-alveolar* origin of this fibrosis is often obscured in the advanced stage of the disease and has been misinterpreted as fibrosing alveolitis. This fibrosis is associated with a pulmonary vascular disease. In assessing the histopathology of the lung in paraquat poisoning a history of oxygen therapy must be taken into account, for prolonged exposure to this gas may in itself induce pulmonary fibrosis.

Poisoning by the herbicide paraquat (1, 1'-dimethyl-4, 4'-bipyridylum dichloride) commonly leads to the development of pulmonary fibrosis and death within a few weeks of ingestion. This fibrosis is often described as being interstitial in nature (Bullivant, 1966; Fennelly, Gallagher, and Carroll, 1968; Matthew, Logan, Woodruff, and Heard, 1968) and is now held by many to be an example of diffuse fibrosing alveolitis, as defined by Scadding and Hinson (1967). However, we have shown that in the rat paraquat-induced pulmonary fibrosis originates in the alveolar spaces and proliferates so as to cause obliteration of the lung architecture (Smith, Heath, and Kay, 1974). In this animal paraquat poisoning does not result in fibrosing alveolitis. In the investigation described in this paper we examined four cases of paraquat poisoning in man to determine if pulmonary fibrosis was *intra-alveolar* or interstitial. We also studied the pulmonary blood vessels in these cases to see if paraquat lung in man is associated with pulmonary vascular pathology.

MATERIALS AND METHODS

Lung tissue from four cases of paraquat poisoning in man was obtained from colleagues whom we gratefully acknowledge below. Histological sections were stained with haematoxylin and eosin, periodic acid Schiff's reagent, and the Humberstone technique to demonstrate elastic fibres

counterstained with van Gieson's stain to demonstrate smooth muscle and collagen.

RELEVANT CLINICAL AND POSTMORTEM FINDINGS

CASE 1 A 16-year-old boy ingested a large mouthful of concentrated paraquat solution (Grammoxone) and was admitted to hospital five days later with jaundice and acute renal failure. Soon afterwards he became increasingly dyspnoeic and was given oxygen to breathe, and there was early electrocardiographic evidence of 'right ventricular strain'. The renal and hepatic failure resolved but the dyspnoea and cyanosis became severe. He died 22 days after taking the paraquat.

At necropsy the cut surface of the lung showed gross consolidation with almost no recognizable alveolar tissue. There was no hypertrophy of the right ventricle.

CASE 2 A 38-year-old man was admitted to hospital with ulceration of the tongue, dyspnoea at rest, and left-sided chest pain. Two days later he was acutely ill. He was found to have accidentally ingested some paraquat several days previously but the precise length of history was never established. A radiograph of the chest taken on the third day showed diffuse shadowing throughout all zones of the lung, but serial radiographs showed no deterioration until the day before his death. On the fourth day he was severely

dyspnoeic, and mechanical respiration with inhalation of oxygen and forced diuresis were commenced. Paraquat was found in the urine. Artificial respiration was continued until his death 13 days after admission.

At postmortem both pleural cavities contained a blood-stained effusion. The pleura showed focal haemorrhage. The lungs were collapsed and consolidated. The wall of the right ventricle was hypertrophied.

CASE 3 A 56-year-old gardener took a mouthful of concentrated paraquat in mistake for home-brewed beer. He was admitted to hospital five hours later suffering from vomiting, abdominal pain, and diarrhoea. These symptoms soon settled after treatment but a chest radiograph taken on the following day showed slight mottling at the right lung base. Two days after admission he became dyspnoeic and cyanosed. He was given oxygen to breathe.

A chest radiograph taken two days later showed mottled opacities throughout both lung fields. He developed renal failure but after haemodialysis his renal function improved. Pulmonary function deteriorated, however, and he died in respiratory failure 20 days after drinking the paraquat solution.

At necropsy the lungs were abnormally heavy. Both lower lobes and the basal regions of the upper lobes showed extensive fibrosis and consolidation. The upper regions of the upper lobes and the right middle lobe showed an early honey-comb appearance. The right ventricle was dilated but not hypertrophied.

CASE 4 A woman aged 24 years ingested paraquat in the form of garden Weedol, which is believed to be much less toxic than the concentrated Grammoxone. Furthermore, the quantity ingested appeared to be very small since the patient stated that splashes of diluted Weedol fell into a drink from a nearby watering can.

Soon after ingesting the paraquat she was admitted to hospital but rapidly developed renal failure and respiratory distress. Both became increasingly severe and were unrelieved by treatment including oxygen therapy. Four days after ingestion of the paraquat she was cyanosed and died in renal failure the following day.

At necropsy death was attributed to acute renal tubular necrosis.

