

Brief Report

FATAL PULMONARY HYPERTENSION
ASSOCIATED WITH SHORT-TERM USE
OF FENFLURAMINE AND PHENTERMINEEUGENE J. MARK, M.D., EVA D. PATALAS, M.D.,
HOWARD T. CHANG, M.D., PH.D.,
RICHARD J. EVANS, M.D., AND STANTON C. KESSLER, M.D.

THE dangers inherent in marked obesity have prompted physicians to advocate more aggressive strategies for weight reduction. One current strategy is the prescription of fenfluramine,^{1,2} either alone or in combination with phentermine, with the knowledge that the risks of the drugs must be balanced against the risks of continued obesity.

Pulmonary hypertension in adults has several causes that can be identified pathologically. In the case of pulmonary hypertension that develops with hypoxia during the course of chronic obstructive or interstitial fibrosing disease of the lung, the pulmonary vessels are characterized by intimal and medial hyperplasia and luminal stenosis. Thromboembolic pulmonary hypertension results from the occlusion of large and small vessels by organizing blood clot with ingrowth of fibroblasts. Pulmonary venous hypertension due to cardiac failure or pulmonary veno-occlusive disease leads to secondary arterial hypertension as well as hemosiderosis. Collagen vascular disease, particularly scleroderma, can cause exuberant intimal proliferation described as onionskin change. Finally, plexogenic arteriopathy, a pathologically distinctive form of arterial remodeling, typically develops in patients with primary pulmonary hypertension.

Most patients with primary pulmonary hypertension are young women with a relatively rapid progression of disease.^{3,4} Although most cases have no apparent cause, some can be traced to specific medical conditions or drugs. Particularly well established causes are cirrhosis^{5,6} and human immunodeficiency

virus infection.^{7,8} Drugs used to suppress appetite can also cause pulmonary hypertension.

A small epidemic of pulmonary hypertension with fatalities in Switzerland, Germany, and Austria in the late 1960s and early 1970s was due to the use of aminorex for weight reduction.⁹⁻¹³ Plexogenic arteriopathy characterized the pulmonary abnormalities.^{10,14,15} Fenfluramine and dexfenfluramine, anorectic drugs currently in use, are also known to cause pulmonary hypertension.^{16,17} We document on the basis of autopsy findings that plexogenic pulmonary hypertension was the cause of death in a woman who took fenfluramine and phentermine to lose weight. She died approximately 8 months after taking this off-label combination of drugs for only 23 days.

CASE REPORT

Clinical Findings

A 29-year-old woman sought medical help for obesity. She was otherwise healthy and did not smoke cigarettes. There was no family history of pulmonary hypertension. She weighed 88 kg (193 lb) and was 1.65 m (65 in.) tall. Her body-mass index (the weight in kilograms divided by the square of the height in meters) was 32. Combination therapy with fenfluramine (Pondimin) at a dose of 10 mg taken orally three times per day and phentermine (Ionamin) at a dose of 15 mg taken orally every morning was prescribed. The medications were discontinued after 23 days. The patient lost 4.5 kg (10 lb) during treatment. The patient subsequently reported an increased heart rate and shortness of breath with moderate exercise. These symptoms resolved over the next several weeks.

She felt well until five months later, when she noticed shortness of breath and pedal edema during an upper respiratory tract infection. Soon thereafter she had two episodes of syncope. Laboratory investigation showed mild polycythemia and respiratory alkalosis. Chest radiographs showed mild prominence of the right ventricular outflow tract and the left pulmonary artery. An electrocardiogram showed right-axis deviation and right ventricular hypertrophy. Cardiac catheterization showed severe pulmonary hypertension and markedly elevated pulmonary vascular resistance. The right ventricular pressure was 100/20 mm Hg; the pulmonary-artery pressure was 100/45 mm Hg, with a mean of 60 mm Hg; the pulmonary-capillary wedge pressure was 6 to 8 mm Hg; and the pulmonary vascular resistance was 20 to 24 Wood units (normal, <2). Ventilation-perfusion scanning showed a very low probability of acute pulmonary embolism, with no segmental perfusion defects. Pulmonary angiography showed vascular pruning and low flow consistent with the presence of high pulmonary vascular resistance and low cardiac output.

