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Dietary pulmonary hypertension

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In 1967 Kay *et al* postulated that some cases of unexplained pulmonary hypertension might be due to the ingestion of drugs or other toxic substances.[1] This concept, later termed dietary pulmonary hypertension,[2 3] was advanced following the observation that the oral administration to rats of the pyrrolizidine alkaloid monocrotaline produced severe pulmonary hypertension.[1] There are no reports of pyrrolizidine alkaloids causing pulmonary hypertension in human subjects, but there have been two epidemics of pulmonary hypertension caused by the ingestion of other substances, and several reports of pulmonary hypertension associated with the administration of drugs (table). The two epidemics of pulmonary hypertension were related to the ingestion of an appetite suppressing drug aminorex,[4] and to the ingestion of denatured rapeseed oil.[5] Pulmonary hypertension has also been reported in two obese patients taking phenformin.[6] Severe pulmonary hypertension associated with haemolytic anaemia and renal failure occurred in a 46 year old man with carcinoma of the colon who was treated with mitomycin.[7] Pulmonary veno-occlusive disease has been described in patients receiving chemotherapy with BCNU[8] and bleomycin alone,[9] or in combination with mitomycin and cisplatin,[10] or mitomycin, cisplatin and vinblastine.[11] The effects of pyrrolizidine alkaloids, anorexigens, L-tryptophan, and toxic oil on the pulmonary vasculature are considered in the following review.

Pyrrolozidine alkaloids and the pulmonary circulation

Alkaloids are plant constituents other than simple amines which contain a basic nitrogen atom. They occur widely and are present in approximately 5% of all plant species.[12] The pyrrolizidine alkaloids are amino alcohols derived from the pyrrolizidine nucleus. Once thought to be characteristic of *Senecio* species, pyrrolizidine alkaloids are now known to be equally common in *Crotalaria* species and in all species in the subfamilies Heliotropioideae and Boraginoideae and the family Boraginaceae.[12] These three main botanical groups, in which the pyrrolizidine alkaloids occur, consist mostly of herbaceous species and a few shrubs. The *Crotalaria* genus is virtually restricted to tropical and subtropical areas, but the Senecioneae and Boraginaceae are worldwide in distribution. The pyrrolizidine alkaloids are toxic, and are thus hazardous to farm animals and to man.[13 14]

Pulmonary hypertension associated with drugs and toxic substances

Drug or substance	*Pulmonary vascular pathology*
Aminorex	Pulmonary arteriopathy with plexiform lesions
BCNU	Pulmonary veno-occlusive disease
Bleomycin	Pulmonary veno-occlusive disease
Combination chemotherapy	Pulmonary veno-occlusive disease
Dexfenfluramine	Pulmonary arteriopathy with plexiform lesions
Fenfluramine	Pulmonary arteriopathy with plexiform lesions
L-tryptophan	Vascular and perivascular chronic inflammation
Mitomycin	Intracapillary thrombi
Phendimetrazine	Pulmonary artery medial hypertrophy and intimal fibrosis
Phenformin	—
Propylhexedrine	—
Spanish toxic oil	Pulmonary artery medial hypertrophy, intimal proliferation with foam cells, perivascular chronic inflammation

Crotalaria spectabilis

Crotalaria spectabilis is indigenous to India but is now widely scattered throughout the tropics and subtropics of both hemispheres.[13] The stems, leaves, and seeds contain the pyrrolizidine alkaloid monocrotaline which is toxic to a wide range of animals including cattle, pigs, hens, turkeys, monkeys, and rats.[13]

When young rats are given a diet containing 0·1% powdered *Crotalaria spectabilis* seeds they develop severe pulmonary hypertension and die within 36–60 days.[1] The pulmonary hypertension is accompanied by right ventricular hypertrophy, thickening of the pulmonary trunk,[15] and medial hypertrophy of the muscular pulmonary arteries.[16] About one third of the rats develop necrotising pulmonary arteritis. Plexiform lesions and intimal fibrosis do not occur. There is muscular thickening of the walls of small pulmonary veins.[16] In addition to the pulmonary vascular disease, the lung parenchyma shows pulmonary oedema, intra-alveolar haemorrhage, interstitial fibrosis, and a proliferation of alveolar cells.[16 17] These parenchymal lesions probably result from obstruction to the small pulmonary veins. Fatal pulmonary hypertension and hypertensive pulmonary vascular disease can be produced in rats by a single intraperitoneal injection of monocrotaline (fig 1).[18]

