

## Aminorex to Fen/Phen: An Epidemic Foretold

To the Editor:

I read the article by Alfred P. Fishman<sup>1</sup> with interest. He refers to “an unexpected outbreak of valvular heart disease related to the use of anorectic agents” and implicates the combination of fenfluramine and phentermine as the cause of this outbreak. He states that the fen/phen combination “enables high levels of circulating serotonin to reach the left side of the heart” and, in commenting on the similarity between the cardiac valvular lesions in patients taking fen/phen and carcinoid syndrome, he states that “in both instances, the lesions are attributable to inordinately high concentrations of serotonin in the blood.” He explains the disparity between the presence of left-sided lesions in fen/phen patients and their absence in patients with carcinoid syndrome by a hypothetical diagram suggesting that both fenfluramine and phentermine impair the pulmonary clearance of serotonin and permit “abnormally high concentrations of serotonin to reach the left side of the heart.”

Although there may have been an outbreak of uncontrolled research papers and abstracts (at the last count, there were 21 such reports) and legal symposia on the proposed association between anorectic drugs and left-sided valve regurgitation, to my knowledge, as a busy cardiologist and echocardiographer, I am not aware of any outbreak of disease per se. My experience is borne out by the only large-scale epidemiological study<sup>2</sup> to date, in which the number of patients with idiopathic cardiac valve disorders was 6 of 2371, 5 of 6532, and 0 of 862 for patients prescribed fenfluramine, dexfenfluramine, and phentermine, respectively. Although fenfluramine and dexfenfluramine have been shown in some (but not all) studies to be associated with mostly hemodynamically nonsignificant valvular regurgitation, phentermine, when taken alone, has not been shown to cause valvular regurgitation.<sup>2</sup> Although the theory regarding serotonin uptake seems very appealing, studies have shown no increase in circulating serotonin in patients taking fenfluramine alone or in combination with phentermine.<sup>3</sup>

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### Response

The main thrust of Dr Tellier's letter seems to be that my article builds a house of pathophysiologic mechanisms without a firm foundation of epidemiologic evidence. His major misgivings center around the prospective International Primary Pulmonary Hypertension Study (IPPHS), which was conducted in 35 centers in Europe.<sup>1</sup> Although some still challenge particular aspects of the study,<sup>2</sup> for those working in the field of primary pulmonary hypertension, the study has generally been heralded as a landmark. Moreover, the recent rebuttal by Abenham et al<sup>3</sup> lends even greater strength to the argument that fenfluramines can cause pulmonary hypertension in genetically predisposed individuals.

In comparison with the IPPHS study, which dealt with pulmonary hypertension, the evidence implicating fen/phen in the pathogenesis of the left-sided cardiac lesions is on less solid footing.<sup>4</sup> The cause-and-effect relationship between fen/phen and the cardiac lesions is based on relatively small numbers of patients, inconsistent protocols, and variable diagnostic techniques. However, the similarity between carcinoid valvular lesions on the right side of the heart and the fen/phen-associated lesions on the valves of the left side supports the idea that impaired pulmonary clearance of serotonin caused by phentermine may enable inordinate concentrations of serotonin to reach the left side of the heart.<sup>5</sup> However, as in the case of carcinoid lesions, it may well be that high levels of serotonin are not the sole mechanism. For example, direct effects of fenfluramines on receptors in the valves and on the pulmonary vessels might also be involved.

Dr Pollick's letter raises 3 issues. The first is a matter of definition. In my view, the unexpected occurrence of valvular heart disease in 24 healthy women qualifies as an “outbreak.” The second question minimizes the significance of a frequency of  $\approx 1:1000$ ; but, in doing so, it does not take into account the fact that if millions were to ingest fenfluramines, the prevalence of valvular heart disease in a ratio of 1:1000 would soon rise exponentially to epidemic proportions. The third question, ie, about levels of circulating serotonin, can be debated. In contrast to the letter by Redmon et al<sup>6</sup> that is cited, more extensive studies by Simonneau et al<sup>7</sup> indicate that dexfenfluramine does increase blood levels of serotonin.

A major point of my article is that impaired clearance by the lungs would allow inordinate concentrations of serotonin to reach and damage the left side of the heart. Dr Pollick questions the levels of serotonin that were achieved by fen/phen. More to the point would be the demonstration of high levels of serotonin in the blood of those who developed left-sided cardiac lesions. Unfortunately, this information is not available. Also unknown is whether phentermine allows high concentrations of fenfluramine to reach, and act directly on, serotonin receptors on the left side of the heart.

As the questions above indicate, taking full stock of the pharmacological, metabolic, clearance, and biochemical behaviors of each of the anorexigenics is a complicated affair. This complexity underscores the need to reserve such agents for the morbidly obese and to remind all concerned that the safest and most effective way to lose weight is still by controlling diet and increasing physical activity.

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