Other studies were performed to rule out various causes of pulmonary hypertension. Liver-function studies showed a mild elevation of alanine aminotransferase and lactate dehydrogenase in the serum. Abdominal ultrasonography revealed no liver abnormalities. Tests for antinuclear antibodies were negative. Administration of oxygen improved the patient's condition, but treatment with nitric oxide did not. A continuous intravenous infusion of epoprostenol was administered through an indwelling catheter two months after her syncopal episodes. The initial dose was 2 μ g per kilogram of body weight per minute and was subsequently increased to 4 μ g per kilogram per minute and then to 5 μ g per kilogram per minute.

The patient was in stable condition and reasonably functional at home for six weeks before a fever developed and she was hospitalized. Cultures for bacteria were negative. Her condition improved with antibiotics, and she was discharged, only to be re-

From the Department of Pathology, Massachusetts General Hospital, and Harvard Medical School (E.J.M., H.T.C.), and the Office of the Chief Medical Examiner, Commonwealth of Massachusetts (E.J.M., E.D.P., R.J.E., S.C.K.) — all in Boston. Address reprint requests to Dr. Mark at the Department of Pathology, Massachusetts General Hospital, 55 Fruit St., Warren Bldg. 219, Boston, MA 02114-2696.

©1997, Massachusetts Medical Society.

admitted two days later with more fever and pleuritic chest pain. An additional antibiotic was given, and she was again sent home. Two days later she died suddenly and unexpectedly in cardiac arrest.

Pathological Findings

An autopsy was performed at the Massachusetts General Hospital under the auspices of the Office of the Chief Medical Examiner of the Commonwealth of Massachusetts. There were no restrictions to the autopsy. A standard dissection protocol was followed. The lungs were inflated with formalin and cut 24 hours later into slabs 1 cm thick. Ten blocks of tissue were examined from each lung. The sections were stained with hematoxylin and eosin, Prussian blue for iron, elastic-van Gieson for elastic tissue, Mallory's trichrome for collagen, and Wilder's stain for reticulin.

At autopsy the body weighed 91 kg (200 lb). The right lung weighed 777 g and the left lung 630 g, approximately twice the normal weights. The lungs were congested but otherwise macroscopically unremarkable. The heart weighed 399 g, which is slightly heavier than normal. There was marked right ventricular hypertrophy. The lateral wall of the right ventricle was 0.6 cm thick (normal, 0.3 cm or less) when measured 1 cm below the tricuspid valve. The circumference of the pulmonary trunk was 6 cm, and the ascending aorta was 5 cm in circumference (Fig. 1), whereas normally the circumference of the ascending aorta is greater than that of the pulmonary trunk in an adult. Neither the aorta nor the main pulmonary arteries had atherosclerosis.

Histopathological examination of the lungs revealed congestion, extensive alveolar and interstitial edema, and evidence of marked pulmonary hypertension. Medial and intimal proliferation (Fig. 2) involved the majority of the muscular pulmonary arteries and arterioles. These findings correspond to a pathological grade of 3 on a 5-point scale in which 0 represents normal findings, 1 medial hypertrophy, 2 intimal hyperplasia, 3 occlusive intimal fibroelastosis, and 4 plexogenic arteriopathy.¹⁸ Plexiform arteriopathy^{14,15,18} (Fig. 3) was present in every slide and involved an average of three arteries per slide. Lesions manifested by dilatation, which are typically found distal to plexogenic lesions, were numerous as well (Fig. 4). Necrotizing arteritis (Fig. 5) with fibrinoid necrosis of the vascular wall, nuclear dust, and regional acute hemorrhage was present in a few slides. The findings are characteristic of plexogenic pulmonary hypertension and correspond to a pathological grade of 4.¹⁸ The pulmonary veins were normal. A few aggregates of clear oval cells representing neuroendocrine cells were present in the basal layer of bronchiolar epithelium. There was no bronchiolitis, bronchopneumonia, or hemosiderosis. No acute or organizing thromboemboli were present. Polarization microscopy showed no birefringent material in blood vessels.

All other organs, including the brain, were macroscopically and microscopically normal. There was no coronary artery disease, hepatic fibrosis, or venous thrombosis.

DISCUSSION

Plexogenic arteriopathy is the usual and most distinctive anatomical finding in primary pulmonary hypertension^{14,15} and was present in European patients who had taken aminorex as an appetite suppressant in the 1960s and 1970s.¹⁰ The morphology of plexogenic and angiomatoid lesions in these patients distinguished their form of the disease from common forms of pulmonary hypertension. Plexogenic lesions are preceded by exuberant proliferation of medial and intimal cells, which constitute lesser degrees of pulmonary hypertension. Necrosis of the arterial wall with repair and local vascular remodeling culminates in a racemose collection of abnormal



Figure 1. Cross Section of the Ascending Aorta (on the Left) and the Pulmonary Trunk (on the Right).