Crotalaria fulva

Crotalaria fulva is one of several plants used in the West Indies for the preparation of bush teas consumed by the indigenous population for medicinal and other purposes.[19] The leaves and seeds of *Crotalaria fulva* contain fulvine which is closely related to monocrotaline. The oral or systemic administration of fulvine to rats leads to right ventricular hypertrophy accompanied by thickening of the pulmonary trunk and medial hypertrophy of muscular pulmonary

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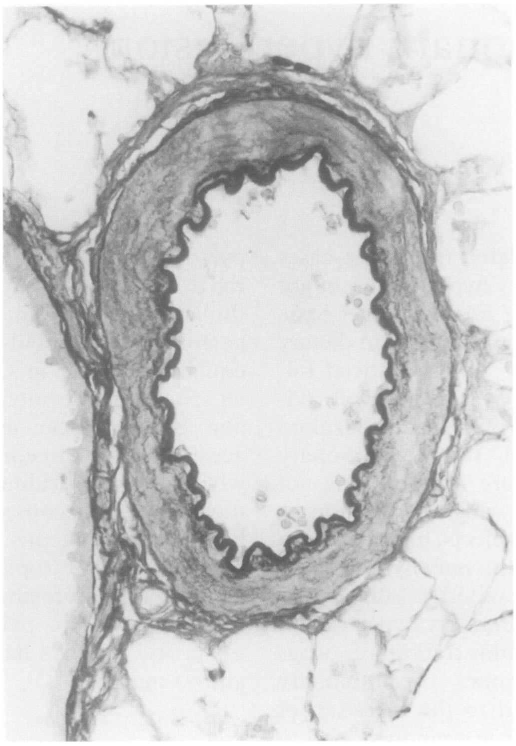

Figure 1 Medial hypertrophy of muscular pulmonary artery in rat killed 20 days after a single intraperitoneal injection of monocrotaline (60 mg/kg). Stain: elastic van Gieson, magnification × 400 reduced to 76% in origination.

arteries.[19] Acute necrotising arteritis also occurs in a small proportion of animals. The pulmonary veins show narrowing of their lumens due to a proliferation of smooth muscle and an increase in collagen.[20 21] Thus monocrotaline and fulvine produce identical pulmonary vascular lesions in rats.

Senecio jacobaea

This is the common ragwort plant which farmers have long recognised as being toxic to cattle (fig 2). Its seeds and leaves contain the pyrrolizidine alkaloids seneciphylline, senecionine, jacobine, jaconine, jacoline, and jacozine.[12] It is available in some health food stores in a dried, chopped form, which is made into an infusion to cure various ailments. When rats are given a diet adulterated with powdered dried *Senecio jacobaea* they develop right ventricular hypertrophy, thickening of the pulmonary trunk, medial hypertrophy of muscular pulmonary arteries, and muscularisation of the pulmonary arterioles.[22] Pure seneciphylline has been shown to induce right ventricular hypertrophy and medial hypertrophy of pulmonary arteries in rats.[23]

MECHANISM OF PULMONARY TOXICITY OF PYRROLIZIDINE ALKALOIDS

The mechanism by which the pyrrolizidine alkaloids produce pulmonary hypertension in laboratory animals is not clear.[24 25] There is considerable variation in the susceptibility of animal species to the pulmonary hypertensive effects of monocrotaline.[26] Pulmonary hypertension has been described in rats and young monkeys given monocrotaline,[27] but mice, rabbits, and hamsters are relatively resistant to its pulmonary hypertensive effects, and dogs are only occasionally susceptible.[26] One of the most intriguing problems is the latent period of several days which elapses between the administration of the alkaloid and the development of pulmonary vascular lesions. Endothelial injury may be an early, or perhaps the earliest, event which occurs in the lungs after the administration of monocrotaline.[28 29] The sequence of events in rats following a single injection of monocrotaline appears to be as follows: endothelial injury is detected by electron microscopy at four days,[28] muscularisation of pulmonary arterioles and medial hypertrophy of muscular pulmonary arteries occurs at seven days, pulmonary hypertension is detectable at 10 days, and right ventricular hypertrophy is present at 12 days.[30] There is evidence that the pyrrolizidine alkaloids themselves are not toxic substances, but that they are dehydrogenated in the liver to produce highly reactive pyrrole derivatives, which may then be transported to the lungs. It has been shown that the metabolism and excretion of a single toxic dose of a pyrrolizidine alkaloid takes place rapidly, and is virtually complete within 24 hours.[14 31] The delayed onset of the pulmonary vascular disease cannot therefore result from a prolonged exposure to a toxic metabolite circulating in the blood for several weeks, but must follow a short exposure during the metabolism of the alkaloid. Numerous investigations of the mechanism of action of monocrotaline have revealed a variety of inhibitory substances.[26] Some of these agents have been more effective than others but none have afforded complete protection. The biochemical pathways whereby the administration of monocrotaline or monocrotaline pyrrole leads to endothelial injury remain obscure despite studies of lung mast cells,[32] 5-hydroxy-

Figure 2 The flowers of Senecio jacobaea approximately half natural size.

