



Contact: Wyeth-Ayerst Laboratories
Andrey Ashby
(610) 971-5823

Doug Petkus
(610) 971-4980

Robinson Lerer & Montgomery
Michael Bulger
(212) 484-7413

PONDIMIN® AND REDUX™ TO BE VOLUNTARILY WITHDRAWN

Action Is Based on New Information

Company Says It Is Taking the Most Prudent Course of Action for Patients and Doctors

Company Will Form Expert Panel to Review All Data

PHILADELPHIA, PA -- September 15, 1997 -- Wyeth-Ayerst Laboratories, a division of American Home Products Corporation (NYSE:AHP), the manufacturer of PONDIMIN® (fenfluramine hydrochloride) tablets C-IV and the distributor of REDUX™ (dexfenfluramine hydrochloride capsules) C-IV, today announced a voluntary and immediate withdrawal of these weight loss medications.

The company is taking this action on the basis of new, preliminary information regarding heart valve abnormalities in patients using these medications. "Our first commitment is to our patients and to their doctors," said Marc W. Deitch, M.D., Senior Vice President Medical Affairs, Global Medical Director. "Even though this new information is not derived from a thorough clinical study and is difficult to evaluate, the company is taking the most prudent course of action. Wyeth-Ayerst is committed to safeguarding the health and well-being of patients and ensuring that health care providers have the latest medical information."

Owing to the unanswered questions prompted by the emerging findings, the company today also announced that it is forming an expert panel of leading physicians and researchers to thoroughly evaluate the data and recommend additional actions to address this situation. The company will work closely with this panel, as well as with the U.S. Food and Drug Administration (FDA), to better understand these findings.

Patients who have used either of these products should contact their physicians. A full-page notice will appear in leading national and regional newspapers announcing this decision and providing a toll-free telephone number (1-800-892-2718) for those requiring further information.

In addition, the company has sent notification of this action to approximately 450,000 physicians and pharmacists nationwide. The company will also offer an opportunity to return unused product.

Based on postmarketing reports from the Mayo Clinic of 24 cases of heart valve disease in some patients treated with the combination of phentermine and fenfluramine, the company advised health care providers in a July 24, 1997, letter of the addition of boxed warnings concerning heart valve disease to the labeling for Pondimin and Redux. The company also announced a joint effort with the Mayo Clinic to initiate a comprehensive study to examine the possible association of unusual valvular disorders with these products. The Mayo Clinic cases were subsequently reported in an article appearing in the August 28, 1997, issue of *The New England Journal of Medicine*.

This article was accompanied by a letter to the editor from the FDA reporting additional cases of heart valve disease in 28 patients taking the combination of phentermine and fenfluramine, two patients taking fenfluramine alone, four patients taking dexfenfluramine alone, and two patients taking dexfenfluramine and phentermine.

Additional adverse event reports of abnormal heart valve findings in patients using dexfenfluramine or fenfluramine alone or in combination with other weight loss agents continue to be received by the company and the FDA. These reports have included shortness of breath, chest pain, fainting, swelling of the ankles or a new heart murmur.

On Friday afternoon, September 12, 1997, the FDA provided Wyeth-Ayerst with new summary information concerning abnormal echocardiogram findings in asymptomatic patients seen in five centers. These patients had been treated with fenfluramine or dexfenfluramine for up to 24 months, most often in combination with phentermine. Abnormal echocardiogram findings were reported in 92 of 291 subjects evaluated, including 80 reports of aortic regurgitation (mild or greater) and 23 reports of mitral regurgitation (moderate or greater). These observations reflect a preliminary analysis of pooled information rather than results of a formal clinical investigation, and are difficult to evaluate because of the absence of matched controls and pretreatment baseline data for these patients. Nevertheless, the company believes it is prudent, in light of this information, to withdraw these products from the market at this time.

Wyeth-Ayerst Laboratories, a division of American Home Products Corporation (NYSE:AHP), is a major research-oriented pharmaceutical company.

###

Full prescribing information available upon request.

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P97-32
FOR IMMEDIATE RELEASE
September 15, 1997

FOOD AND DRUG ADMINISTRATION
Lawrence Bachorik: (301) 827-6250
Broadcast Media: (301) 827-3434
Consumer Hotline: (800) 532-4440

FDA ANNOUNCES WITHDRAWAL OF FENFLURAMINE AND DEXFENFLURAMINE

The Food and Drug Administration, acting on new evidence about significant side-effects associated with fenfluramine and dexfenfluramine, has asked the manufacturers to voluntarily withdraw both treatments for obesity from the market. Dexfenfluramine is manufactured for Interneuron Pharmaceuticals and marketed under the name of Redux by Wyeth-Ayerst Laboratories, a subsidiary of American Home Products Corp. of Madison, N.J., which also manufactures and markets fenfluramine under the brand name Pondimin. Both companies have agreed to voluntarily withdraw their drugs. The FDA is not requesting the withdrawal of phentermine, the third widely used medication for obesity.