The pulmonary trunk is larger than the aorta, which is an abnormal finding indicative of pulmonary hypertension.

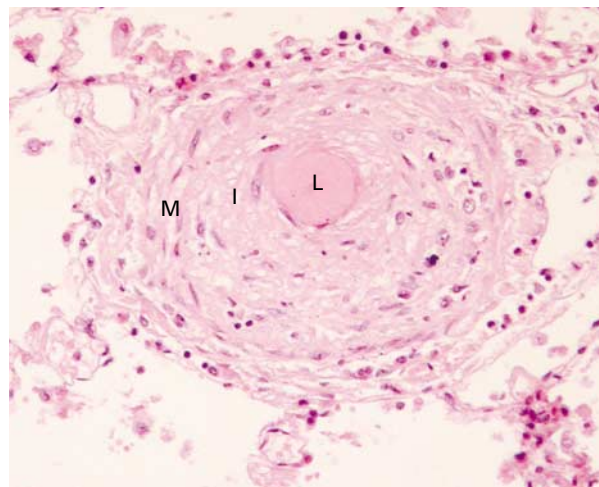


Figure 2. Pulmonary Hypertension with Marked Intimal (I) and Medial (M) Hyperplasia in a Muscular Pulmonary Artery (Hematoxylin and Eosin, $\times 20$).

The lumen (L) is one fourth the normal diameter.

channels outside the original artery. The proliferating cells are myofibroblasts¹⁹ and endothelial cells with increased expression of endothelin-1.²⁰ Shunts develop between the pulmonary and bronchial arterial systems.^{21,22} Vascular scarring leads to post-stenotically dilated blood vessels with thinned walls. All phases of plexogenic arteriopathy were observed in patients who took aminorex and in our patient, who took fenfluramine and phentermine.

The risk of pulmonary hypertension after treatment with aminorex was estimated to be only 2 in 1000,¹¹ but this figure was still 20 times the risk in the general population.¹⁴ The latent period between drug therapy with aminorex and the development of the disease may have been related to the dose, but

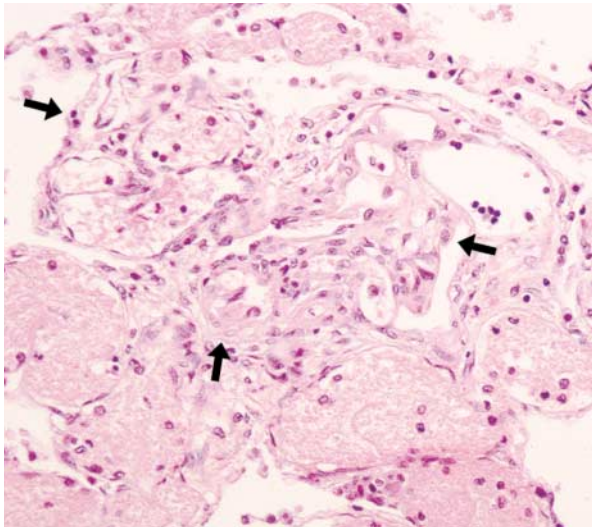


Figure 3. Plexogenic Arteriopathy (Hematoxylin and Eosin, $\times 20$). Interwoven vessels, which have the diameter of capillaries, form a plexus (arrows).