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Figure 3 Plexiform lesion (top) in lateral branch of a muscular pulmonary artery (bottom) in a woman aged 44 years who died of pulmonary hypertension after taking aminorex. Stain: elastic van Gieson, magnification ×155 reduced to 76% in origination.

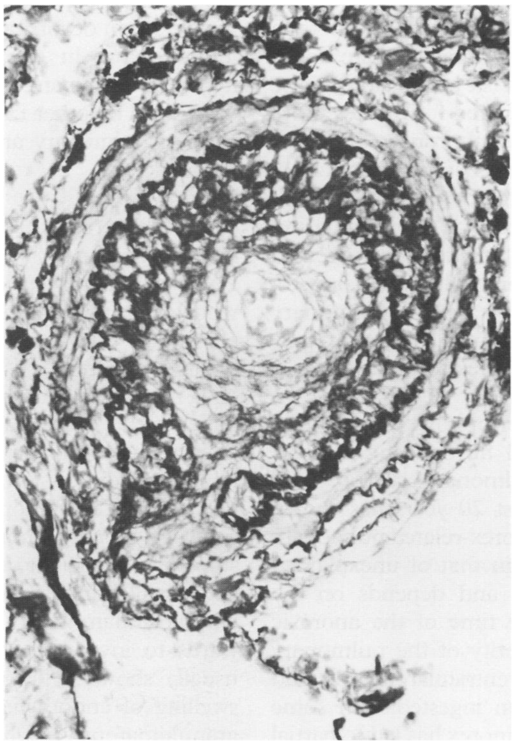

Figure 4 Muscular pulmonary artery showing medial hypertrophy and concentric laminar intimal fibrosis in the same patient as in fig 3. Stain: elastic van Gieson, magnification ×400 reduced to 76% in origination.

tryptamine,[33 34] platelets,[35] angiotensin converting enzyme,[30] polyamines,[36] arachidonic acid metabolites,[37] immune mechanisms,[38] and elastin and collagen synthesis.[39]

TOXICITY OF PYRROLIZIDINE ALKALOIDS IN HUMAN SUBJECTS

It is now generally accepted that fulvine, and possibly other pyrrolizidine alkaloids, in bush tea are the cause of veno-occlusive disease of the liver in the West Indies.[40] Pyrrolizidine alkaloids have caused massive outbreaks of hepatic veno-occlusive disease in Afghanistan[41] and India[42] and have caused sporadic cases in the USA[43] and UK.[44] The clinical and pathological features of hepatic veno-occlusive disease are well described elsewhere,[45] and are outside the scope of this paper. Hypertensive pulmonary vascular disease has never been described in human cases of hepatic veno-occlusive disease. The pulmonary arteries and veins in these patients are normal.[46] It is not clear why human pulmonary arteries and veins are apparently unaffected by the pyrrolizidine alkaloids when they exert such toxic effects on the small hepatic veins. When injections of monocrotaline were given to two groups of stumptail monkeys aged one month and 15 months, respectively, the younger animals developed pulmonary hypertension while the older animals got hepatic veno-occlusive disease.[27] It was suggested that the different responses of infant and older monkeys were related to differences in hepatic microsomal enzyme activity. It was hypothesised that the enzyme systems associated with the production of metabolites which are toxic to the lung were better developed in the infant than in the older animals. It should be noted, however, that when children ingest pyrrolizidine alkaloids in bush tea they develop hepatic veno-occlusive disease and not pulmonary vascular disease.[47]

Anorexigens

AMINOREX

Aminorex is an appetite suppressing drug which was available in Switzerland from November 1965 to October 1968. In 1967 a sudden 20-fold increase in the incidence of unexplained pulmonary hypertension was observed in a Swiss medical clinic.[48] It was noted that a considerable number of these patients had taken aminorex to reduce weight. A similar increase in the incidence of unexplained pulmonary hypertension was encountered in other clinics in Switzerland, and in Austria and Germany where aminorex was also available. An increased incidence of the disease was not reported in countries where the drug was not available. A threefold to fivefold increase in unexplained pulmonary hypertension occurred in Switzerland that was not associated with the ingestion of aminorex. It is not clear whether this was due to increased awareness of the disease resulting from wide publicity, or a possible concealment of aminorex consumption, or whether it reflected the operation of other unsuspected aetiological factors. A survey of the prescription forms of a health insurance company in West Germany identified 731 patients known to have taken aminorex.[49] In this group 22 cases of unexplained pulmonary hypertension were found. It was shown that there was a highly significant relation in women be-