The action is based on new findings from doctors who have evaluated patients taking these two drugs with echocardiograms, a special procedure that can test the functioning of heart valves. These findings indicate that approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. This is a much higher than expected percentage of abnormal test results.

-More-

ATTENTION TV BROADCASTERS: Please use open caption for the hearing impaired.

"These findings call for prompt action," said Michael A. Friedman, M.D., the Lead Deputy Commissioner of the FDA. "The data we have obtained indicate that fenfluramine, and the chemically closely related dexfenfluramine, present an unacceptable risk at this time to patients who take them."

FDA recommends that patients using either of these products stop taking them. Users of these two products should contact their doctors to discuss their treatment.

These new findings suggest fenfluramine and dexfenfluramine are the likely cause of heart valve problems of the type that prompted FDA's two earlier warnings concerning "fen-phen," a combination of fenfluramine and phentermine. "Fen-phen" has been widely used off-label in recent years for the long-term management of obesity.

In July, researchers at the Mayo Clinic and Mayo Foundation reported 24 cases of rare valvular disease in women who took the "fen-phen" combination therapy. FDA alerted medical doctors that it had received nine additional reports of the same type, and requested all health care professionals to report any such cases to the agency's MedWatch program (1-800-FDA-1088/fax 1-800-FDA-0178) or to the respective pharmaceutical manufacturers.

Subsequently, FDA received 66 additional reports of heart valve disease associated mainly with "fen-phen." There were also reports of cases seen in patients taking only fenfluramine or dexfenfluramine. FDA requested that the manufacturers of

fenfluramine and dexfenfluramine stress the potential risk to the heart in the drugs' labeling and patient package inserts. FDA continues to receive reports of cardiac valvular disease in persons who have taken these drugs.

###

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337

AUGUST 28, 1997

NUMBER 9



VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE-PHENTERMINE

HEIDI M. CONNOLLY, M.D., JACK L. CRARY, M.D., MICHAEL D. MCGOON, M.D., DONALD D. HENSrud, M.D., M.P.H.,
BROOKS S. EDWARDS, M.D., WILLIAM D. EDWARDS, M.D., AND HARTZELL V. SCHAFF, M.D.

ABSTRACT

Background Fenfluramine and phentermine have been individually approved as anorectic agents by the Food and Drug Administration (FDA). When used in combination the drugs may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent and perhaps fewer side effects. Although the combination has not been approved by the FDA, in 1996 the total number of prescriptions in the United States for fenfluramine and phentermine exceeded 18 million.

Methods We identified valvular heart disease in 24 women treated with fenfluramine-phentermine who had no history of cardiac disease. The women presented with cardiovascular symptoms or a heart murmur. As increasing numbers of these patients with similar clinical features were identified, there appeared to be an association between these features and fenfluramine-phentermine therapy.

Results Twenty-four women (mean [\pm SD] age, 44 \pm 8 years) were evaluated 12.3 \pm 7.1 months after the initiation of fenfluramine-phentermine therapy. Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients. Both right-sided and left-sided heart valves were involved. Eight women also had newly documented pulmonary hypertension. To date, cardiac surgical intervention has been required in five patients. The heart valves had a glistening white appearance. Histopathological findings included plaque-like encasement of the leaflets and chordal structures with intact valve architecture. The histopathological features were identical to those seen in carcinoid or ergotamine-induced valve disease.

Conclusions These cases arouse concern that fenfluramine-phentermine therapy may be associated with valvular heart disease. Candidates for fenfluramine-phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease. (N Engl J Med 1997;337:581-3.)

©1997, Massachusetts Medical Society.