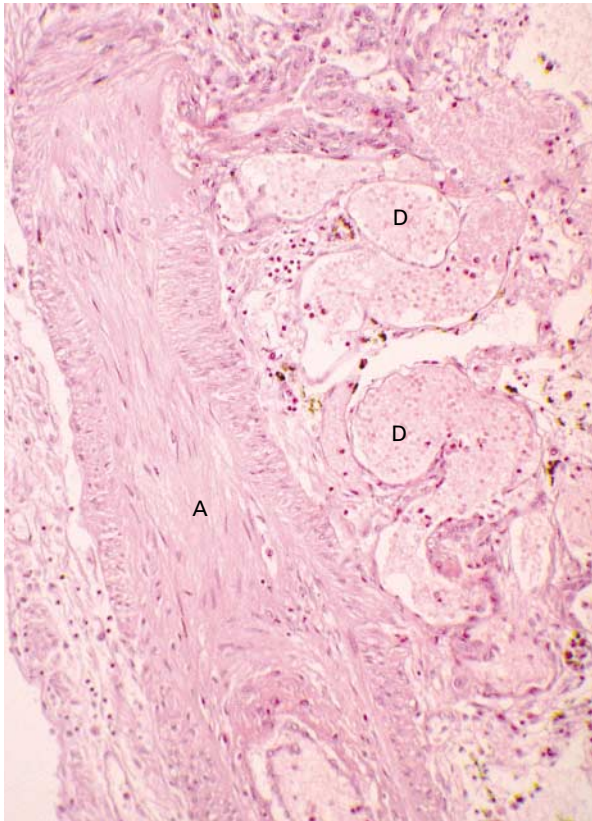


Figure 4. Dilated Blood Vessels with Thin Walls ("Dilatation Lesions," D) (Hematoxylin and Eosin, $\times 10$). Abnormal ectatic blood-filled vessels with thin walls lie adjacent to an artery occluded by intimal fibrosis (A).

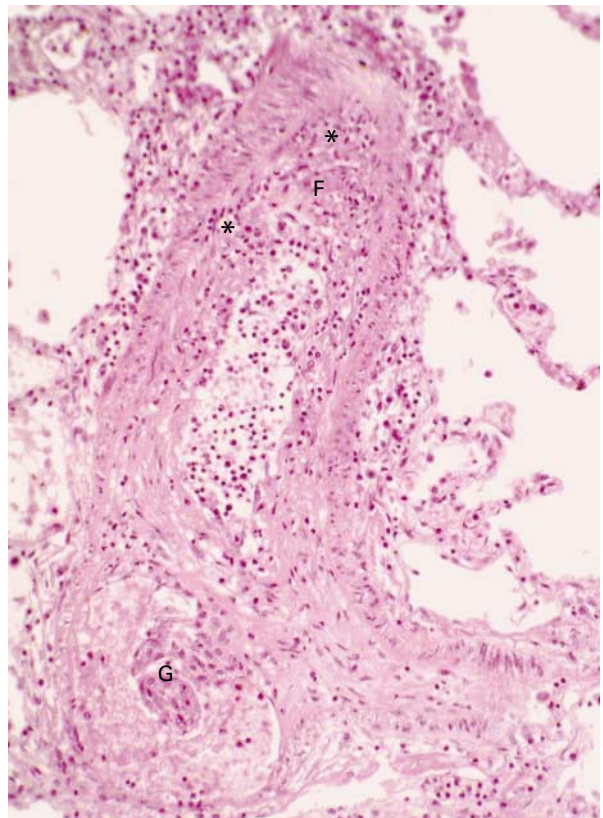


Figure 5. Necrotizing Arteritis (Hematoxylin and Eosin, $\times 10$). Neutrophils and nuclear dust (asterisks) infiltrate all layers of small elastic artery. Fibrinoid necrosis (F) is present. A glomeruloid (G) proliferation of endothelial cells protrudes into a curious aneurysmal structure.

the dose was sometimes small and often bore little relation to the degree of elevation in pressure.¹⁴ Primary pulmonary hypertension has a familial basis in some instances.²³ In one case during the aminorex epidemic, pulmonary hypertension developed in a mother and daughter who were both taking the drug.¹² In one study of 32 patients in Switzerland in whom pulmonary hypertension developed during or after therapy with aminorex, 1 patient took the drug for only three weeks, another 3 took it for one month, and 23 took it for three months or longer.¹² Disease developed in 18 patients during treatment, in 4 within three months after therapy, in 2 between three and six months after therapy, and in 1 more than a year after therapy.¹² Since our patient took fenfluramine and phentermine for 23 days and died of pulmonary hypertension 8 months later, the time course of her disease falls within previously documented time frames for aminorex-associated pulmonary hypertension. The relative risk of pulmonary hypertension after treatment with dexfenfluramine for more than three months is approximately 30,¹⁷ which is similar to that associated with aminorex.