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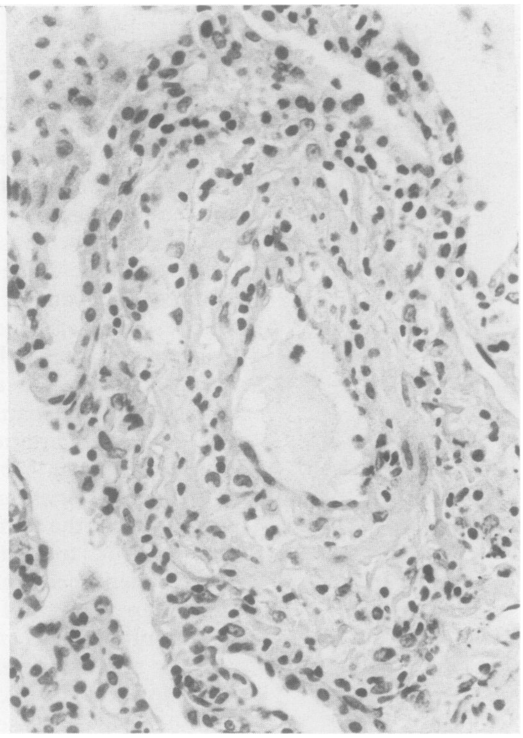

Figure 5 Small muscular pulmonary artery in woman aged 34 who developed pulmonary hypertension after ingesting L-tryptophan. There is swelling of endothelial cells and the entire thickness of the wall is infiltrated by lymphocytes and eosinophils. Stain: haematoxylin and eosin, magnification × 400 reduced to 76% in origination.

tween the logarithm of the risk of developing pulmonary hypertension and the number of aminorex tablets ingested. Specifically, after the ingestion of more than eight packs of aminorex tablets there was a 10% risk of developing the disease. Women were affected four times more frequently than men, and the onset of symptoms of pulmonary hypertension generally occurred 12 months after the commencement of aminorex therapy. There was no correlation between the total amount of aminorex ingested and the degree of pulmonary hypertension.

In a study of 17 fatal cases of pulmonary hypertension following aminorex ingestion pulmonary arteriopathy with plexiform lesions was present in five cases (fig 3). There were 11 cases of pulmonary arteriopathy with medial hypertrophy and intimal fibrosis (fig 4), and one case of thrombotic pulmonary arteriopathy.[46] Experience during the last 20 years has shown that the prognosis of aminorex-related pulmonary hypertension is better than that of unexplained pulmonary hypertension, and depends on the age of the patient at the time of the anorexic treatment, the initial severity of the pulmonary hypertension and right ventricular failure, and the amount of anorexigen ingested.[50] In some patients withdrawal of aminorex has led to partial remission of the pulmonary hypertension.[50] In a 15 year follow up of a female patient with aminorex-related pulmonary hypertension a fusiform aneurysm of the pulmonary trunk was observed.[51]

The mechanism whereby aminorex produces pulmonary hypertension is not clear. In experimental studies on animals, acute and subacute administration of aminorex leads to a significant, but transient, increase in pulmonary arterial pressure and in pulmonary vascular resistance in most of the species tested.[50] It has not proved possible, however, to induce chronic pulmonary hypertension or pulmonary vascular disease after chronic administration of the drug.[4 46]

FENFLURAMINE

Pulmonary hypertension has been described in patients receiving fenfluramine.[52 53 66] In some cases the pulmonary hypertension has regressed after withdrawal of the drug. In fatal cases the lungs show pulmonary arteriopathy with plexiform lesions.[54 66]

PROPYLHEXEDRINE

Pulmonary hypertension has been reported in two patients receiving propylhexedrine,[55] which regressed after discontinuation of the drug.

PHENDIMETRAZINE

Pulmonary hypertension developed in a patient receiving phendimetrazine.[56] An open lung biopsy showed pulmonary arteriopathy with medial hypertrophy and intimal fibrosis. The pulmonary hypertension regressed after discontinuation of the drug.

