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Brief Reviews

Dietary Pulmonary Hypertension

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■ The regulation of the pulmonary circulation is inextricably linked to the role of the lungs in gas exchange. Accordingly, it is not surprising that hypoxia and acidosis predominate as stimuli for vasomotor activity or that their main effects are exerted locally on the pulmonary vascular tree. Although pulmonary vasomotor nerves do exist, they operate more to adjust the distensibility of capacitance vessels than to modulate the caliber of resistance vessels (1). Clearly this heavy reliance on local control of the pulmonary circulation is diametric to the situation in the systemic circulation where an elaborate baroregulatory apparatus and the renin-angiotensin system, exerting their influences from afar, dominate circulatory control.

Since regulatory devices in the pulmonary circulation are so primitive and the pulmonary vascular bed is so extensive and capacious, it is reasonable to anticipate that pulmonary arterial hypertension would be difficult to generate (2). This expectation has been fulfilled both in experimental animals and in man. Except for those who reside at high altitude, pulmonary hypertension is a rarity in subjects who are free of heart or lung disease (3). Moreover, the pulmonary hypertension of high altitude is generally benign and reversible when hypoxia is relieved. In contrast, pulmonary hypertension at sea level is usually a distressful complication of heart, lung, or vascular disease which, in one way or another, has led to curtailment of the pulmonary vascular bed and to impediment to blood flow through it. In addition, once started, secondary pulmonary hypertension at sea level tends to be self-perpetuating and progressive in its course. Also, contained within the universe of pulmonary hypertension in which the causes are known is a sprinkling of patients with "primary pulmonary hypertension" in whom initiating mechanisms elude all attempts at identification and whose clinical course is generally malignant.

Few models of experimental pulmonary hypertension exist, and most depend on inflicting a severe hemodynamic stress on the pulmonary vascular tree (2). But there are some models in which injury to the pulmonary circulation is biochemical rather than physical and in which the intimate mechanism of injury is enigmatic. A recent addition to this list is the dietary pulmonary hypertension produced by feeding rats the seeds of a leguminous plant, *Crotalaria spectabilis* (4, 5).

Crotalaria is a genus of annual shrubs indigenous to the tropics and subtropics. About fifty years ago, one of its members, *Crotalaria spectabilis* was introduced into southern states as an intermediate crop that would restore and protect the soil between major crops. Unfortunately, *Crotalaria* is also poisonous to man and animals because of the pyrrolizidine alkaloids that it contains. The major offending pyrrolizidine alkaloid in *Crotalaria spectabilis* is monocrotaline. Other species of the shrub such as *Crotalaria fulva* contain their own distinctive alkaloids, e.g., fulvine. Veterinarians have long been aware that ingestion of *Crotalaria* by domestic animals (and man) leads to incapacitating damage of the liver, lungs, and central nervous system (6). In the West Indies, where poisoning by *Crotalaria spectabilis* is endemic in the native population, hepatotoxicity predominates. However, the rat (4, 5, 7) and the nonhuman primate (*Macaca*) (6) manifest primarily the sequelae of pulmonary arterial hypertension, i.e., right heart failure and death.

The pyrrolizidine alkaloid, monocrotaline, does not act directly on the pulmonary circulation of the rat, since the pulmonary pressor effects of a single dose only become manifest days after the injected monocrotaline has been entirely eliminated from

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the body (5). Instead, it seems likely that monocrotaline is converted by the liver to dehydromonocrotaline (8, 9) as a prerequisite for pulmonary vascular toxicity. At autopsy, the pulmonary vascular lesions resemble those produced by severe, long-standing mitral stenosis in man: medial hypertrophy, necrotizing arteriolitis, and proliferation of mast cells. Moreover, the lesions appear to be morphologically distinct from those of primary pulmonary hypertension (10), since neither plexiform lesions nor intimal fibrosis (11) are regular features.