How reversible is the pulmonary hypertension due to anorectic agents? Intimal and medial proliferations are believed to be potentially reversible. The necrotizing arteritis and ensuing plexogenic arteriopathy are probably permanent, but only a minority of the arteries generally show this change. In adults with idiopathic forms of plexogenic arteriopathy and in children in whom plexogenic arteriopathy develops as a result of congenital heart disease with left-to-right shunts, plexogenic lesions are believed to be irreversible and a bad prognostic sign.^{13,15,24} However, the pulmonary hypertension caused by aminorex was sometimes reversible. The drug was sold in Europe from 1965 to 1968 and then withdrawn from the market. The epidemic of pulmonary hypertension had subsided by 1972. Ten years later, half the patients who had had signs and symptoms of pulmonary hypertension had died, the majority of right-sided heart failure. The average survival of those who died was 3½ years after the initial diagnosis. Pulmonary vascular obstruction regressed in half the survivors.¹³

Fenfluramine and phentermine are chemical congeners of amphetamine¹ and are structurally similar to aminorex (Fig. 6). Fenfluramine differs from most derivatives of amphetamine by depressing rather than stimulating the central nervous system. It may suppress appetite by stimulating the ventromedial nucleus of the hypothalamus, possibly by promoting the release of serotonin and blocking its neuronal reuptake.¹ Since fenfluramine affects the cellular processing of serotonin and since intimal proliferation and fibrosis may develop in the veins and endocardium of patients with carcinoid syndrome and circulating serotonin or its metabolites,^{25,26} drug-related hyperplasia of vascular myofibroblasts and endothelial cells is not entirely a surprise. The numbers of pulmonary endocrine cells, especially those containing gastrin-releasing peptide, are increased in plexogenic arteriopathy and not in other varieties of pulmonary hypertension.²⁷

The histopathological findings related to pulmonary hypertension in our patient had four attributes with clinical correlates: it was partly irreversible, because there were plexogenic lesions in addition to intimal and medial proliferation; it was severe, present in every slide of lung tissue, whereas in some cases of idiopathic pulmonary hypertension the pathologist finds a plexogenic lesion in only every 5th or even every 10th block of tissue; it was in part established and ongoing, correlating with an onset months previously; and it was in part acute and necrotizing, correlating with rapid clinical deterioration terminally. The right ventricular hypertrophy and cor pulmonale attest to the severity of the pulmonary hypertension.

In summary, classic and severe plexogenic pulmonary arteriopathy developed in a patient who had

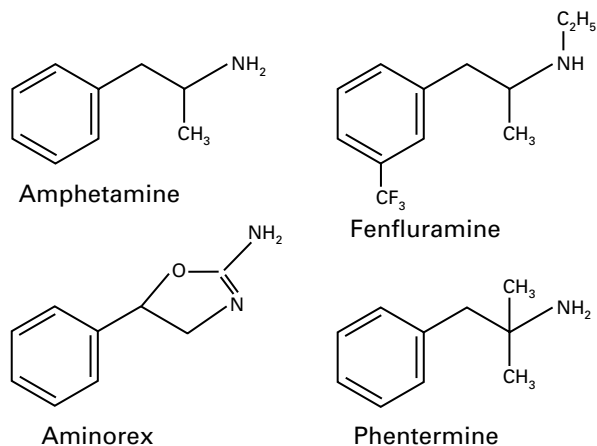


Figure 6. Chemical Structures of Amphetamine, Fenfluramine, Aminorex, and Phentermine.

taken anorectic agents for only 23 days. Although we cannot rule out preexisting disease, the histologic age of the lesions was consistent with the time elapsed since ingestion of the drugs. The patient died abruptly with cor pulmonale and necrotizing arteritis in the lungs. Pulmonary edema was a terminal event.