HISTOPATHOLOGY OF THE LUNG PARENCHYMA

CASE 1 The lung was consolidated with obliteration of nearly all the alveoli. There was no honey-

comb change. The consolidation was caused by dense cellular fibroblastic tissue consisting of numerous plump, basophilic fibroblasts (Figs 1 and 2) but in which very little collagen could be demonstrated by van Gieson's stain. The fibrous tissue included large numbers of red blood cells contained within an extensive capillary network. Clumps of extravasated erythrocytes were also common, particularly within the lumina of respiratory bronchioles (Fig. 2). Also included in the pulmonary fibrosis was an extensive fibrinous exudate in which were scattered a few neutrophil

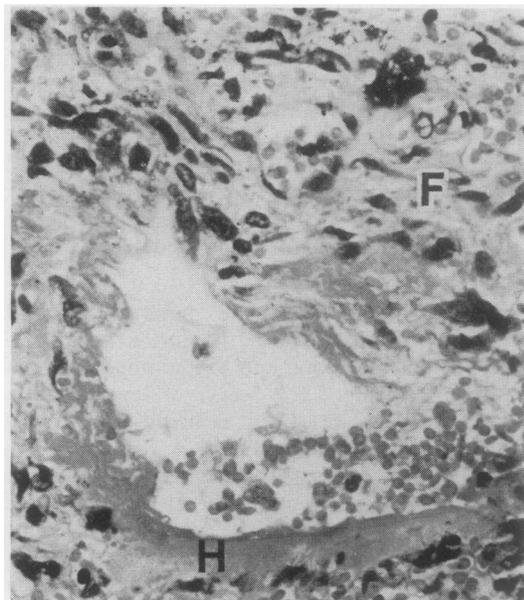


FIG. 1. Case 1. A respiratory bronchiole contains extravasated erythrocytes and is lined by a hyaline membrane (H). The surrounding lung architecture is obliterated by fibroblastic tissue (F) (Haematoxylin and eosin $\times 375$).

polymorphs and larger numbers of lymphocytes and plasma cells. Fibrin accounted for the bulk of the intercellular matrix but in the close vicinity of fibroblasts there were small deposits of immature collagen. Both alveolar walls and spaces were completely obliterated by this fibrosis to such an extent that it was impossible to determine whether the fibrosis was intra-alveolar or interstitial in nature. The lumina of respiratory bronchioles were patent but often showed invasion at their periphery by large fibroblasts (Fig. 2). Eosinophilic hyaline membranes were occasionally encountered in respiratory bronchioles (Fig. 1).

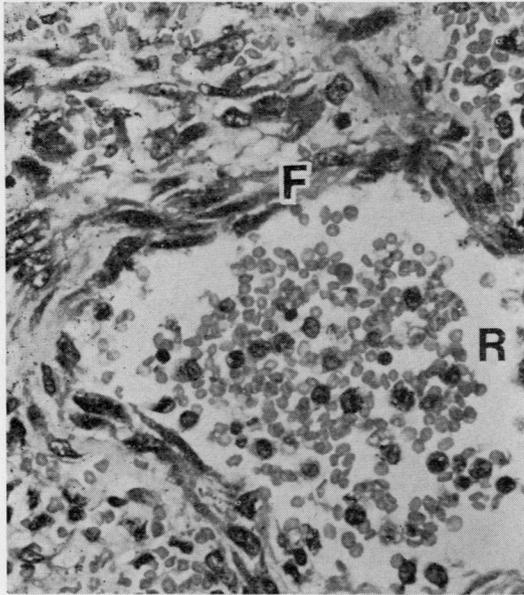


FIG. 2. Case 1. A respiratory bronchiole (R) contains extravasated erythrocytes and is surrounded by plump fibroblasts (F) with associated capillaries (H and E $\times 375$).

A proliferation of the bronchiolar epithelium was not seen, but rarely a continuous epithelium of granular pneumocytes was found lining a few surviving air spaces.

CASE 2 Most of the alveolar spaces in the lung of this case were occupied by loose, cellular, fibroblastic tissue. The fibrosis was less dense than in case 1 and had caused less obliteration of the lung architecture. Also the alveolar walls, although damaged, had persisted and were easily identified as chains of capillaries containing red blood cells (Fig. 3). These acted as markers for the situation of the pulmonary fibrosis which was present exclusively in the alveolar spaces (Figs 3 and 4). Some of the cells comprising this fibrosis were round or oval with an irregular 'ragged' outline, unvacuolated, moderately eosinophilic cytoplasm, and large darkly staining nuclei (Fig. 3). Fibroblasts were elongated, strap-shaped cells with a deeply basophilic cytoplasm (Fig. 4). There extended from them long cytoplasmic prolongations which merged imperceptibly with ground substance and fine collagen fibrils. The collagen stained only faintly with van Gieson's stain.