FENFLURAMINE and phentermine are prescription medications that have been individually approved by the Food and Drug Administration (FDA) as appetite suppressants for the treatment of obesity. When used in combination they may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent, fewer side effects, and improved patient tolerance.¹ Even though the FDA has not approved the use of the combination, in 1996 the total number of prescriptions for fenfluramine and phentermine in the United States exceeded 18 million.²

Pulmonary hypertension has been reported in association with treatment with fenfluramine^{3,4} or phentermine⁵ alone. The *D*-isomer of fenfluramine, dex-fenfluramine, also increases the risk of pulmonary hypertension,⁶ particularly when patients receive high doses for more than three months. These drugs may cause pulmonary hypertension through the vasoconstrictor action of serotonin or by altering the depolarization of pulmonary vascular smooth-muscle membrane.⁷

Valvular disease has been reported after exposure to serotonin-like drugs such as ergotamine and methysergide⁸ and with increased serotonin levels associated with carcinoid disease.^{9,10} Valvular heart disease has not been reported in patients taking anorectic agents. We report 24 cases of unusual valvular disease in patients taking fenfluramine-phentermine.

METHODS

All the patients (Table 1) were identified during the course of routine evaluation for various clinical problems. No attempt was

From the Divisions of Cardiovascular Diseases and Internal Medicine (H.M.C., M.D.M., B.S.E.), Preventive and Occupational Medicine, Endocrinology, and Internal Medicine (D.D.H.), Anatomic Pathology (W.D.E.), and Thoracic and Cardiovascular Surgery (H.V.S.), Mayo Clinic and Mayo Foundation, Rochester, Minn., and the MeritCare Medical Center, Heart Services, Fargo, N.D. (J.L.C.). Address reprint requests to Dr. Connolly at the Mayo Clinic, 200 First St. SW, Rochester, MN 55905.

VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE-PHENTERMINE

TABLE 1. CONTINUED.

PRESENTATION	CARDIOVASCULAR FINDINGS		SURGERY		
	ECHOCARDIOGRAPHY	CARDIAC CATHETERIZATION	PROCEDURE	GROSS PATHOLOGICAL FINDINGS	MICROSCOPICAL PATHOLOGICAL FINDINGS
Murmur, dyspnea	Severe MR, thickened MV	Severe MR, normal coronary arteries	MV repair	Glistening white, thickened, tethered leaflets	NA
CHF, dyspnea, murmur	Severe AR and MR; moderate TR; EF, 40%	Severe AR and MR; PAP, 55/31 mm Hg	AVR, MVR, tricuspid-valve repair	No chordal rupture or flail segment; tri-leaflet aortic valve	"Stuck-on" appearance of plaque on leaflets†
Dyspnea, edema	Severe MR, moderate AR	Severe MR; normal coronary arteries; PAP, 35/16 mm Hg	MVR	No prolapse or chordal rupture	"Stuck-on" appearance of plaque on leaflets‡
CHF, murmur, dyspnea	RVSP, 75 mm Hg; severe MR	Normal coronary arteries	MV repair	Distinctly unusual; posterior leaflet thickened, tethered	NA
Dyspnea	RVSP, 52 mm Hg; severe MR	Moderate MR; EF, 50%	MVR	Glistening white, thickened leaflets and chordae	"Stuck-on" appearance of plaque on leaflets‡
Murmur, dyspnea, edema	Moderate AR and TR, severe MR	Not done			
Dyspnea	RVSP, 74 mm Hg; moderate AR	PAP, 75/30 mm Hg			
CHF	Severe TR and MR; moderate AR; RVSP, 75 mm Hg; EF, 65%	Not done			
Dyspnea	Moderate MR; RVSP, 60 mm Hg	Not done			
Murmur, palpitations	Moderate AR, mild MR	Not done			
Murmur, edema	Moderate AR; severe MR and TR; RVSP, 72 mm Hg	Not done			
Murmur	Moderate MR; mild AR and TR; RVSP, 23 mm Hg; normal EF	Not done			
Murmur, edema	Moderate MR, TR, and AR; RVSP, 54 mm Hg; normal EF	Not done			
Murmur, edema, dyspnea	Severe MR; moderate AR and TR; RVSP, 93 mm Hg	Not done			
Murmur	Moderate AR; mild MR; EF, 75%	Not done			
Murmur, edema	Moderate AR, TR, and MR; EF, 65%	Not done			
Palpitations	Moderate AR; mild MR; EF, 70%	Not done			
Murmur	Moderate AR, mild MR and TR	Not done			
Supraventricular tachycardia	Mild MR and TR, normal left ventricle	Not done			
Dyspnea	Moderate AR; EF, 66%	Not done			
Murmur	Mild MR, AR, and TR	Not done			
Chest pain	Mild MR, TR, and AR; normal EF	Not done			
Murmur, dyspnea, edema	Severe AR and MR; RVSP, 45 mm Hg	Not done			
Palpitations, chest pain	Mild AR	Not done			

*MR denotes mitral regurgitation, MV mitral valve, NA not available, CHF congestive heart failure, AR aortic regurgitation, TR tricuspid regurgitation, EF ejection fraction, PAP pulmonary-artery pressure, AVR aortic-valve replacement, MVR mitral-valve replacement, RVSP right ventricular systolic pressure, and SEM systolic ejection murmur.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡"Stuck-on" refers to the fact that the valve architecture was intact.