DEXFENFLURAMINE

There have been two case reports of pulmonary hypertension occurring in patients receiving dexfenfluramine. In one of these the pulmonary hypertension reversed when the drug was withdrawn.[57] The other case was fatal and the lungs showed pulmonary arteriopathy with plexiform lesions.[58]

L-Tryptophan

Pulmonary hypertension may develop in people who ingest preparations of L-tryptophan. Usually it is a component of the eosinophilia-myalgia syndrome.[59 60] However, some patients have neither eosinophilia nor myalgia.[61] In some patients the pulmonary hypertension regresses after withdrawal of the L-tryptophan and the administration of steroids,[59] but in others it persists.[61] Open lung biopsy specimens have shown small pulmonary arteries and pulmonary veins surrounded by tight cuffs of lymphocytes mixed with small numbers of eosinophils (fig 5). This chronic inflammatory cell infiltrate extends inwards to involve the media and intima which usually shows a fibromyxoid proliferation and swelling of endothelial cells.[59–61] In one case a granulomatous vasculitis was seen, characterised by palisading histiocytes within the vessel wall associated with giant cells and a focus of necrosis.[59]

Toxic oil syndrome

The toxic oil syndrome epidemic occurred in Spain during the spring and summer of 1981.[5] It was one of the largest epidemics of an intoxication ever recorded, resulting in about 20 000 cases,

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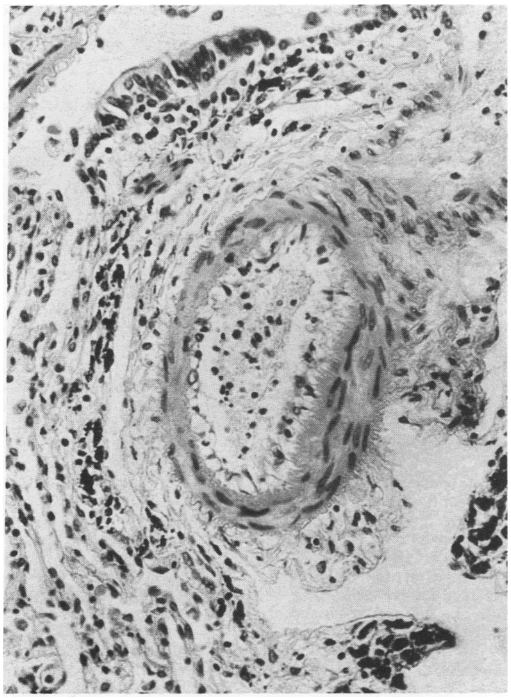

Figure 6 Muscular pulmonary artery from a young woman dying from the toxic oil syndrome showing pronounced medial hypertrophy with prominence of the nuclei of smooth muscle cells. There is an intimal proliferation of cells with a vacuolated appearance. The adventitia is infiltrated by scanty lymphocytes and mononuclear cells. Stain: haematoxylin and eosin, magnification × 375 reduced to 76% in origination.

12 000 hospital admissions, and more than 300 deaths during the first 12 months.[62] The condition was shown to be related to the ingestion of denatured rapeseed oil sold illegally as an inexpensive substitute for olive oil. Pure rapeseed oil is prohibited for human consumption in Spain because animal studies have shown growth retardation and accelerated atherosclerotic effects. Accordingly, only denatured rapeseed oil can be legally imported for industrial use. To produce an inexpensive cooking oil the perpetrators imported industrial grade rapeseed oil denatured with aniline. They attempted to remove the red colour of the aniline by a heating and refining process. Small quantities of soya oil, castor oil, olive oil, and animal fats were also added. During this illegal refining process toxic agents – as yet unidentified – were probably produced.

The clinical course of the toxic oil syndrome had three phases. The first phase was characterised by the adult respiratory distress syndrome. About 50% of the patients recovered from this early phase. The remainder progressed to the second phase of severe myalgia, eosinophilia, and thromboembolic complications. The first cases of pulmonary hypertension were described in this phase. The third phase was characterised by neuromuscular complications and pulmonary hypertension.[62 63] In some patients the pulmonary hypertension regressed but in others it progressed rapidly, leading to death.[64] Postmortem examinations of patients who died with pulmonary hypertension showed medial hypertrophy of muscular pulmonary arteries accompanied by a peculiar but characteristic intimal proliferation involving cells with vacuolated, faintly basophilic cytoplasm that displaced the nucleus to one side (fig 6). The intimal proliferation was associated with narrowing or even occlusion of the lumen. The endothelial cells were swollen and there was a perivascular infiltrate of lymphocytes, plasma cells, histiocytes, and eosinophils.[65] One report mentioned plexiform lesions, but the single illustration in this paper is not convincing.[64] The toxic oil syndrome bears some resemblance to the esosinophilia-myalgia syndrome associated with L-tryptophan ingestion.[62]

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