An extensive fibrinous exudate was present throughout the lung which was heavily infiltrated with lymphocytes and plasma cells (Fig. 3). Haemorrhage was slight. In some areas the res-

piratory bronchioles were dilated so that the lung had a honeycomb appearance. Eosinophilic hyaline membranes were adherent to the walls of these dilated airways.

CASE 3 In this case the upper and lower lobes presented different histological pictures. The lower lobes were solid and consisted of a dense fibrosis in which there were a few fibroblasts surrounded by an extensive acellular matrix of mature collagen, which stained intensely with van Gieson's stain. There was an associated heavy infiltration of chronic inflammatory cells.

In the upper lobes the lung was honeycombed. The honeycombing was produced by gross dilatation of respiratory bronchioles with collapsed and fibrosed alveoli forming the intervening septa. In the upper lobes the fibrosis contained more fibroblasts than in the lower lobes, although there was considerably more mature collagen than in the previous two cases (Figs 5 and 6). The plump, basophilic, strap-shaped fibroblasts, typical of cases 1 and 2, were uncommon in this case except in the vicinity of respiratory bronchioles (Figs 5 and 6) where they appeared to be infiltrating the air spaces.

There was a pronounced proliferation of the bronchiolar epithelium forming large islets several cells thick in which acini were poorly defined or absent. These islets of bronchiolar cells were embedded in fibrous tissue and surrounded the parent bronchioles. The few surviving alveoli were lined by a continuous epithelium of granular pneumocytes (Fig. 5). These had often sloughed off to form an intact ring within the air space.

CASE 4 The changes in the lung of this case were uniform and consisted primarily of alveolar capillary congestion with widespread alveolar pulmonary oedema (Fig. 7). The oedema contained fine strands of fibrin and many neutrophil polymorphs. All the respiratory bronchioles contained hyaline membranes with the same tinctorial properties as fibrin. In the vicinity of terminal bronchioles the alveoli contained irregular basophilic cells resembling fibroblasts without any associated collagen.

The changes in the lung parenchyma of all four cases are summarized in the Table.

HISTOPATHOLOGY OF THE PULMONARY VASCULATURE

CASE 1 Many of the smaller pulmonary arteries with an external diameter less than 200 μm

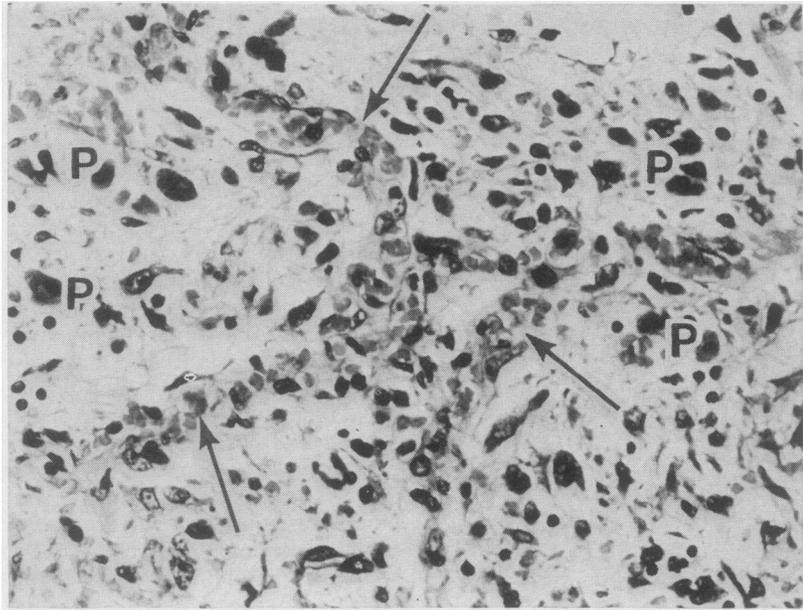


FIG. 3. Case 2. Early intra-alveolar fibrosis. Alveolar walls persist and can be seen as chains of capillaries (arrowed). The alveolar spaces contain fibroblasts and a few atypical fibroblastic cells (P). The intercellular fibrillary substance is mostly fibrin (H and E $\times 150$).