These provocative experiments have demonstrated conclusively that substances taken by mouth can cause obliterative vascular lesions in the pulmonary circulation. In some species, the liver (and the hepatic veins) appears to bear the brunt of the toxic blow, as might be expected from a poison that enters the body by way of the gut. But in others, such as the rat, the hepatic damage appears to be secondary to the right heart failure rather than primary (5). Extensive research has failed to implicate intrinsic lung damage or release of vasoactive substances from the pulmonary mast cells in the pathogenesis of the pulmonary hypertension. Instead, attention has shifted to the intriguing prospect that malfunctioning of the pulmonary capillary endothelium and platelet aggregation in the minute vessels of the lungs may be central to the problem (9, 12, 13). This prospect will be considered further later in this review.

Apparently entirely unrelated to *Crotalaria* was an epidemic of pulmonary hypertension that exploded in Switzerland, Austria, and Germany between 1966 and 1968 (14). In these countries, the incidence of pulmonary hypertension suddenly increased twentyfold. In contrast to the pulmonary vascular lesions produced by pyrrolizidine alkaloids in the rat, the pathology in man was typical of primary pulmonary hypertension, including the plexiform lesions and intimal fibrosis; the liver was spared. By coincidence or as a consequence, the epidemic followed the introduction of an appetite depressant agent, Aminorex (5-amino-5-phenyloxazoline), in November, 1965. Aminorex resembles epinephrine and amphetamine in chemical structure; both of these agents release endogenous stores of catecholamines. But as yet, the clinical entity of "catecholamine pulmonary hypertension" does not exist; neither amphetamine nor epinephrine has been shown to be related to the outbreak.

Aminorex was banned in 1968. Thereafter, the epidemic subsided, and both the clinicians and the research scientists were left to interpret a temporal and geographic association between the appearance of an epidemic of pulmonary hypertension in Europe and the marketing of Aminorex. The case against Aminorex was not solid. In fact, some clinicians and research scientists have remained unconvinced that Aminorex was the offending agent. After all, although 80% of those patients with pulmonary hypertension did give a history of ingesting Aminorex, the quantities that were taken were often minimal. Moreover, what about the 20% that did not take Aminorex? Certainly if Aminorex were the culprit, its effects in man are not as consistent as those of monocrotaline in the rat, since only a few who ingested the medication developed the syndrome. Nonetheless, despite these reservations, most clinicians have interpreted the outbreak of primary pulmonary hypertension to be a consequence of Aminorex ingestion. To explain the peculiar pulmonary pressor effect of Aminorex, they have invoked some type of predisposition, possibly genetic, as a prerequisite for the obliterative pulmonary vascular lesions. But the nature of this predisposition remains speculative (15).

Prompted by the experience with Aminorex in man, attempts were immediately begun to reproduce dietary pulmonary hypertension by administering Aminorex to animals. Unfortunately, these attempts have been uniformly unsuccessful. Not only did large oral doses to rats (for up to 43 weeks) and to dogs (20 weeks) fail to elicit the vascular lesions of pulmonary hypertrophy (16), but also prior hypersensitization by chronic exposure to the hypoxia of high altitude proved to be of no avail (17). Despite this consistent failure, the consensus persists that agents taken by mouth can evoke pulmonary hypertension in susceptible individuals. Recently, this view was buttressed somewhat by the coincidence of pulmonary hypertension and the ingestion of biguanides (phenformin) (18). Also supportive was the occurrence of pulmonary hypertension, originating in pulmonary venous occlusion, after medicinal use of "bush tea" prepared from *Crotalaria retusa* (19).

The experience with bush tea brings the liver back into focus. In both animals and man, poisoning with bush tea can also produce veno-occlusive disease of the liver (19). This observation, coupled with the fact that pyrrolizidine alkaloids are metabolized in the liver (20), and the coincidence of severe liver disease and pulmonary hypertension in man (21) have heightened suspicion that metabolites of ingested foods may induce pulmonary hypertension if they gain access to the pulmonary circulation. Another explanation is that these metabolites might block a metabolic pathway that ordinarily exerts a pulmonary antihypertensive effect. Alternatively, by damaging the liver, vasoactive substances such as histamine, serotonin and catecholamines might escape metabolic pathways to reach and injure the pulmonary vessels. Indeed, nucleotides that gain access to the pulmonary circulation have been shown to increase pulmonary arterial blood pressure by producing extensive pulmonary vascular obstruction (22). Thus, it is possible to imagine a wide variety of gut-liver-pulmonary interplays that might evoke pulmonary hypertension.