REFERENCES

1. Pinder RM, Brogden RN, Sawyer PR, Speight TM, Avery GS. Fenfluramine: a review of its pharmacological properties and therapeutic efficacy in obesity. *Drugs* 1975;10:241-323.
2. Weintraub M. Long-term weight control: the National Heart, Lung, and Blood Institute funded multimodal intervention study. *Clin Pharmacol Ther* 1992;51:581-646. [Erratum, *Clin Pharmacol Ther* 1992;52:323.]
3. Case Records of the Massachusetts General Hospital (Case 8-1976). *N Engl J Med* 1976;294:433-9.
4. Rubin LJ. Primary pulmonary hypertension. *Chest* 1993;104:236-50.
5. Ruttner JR, Bartschi J-P, Niedermann R, Schneider J. Plexogenic pulmonary arteriopathy and liver cirrhosis. *Thorax* 1980;35:133-6.
6. Case Records of the Massachusetts General Hospital (Case 25-1992). *N Engl J Med* 1992;326:1682-92.
7. Jacques C, Richmond G, Tierney L, Curtis JL, McKerrow J, Warnock ML. Primary pulmonary hypertension and human immunodeficiency virus infection in a non-hemophiliac man. *Hum Pathol* 1992;23:191-4.
8. Mette SA, Palevsky HI, Pietra GG, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection: a possible viral etiology for some forms of hypertensive pulmonary arteriopathy. *Am Rev Respir Dis* 1992;145:1196-200.
9. Gurtner HP, Gertsch M, Salzmann C, Scherrer M, Stucki P, Wyss F. Häufen sich die primär vasculären Formen des chronischen Cor pulmonale? *Schweiz Med Wochenschr* 1968;98:1579-89.
10. Widgren S, Kapanci Y. Menocilbedingte pulmonale Hypertonie: Vorläufige morphologische Ergebnisse über 8 pathologisch-anatomisch untersuchte Fälle. *Z Kreislaufforsch* 1970;59:924-30.
11. Gahl K, Fabel H, Greiser E, Harmjanz D, Ostertag H, Stender H-S. Primär vasculäre pulmonale Hypertonie: Bericht über 21 Patienten. *Z Kreislaufforsch* 1970;59:868-83.
12. Follath F, Burkart F, Schweizer W. Drug-induced pulmonary hypertension? *BMJ* 1971;1:265-6.
13. Gurtner HP. Aminorex and pulmonary hypertension: a review. *Cor Vasa* 1985;27:160-71.
14. Wagenvoort CA, Wagenvoort N. Pathology of pulmonary hypertension. New York: John Wiley, 1977:103-18.
15. Wagenvoort CA, Mooi WJ. Biopsy pathology of the pulmonary vasculature. London: Chapman and Hall Medical, 1989:327-39.
16. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986;293:51-2.
17. Abenheim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs

and the risk of primary pulmonary hypertension. *N Engl J Med* 1996;335:609-16.

18. Mark EJ. Lung biopsy interpretation. Baltimore: Williams & Wilkins, 1984:132.

19. Caslin AW, Heath D, Madden B, Yacoub M, Gosney JR, Smith P. The histopathology of 36 cases of plexogenic pulmonary arteriopathy. *Histopathology* 1990;16:9-19.

20. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993;328:1732-9.

21. Yaginuma G, Mohri H, Takahashi T. Distribution of arterial lesions and collateral pathways in the pulmonary hypertension of congenital heart disease: a computer aided reconstruction study. *Thorax* 1990;45:586-90.

22. Jamison BM, Michel RP. Different distribution of plexiform lesions in primary and secondary pulmonary hypertension. *Hum Pathol* 1995;26:987-93.

23. Loyd JE, Slovis B, Phillips JA III, et al. The presence of genetic anticipation suggests that the molecular basis of familial primary pulmonary hypertension may be trinucleotide repeat expansion. *Chest* 1997;111:Suppl:82S-83S.

24. Petersen RC, Edwards WD. Pulmonary vascular disease in 57 necropsy cases of total anomalous pulmonary venous connection. *Histopathology* 1983;7:487-96.

25. Isler P, Hedinger C. Metastasierendes Dünndarmcarcinoid mit schweren, vorwiegend das rechte Herz betreffenden Klappenfehlern und Pulmonalstenose — ein eigenartiger Symptomenkomplex? *Schweiz Med Wochenschr* 1953;83:4-8.

26. Case Records of the Massachusetts General Hospital (Case 16-1979). *N Engl J Med* 1979;300:909-16.

27. Heath D, Yacoub M, Gosney JR, Madden B, Caslin AW, Smith P. Pulmonary endocrine cells in hypertensive pulmonary vascular disease. *Histopathology* 1990;16:21-8.

CORRECTION

Fatal Pulmonary Hypertension Associated with Short-Term Use of Fenfluramine and Phentermine

Fatal Pulmonary Hypertension Associated with Short-Term Use of Fenfluramine and Phentermine . On page 602, the sentence that begins eight lines from the bottom of the right-hand column should have read, "The initial dose was 2 *ng* per kilogram of body weight per minute and was subsequently increased to 4 *ng* per kilogram per minute and then to 5 *ng* per kilogram per minute," not "2 μ g, ... 4 μ g, ... and ... 5 μ g," as printed.