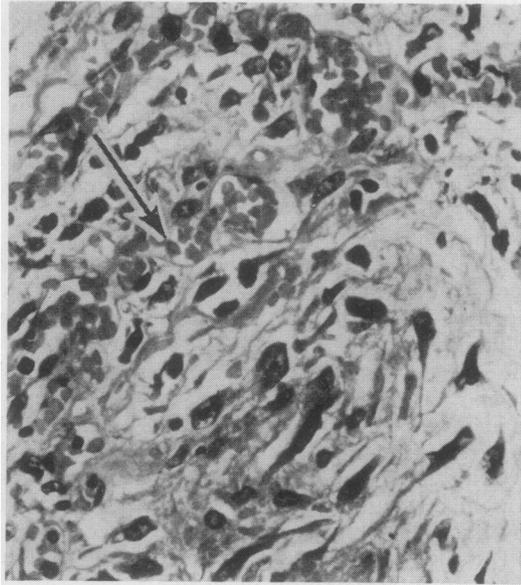


FIG. 4. Case 2. Mature intra-alveolar fibrosis. A damaged alveolar wall can be seen as a chain of capillaries (arrow). Numerous elongated basophilic fibroblasts are seen exclusively within the alveolar space. The intercellular matrix consists of fine collagen fibrils (H and E $\times 375$).

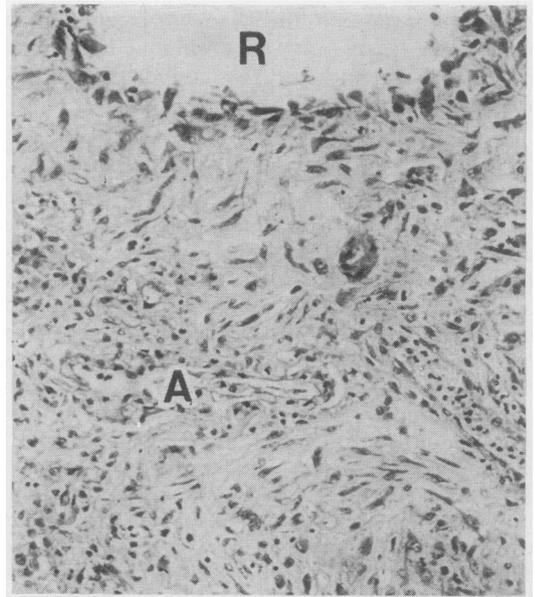


FIG. 5. Case 3. A dense pulmonary fibrosis consisting of fibroblasts and large quantities of collagen has obliterated the lung architecture. Fibroblasts adjacent to what appears to be a respiratory bronchiole (R) are larger than elsewhere and appear to be invading the airway. A small surviving airspace (A) is lined by granular pneumocytes (H and E $\times 150$).

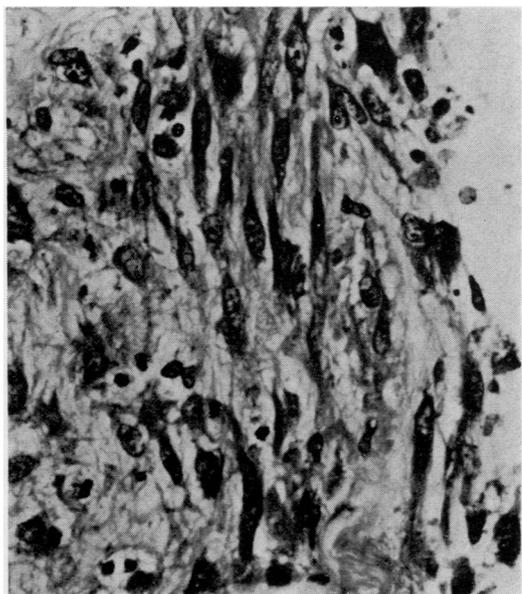


FIG. 6. Case 3. Numerous large strap-shaped basophilic fibroblasts adjacent to a surviving respiratory bronchiole. Fibroblasts of this type were found only in this situation in case 3. Note the fibrillary collagenous matrix between the cells (H and E $\times 375$).

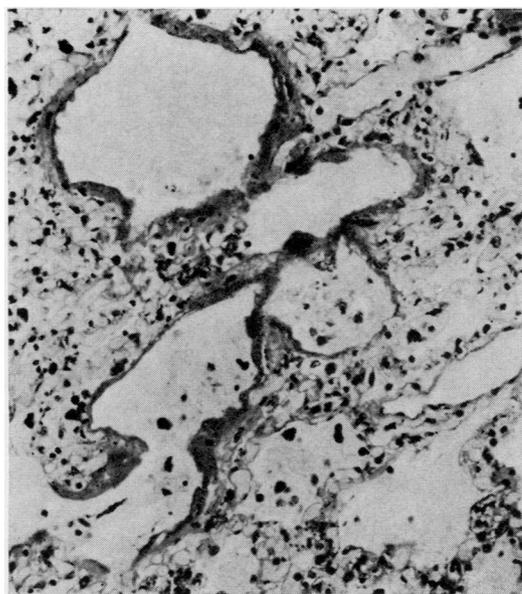


FIG. 7. Case 4. The lung shows capillary congestion and extensive alveolar oedema. Terminal and respiratory bronchioles contain eosinophilic hyaline membranes (H and E $\times 150$).