But, this burst of enthusiasm for vasoactive substances that might harm the pulmonary circulation if the liver should be bypassed is dampened by the fact that no one has as yet identified a product of digestion that is capable of eliciting pulmonary hypertension. Indeed, an intestinal hormone has recently been identified that has potent vasodilator properties (23). Also, in patients with hepatic cirrhosis the pressor response to hypoxia may be seriously impaired (24). Finally, if entry of intestinal hormones and the products of digestion into the pulmonary circulation caused as much upset as the foregoing considerations imply, portocaval shunts would be an inevitable disaster. However, they are not.

Nonetheless, it seems clear that substances released from the gut are capable of eliciting pulmonary vasomotor activity and that the occasional coincidence of severe hepatic injury and pulmonary hypertension can no longer be discounted as happenstance. Granting that the association is real, the question of individual susceptibility again emerges, since so few patients with severe liver disease develop pulmonary hypertension.

If the syndrome of dietary pulmonary hypertension does exist, how does it come about? Neither multiple pulmonary emboli nor familial pulmonary hypertension (25) can be invoked, since the vascular lesions do not appear to be thrombotic in origin. Perhaps the anatomical hallmarks of the pulmonary vascular lesions produced by *Crotalaria*, i.e., intimal fibrosis and medial hypertrophy constitute the missing clue. Could this combination represent the consequences of subtle endothelial injury and failure to inactivate vasoconstrictor substances brought to the lungs? Do the "exudative lesions" in the lungs (5) represent more overt expression of endothelial damage and increased capillary permeability? After the original insult to the endothelium, is the damage self-perpetuating because of platelet aggregation, local release of vasoactive substances, endothelial dehiscence, naked basement membranes, and obstruction of the minute pulmonary vessels (9, 12, 13)?

If damage to the endothelium is truly the initiating event, dietary pulmonary hypertension emerges as a pathophysiological expression of failure of the metabolic and waterproofing function of the pulmonary capillary linings. Clearly this view is consistent with mounting evidence that pulmonary capillary endothelium is an important metabolic machine for coping with the biologically active substances that cross its surface. Also, once endothelial injury allows large circulating macromolecules to penetrate to the pulmonary interstitium, the way is clear for interstitial organization and fibrosis. Could this be a common denominator by which certain drugs such as nitrofurantin, busulfan, or apresoline stimulate interstitial fibrosis in predisposed individuals (26)? These prospects are tantalizing. But further speculation about endothelial inadequacy would, at this point, simply be an exercise in fantasy.

It is unlikely that the saga of dietary pulmonary hypertension will end with monocrotaline, fulvine, Aminorex, and phenformin. In favor of this grim augury is the unending stream of new drugs, nostrums, and "natural foods" that contain mysterious herbal ingredients. Inevitably the same uncertainties that attended the discovery of an association between pulmonary hypertension and Aminorex will resurface: are we witnessing cause and effect? Is dietary indiscretion truly a pathogenetic element in some forms of primary hypertension? Do dietary and hypoxic pulmonary hypertension share a common pulmonary pressor mechanism? If so, it is unlikely that histamine is the common denominator (27). Why does vulnerability vary from individual to individual and from species to species? Is liver failure a prerequisite for some forms of dietary pulmonary hypertension? What are the respective roles of the liver and the pulmonary capillary endothelium in coping with vasoactive substances that enter by way of the gut? Does pulmonary vasoconstriction, mechanical obstruction by platelet aggregates, or a combination of the two represent the initiating event?

Obviously few answers are as yet available to many of these questions. But the questions do merit serious consideration, because they focus attention both on the interdependence of pulmonary vasomotor activity and the metabolic functions of the lungs. They also emphasize the important physiological implications of the anatomical disposition of the pulmonary circulation in series with the intestinal tract and the gastrointestinal tract and at the gateway to the systemic circulation and the vital organs. The implications are broad, not only for unraveling obscure pathophysiological mechanisms but also for providing a comprehensive view of the remarkable synchronization of mechanisms that regulate the normal and the abnormal pulmonary circulation.

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