Dietary Pulmonary Hypertension

By Alfred P. Fishman

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

These provocative experiments have demon-
strated conclusively that substances taken by
mouth can cause obliterator 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 hyper-
tension. Instead, attention has shifted to the in-
triguing prospect that malfunctioning of the pul-
monary capillary endothelium and platelet aggre-
gation 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 ex-
ploded in Switzerland, Austria, and Germany be-
tween 1966 and 1968 (14). In these countries, the
incidence of pulmonary hypertension suddenly in-
creased twentyfold. In contrast to the pulmonary
vascular lesions produced by pyrrolizidine alka-
loids 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-phenylox-
azoline), in November, 1965. Aminorex resembles
epinephrine and amphetamine in chemical struc-
ture; 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 appear-
ance 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 predis-
position, possibly genetic, as a prerequisite for the
obliterator 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 repro-
duce dietary pulmonary hypertension by adminis-
tering 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 hypertension (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 individu-
als. 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 hyper-
tension, originating in pulmonary venous occlu-
sion, 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, poison-
ing with bush tea can also produce veno-occlusive
disease of the liver (19). This observation, coupled
with the fact that pyrrolizidine alkaloids are me-
tabolized in the liver (20), and the coincidence of
severe liver disease and pulmonary hypertension in
man (21) have heightened suspicion that metabo-
lites 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 presents the missing clue. Could this combination represent an exercise in fantasy. 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.

References

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