TABLE
CHANGES IN THE LUNG PARENCHYMA IN FOUR CASES OF
PARAQUAT POISONING

Lesion	Case 1	Case 2	Case 3	Case 4
Alveolar pulmonary oedema	—	—	—	++
Fibrinous exudate	++	++	—	+++
Hyaline membranes	++	++	+	+++
Pulmonary haemorrhage	++	++	—	++
Neutrophil polymorphs	+	+	+	++
Lymphocytic infiltrate	++	++	++	++
Cellular fibroblastic tissue	++	++	++	—
Collagenous fibrosis	+	++	++	—
Bronchiolar epithelial proliferation	—	—	++	—
Hyperplasia of granular pneumocytes	+	—	+	—
Honeycomb change	—	+	++	—

— absent; + present but scarce; ++ common.

showed medial hypertrophy. Several pulmonary arterioles were muscularized having developed a media of circularly orientated smooth muscle sandwiched between two well-defined elastic laminae.

The intima was normal throughout most of the pulmonary arterial tree, although a few muscular pulmonary arteries contained small intimal plaques consisting of elastic fibres and longitudinally orientated smooth muscle cells. Many of the small muscular pulmonary arteries and the muscularized pulmonary arterioles showed focal fragmentation of their external elastic laminae.

CASE 2 Many of the pulmonary arteries showed medial hypertrophy with crenation of elastic laminae (Fig. 8). There was pronounced muscularization of pulmonary arterioles. In both the pulmonary arteries and arterioles there was a cellular intimal proliferation consisting of fine elastic fibres and longitudinally orientated smooth muscle cells (Fig. 8).

Some muscular pulmonary arteries showed focal atrophy of the media and this was associated with fragmentation of the external elastic lamina (Fig. 9). In a minority of vessels virtually the whole circumference of the media was atrophic. In these atrophic vessels the intima consisted of an open network of fine fibrils which stained faintly with van Gieson's stain.

All the pulmonary venules contained an intimal fibrosis of fine collagen fibrils. This was sometimes so extensive as to cause almost total occlusion of the affected vessel.

CASE 3 There was no medial hypertrophy of muscular pulmonary arteries in this case. In the larger muscular pulmonary arteries the circular

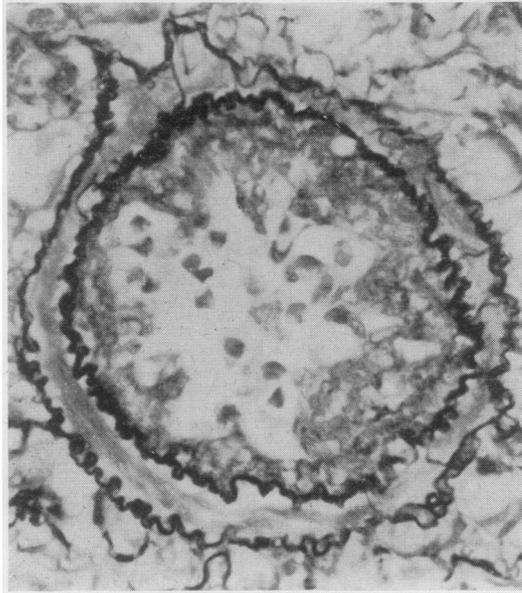


FIG. 8. Case 2. A small muscular pulmonary artery showing hypertrophy of its media and an intimal proliferation of longitudinally orientated smooth muscle cells and fine elastic fibrils. (Elastic van Gieson $\times 600$).

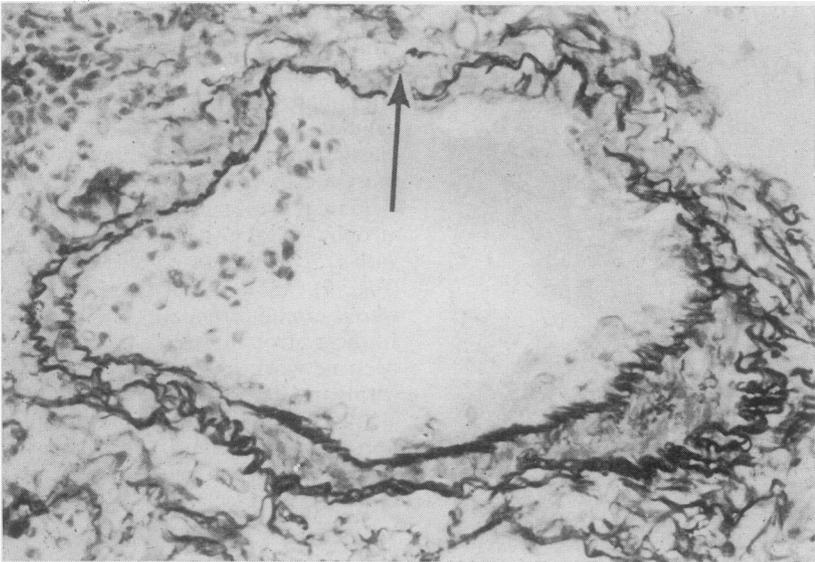


FIG. 9. Case 2. Muscular pulmonary artery with a focus of medial atrophy (arrowed). There are also discontinuities in the internal elastic lamina and fragmentation of the external elastic lamina (EVG $\times 375$).

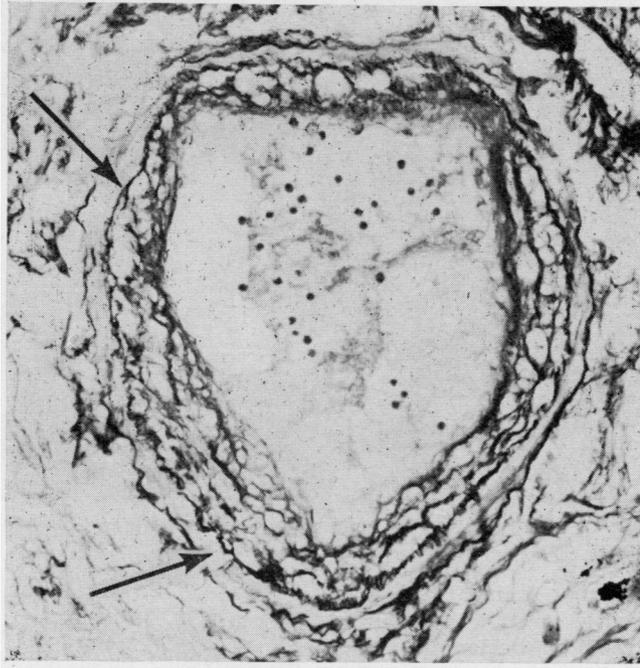


FIG. 10. *Case 3. Muscular pulmonary artery in which medial atrophy is so severe that in some segments (arrowed) the elastic laminae have an empty space between them. There is also focal fragmentation of the external elastic laminae. The intima contains a thick layer of fibro-elastic tissue (EVG $\times 315$).*

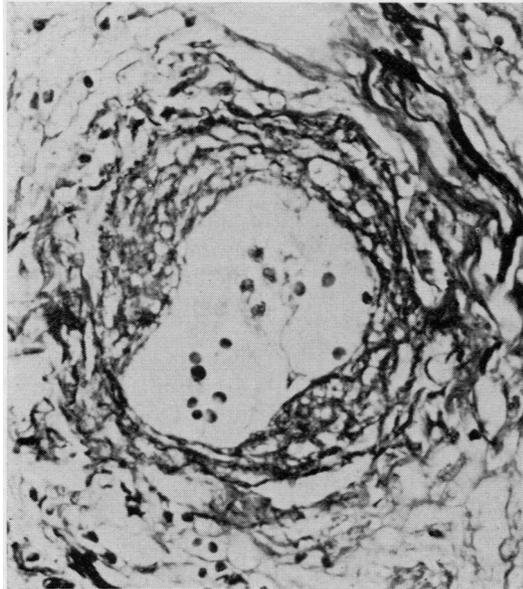


FIG. 11. *Case 3. Muscular pulmonary artery in which the media has become obliterated by fibro-elastic tissue (EVG $\times 375$).*

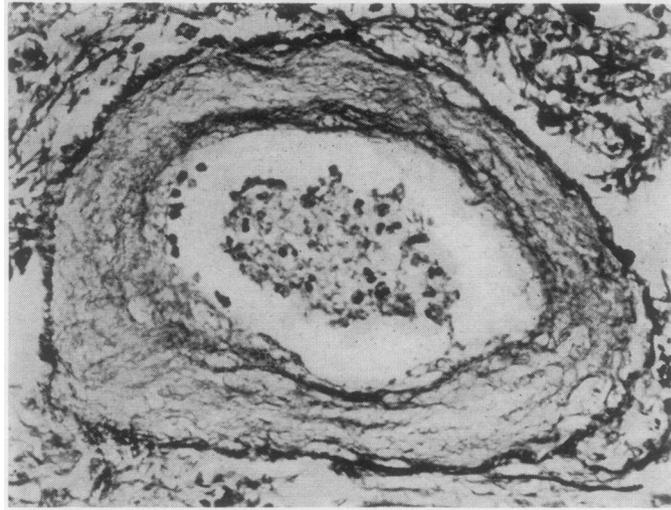


FIG. 12. Case 3. Small pulmonary vein containing a profuse intimal proliferation of fine collagen fibrils (EVG $\times 375$).

muscle was atrophic so that individual smooth muscle cells were widely separated. There was no fibrinoid necrosis. External elastic laminae were usually fragmented and discontinuous and tended to merge into the surrounding fibrous tissue. All the larger pulmonary arteries contained an intimal proliferation of anastomosing elastic fibres with fine collagen fibres in its interstices. This intimal proliferation often included a few longitudinally orientated smooth muscle cells.

In the smaller muscular pulmonary arteries the media was distinctly atrophic (Fig. 10). There were frequently segments of vessels in which the media was absent, leaving the elastic laminae with an empty space between (Fig. 10). In these vessels the intimal fibro-elastosis was profuse and contained no smooth muscle. In a minority of the pulmonary arteries medial atrophy and fragmentation of elastic laminae were so severe that they consisted merely of an irregular ring of fibro-elastic tissue with a diminished lumen (Fig. 11). This merged imperceptibly into the surrounding fibrosis so that the original boundary of the vessel could not be determined (Fig. 11).

The elastic laminae of pulmonary arterioles were split into many fine fibrils. The arterioles also contained a prolific intimal fibro-elastosis which often caused ablation of the affected vessel.

The small pulmonary veins contained an extensive intimal fibrosis of fine collagen fibrils (Fig. 12). Some venules, particularly those in the lower lobes, were totally occluded by fibrosis.

CASE 4 The pulmonary vasculature was normal.

DISCUSSION

The four cases described in this study illustrate the variability in the histological changes which may occur in the lungs in paraquat poisoning. Lesions range from an acute inflammatory exudate and oedema to dense collagenous fibrosis with honeycomb change. The origin of paraquat-induced pulmonary fibrosis cannot always be determined from examination of postmortem material. Thus in cases 1 and 3 obliteration of lung architecture was so severe that it was impossible to determine whether the fibrosis was intra-alveolar or interstitial in nature. However, in case 2 the alveolar architecture was intact, and it could be demonstrated that fibroblastic tissue was present exclusively within the alveolar spaces and did not involve the alveolar walls. In this case death supervened before the pulmonary fibrosis had become extensive and obliterated the alveolar architecture.

The pathogenesis of paraquat-induced pulmonary fibrosis has been studied in detail in the rat (Smith *et al.*, 1974). Initially there is a heavy infiltration into the alveolar spaces of primitive connective tissue cells or profibroblasts. These undergo maturation into large basophilic fibroblasts which occlude many alveolar spaces. Later, alveolar walls disintegrate, permitting the individual clumps of fibroblastic tissue to coalesce, resulting in obliteration of the lung architecture. The fibroblasts lay down small quantities of collagen but death from respiratory failure usually supervenes before this has become extensive. This

final stage of the disease, like that in man, is reminiscent of interstitial fibrosis of the lung, but obliteration of the alveolar walls belies its true intra-alveolar origin.

The pathogenesis of human paraquat lung may parallel that in the rat. Thus the atypical irregular fibroblasts seen on histological examination in cases 2 and 4 would likely prove on electron microscopy to be profibroblasts, as described in the rat (Smith *et al.*, 1974). Similar cells were observed in a human lung biopsy specimen (Toner, Veters, Spilg, and Harland, 1970), but they were interpreted as representing a monocyte infiltration. At a subsequent postmortem examination of this case these workers described an extensive pulmonary intra-alveolar fibrosis.

It has been suggested that paraquat causes interstitial pulmonary fibrosis simply by organization of inflammatory exudate (Vijayaratnam and Corrin, 1971). Certainly incorporation of organizing inflammatory exudate or cellular debris into the alveolar walls can lead to interstitial fibrosis as, for example, in busulphan lung (Littler, Kay, Hasleton, and Heath, 1969). However, chronic administration of paraquat to rats induces an extensive fibrosis following only a slight fibrinous exudate (Smith *et al.*, 1974). Also Gage (1968) has shown that inhalation of paraquat aerosols by animals causes an extensive exudation of fluid into the alveoli but that pulmonary fibrosis never results from this. It seems that the formation of a fluid exudate during the early stages of paraquat poisoning is not necessary for the development of pulmonary fibrosis and that paraquat, or its metabolites, directly stimulates an infiltration of profibroblasts into the lung. The experimental evidence from rats, plus our own observations on human cases presented here, suggests that the pathogenesis of paraquat lung is similar in the two species. We think that the basic pathological change in the human lung due to paraquat poisoning is a diffuse, cellular, intra-alveolar fibrosis and not fibrosing alveolitis.

Caution must be exercised when comparing the pathology of controlled animal experiments with that of human disease since the latter is often modified by treatment. Thus oxygen therapy was given in all four cases described here as well as in many other reported cases of paraquat poisoning (Almog and Tal, 1967; Campbell, 1968; Matthew *et al.*, 1968; Oreopoulos *et al.*, 1968; Toner *et al.*, 1970). Prolonged respiration of gases containing more than 40% oxygen carries the grave risk of oxygen poisoning (Sevitt, 1974). In this condition there is an early exudative phase

in which hyaline membranes are prominent, followed by a proliferative phase in which there is a hyperplasia of granular pneumocytes and the development of interstitial pulmonary fibrosis (Nash, Blennerhassett, and Pontoppidan, 1967; Sevitt, 1974). In some cases reviewed by Sevitt there was also an intra-alveolar fibrosis. One should consider the possibility that oxygen toxicity may be a contributory factor in the pathogenesis of the pulmonary fibrosis in some cases of paraquat poisoning in man. There is no questioning the fact that paraquat is capable of producing pulmonary damage on its own for intra-alveolar fibrosis occurs when paraquat is given to rats breathing only atmospheric oxygen. Furthermore, the histopathology of paraquat lung and oxygen poisoning is somewhat different in that, although intra-alveolar fibrosis may occur in the latter, there is always a prominent interstitial component. Neither is there a profuse hyperplasia of granular pneumocytes in paraquat lung since most alveolar walls disintegrate and become engulfed by fibroblastic tissue. It is, however, impossible to exclude completely oxygen toxicity as a contributory factor in the pathogenesis of pulmonary fibrosis in some cases of paraquat poisoning in man.

Electron microscopic studies on rats have shown that pulmonary fibrosis in paraquat poisoning is preceded by destruction of the alveolar epithelium. There is an increase in thickness of the alveolar epithelium only 4 hours after administration of paraquat (Smith and Heath, 1974). This is followed by intracytoplasmic oedema and ballooning of epithelial cells (Vijayaratnam and Corrin, 1971; Smith and Heath, 1974) and total loss of the epithelium by two or three days (Vijayaratnam and Corrin, 1971; Smith *et al.*, 1974; Smith and Heath, 1974). This pulmonary damage is associated with pulmonary oedema and acute inflammation. In case 4, death from renal failure supervened while pulmonary lesions were at an early stage in their development. In this case there was an acute inflammatory exudate and alveolar pulmonary oedema similar to that in the rat. Destruction of alveolar epithelium could not be demonstrated without electron microscopic examination but Toner *et al.* (1970) have convincingly shown fragmentation of the alveolar epithelium in a human lung biopsy specimen of paraquat poisoning. Clinical evidence of pulmonary oedema three days after paraquat ingestion has been reported (Gardiner, 1972).

The pulmonary oedema in case 4 was associated with the presence of eosinophilic hyaline membranes. These two changes can be explained as

at least partly the result of renal failure. However, hyaline membranes were common to all four cases and are such a consistent finding in paraquat poisoning in both man and animals that this disease has been proposed as an experimental model for the idiopathic respiratory distress syndrome (Manktelow, 1967; Robertson *et al.*, 1971). Gardiner (1972) has suggested that the pulmonary oedema in paraquat poisoning is caused by a loss of pulmonary surfactant consequent upon destruction of granular pneumocytes.

The lesions of the lung parenchyma in cases 1 to 3 were associated with striking pulmonary vascular changes. In cases 1 and 2 there was a slight increase in medial thickness of pulmonary arteries, a pronounced muscularization of arterioles, and longitudinal muscle in the intima of both types of vessel. These changes are characteristic of hypertensive pulmonary vascular disease (HPVD) brought about by conditions of chronic hypoxia (Hasleton, Heath, and Brewer, 1968). Thus it is possible that the pulmonary fibrosis in paraquat poisoning produces alveolar hypoxia of sufficient severity to induce the changes of hypoxic HPVD, despite the fact that death occurs a mere three weeks after ingestion of the paraquat. Muscularization of pulmonary arterioles has been described in rats following repeated doses of paraquat (Smith *et al.*, 1974).

In case 3 there was fragmentation of the elastic laminae, atrophy of the muscular media, and extensive intimal fibro-elastosis. This degeneration of the pulmonary arterial tree was too severe to be attributable to the mild degree of pulmonary hypertension associated with chronic hypoxia. Similar changes have been described in the pulmonary arteries of honeycomb lung complicating a variety of diseases (Heath, Gillund, Kay, and Hawkins, 1968), and atrophy and intimal fibro-elastosis in the pulmonary arteries of case 3, and to a lesser extent case 2, may be the result of honeycomb change in the lung parenchyma. Thus in case 2, honeycombing was at an early stage in its development and the arteries showed only moderate atrophy of muscle with no intimal fibrosis whereas in case 3 honeycombing was pronounced and the arteries showed a prominent intimal fibrosis with extensive medial atrophy. So far as we are aware, this is the first time that pulmonary vascular pathology has been described in paraquat lung.

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