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS.*

PATIENT NO.	AGE (YR)/SEX	BEFORE APPETITE SUPPRESSANTS					APPETITE SUPPRESSANTS		
		WEIGHT	HEIGHT	BODY-MASS INDEX†	MEDICATIONS	CARDIO-VASCULAR EXAMINATION	MAXIMAL DOSE OF PHEN-TERMINE	MAXIMAL DOSE OF FENFLUR-AMINE	DURATION OF THERAPY
		kg	cm				mg/day		mo
1	41/F	108	165	39.7	None	Normal	48	120	25
2	44/F	91	160	35.5	Lisinopril, conjugated estrogens, theophylline	Normal	30	60	12
3	48/F	85	157	34.5	Sertraline, hydrochlorothiazide	Normal	30	60	9
4	52/F	69	158	27.6	Fluoxetine	Normal	15	40	12
5	49/F	96	158	38.5	Nortriptyline, propylthiouracil	Normal	30	60	11
6	51/F	133	153	56.8	Conjugated estrogens, medroxyprogesterone acetate, hydrochlorothiazide-benazepril	Normal	30	60	7
7	44/F	85	167	30.5	None	Normal	60	220	12
8	41/F	100	161	38.6	None	Normal	15	60	6
9	50/F	92	158	36.9	None	Normal	30	40	4
10	50/F	84	152	36.4	None	Normal	15	40	6
11	42/F	67	150	29.8	Bronchodilators	Normal	30	60	1
12	41/F	124	157	50.3	Sertraline	Normal	30	40	6
13	48/F	93	158	37.3	None	Normal	30	20	15
14	34/F	152	163	57.2	None	1/6 SEM	30	60	15
15	35/F	91	157	36.9	None	Normal	30	40	14
16	63/F	68	153	29.0	Fluoxetine	Normal	30	60	8
17	38/F	101	165	37.1	None	Normal	30	40	6
18	43/F	78	150	34.7	None	Normal	30	20	28
19	56/F	62	150	27.6	None	Normal	30	40	17
20	44/F	98	165	36.0	None	Normal	30	40	17
21	41/F	94	162	35.3	Sertraline	1/6 SEM	30	40	7
22	33/F	122	170	42.2	None	Normal	30	40	2
23	30/F	70	165	25.7	None	Normal	30	60	20
24	38/F	NA	NA	NA	None	Normal	30	40	4
Mean ±SD	44±8	96±22.1	159±5.3	37.9±7.9			30.3±8.5	56.5±40.7	11±6.9

made to identify patients by reviewing data bases, conducting cross-index searches of patient files, or soliciting reports of suspected cases from clinical practices. As increasing numbers of patients were identified with similar clinical features, a perceived association between these features and previous or current use of fenfluramine-phentermine evolved. The serendipitous connection between these individual cases was identified as a result of communication among several physicians beginning in May 1996.

May 1996

In May 1996, Patient 1 underwent mitral-valve repair at the Mayo Clinic for the treatment of severe mitral regurgitation. Intraoperatively, the valve was noted to have a glistening white appearance, suggesting ergotamine-induced valvular injury as observed in previous patients,¹ but the patient had no history of ergotamine ingestion.

July 1996

In July 1996, Patient 1 was evaluated by another physician for severe symptomatic tricuspid regurgitation. Echocardiography confirmed severe tricuspid regurgitation and thickening of the valve leaflets. These findings were similar to those seen in patients with carcinoid or ergotamine-induced valve disease. A history was obtained indicating fenfluramine-phentermine use for 35 months until 1 month before mitral-valve surgery. A 24-hour urinary 5-hydroxyindoleacetic acid value was normal.

January 1997

In January 1997, a woman (Patient 7) with pulmonary hypertension was evaluated at the Mayo Clinic, and echocardiography demonstrated thickened aortic-valve leaflets and aortic regurgitation. An echocardiogram obtained two years previously revealed no abnormalities. The patient had taken fenfluramine-phentermine for one year before the more recent echocardiographic examination.

Also in January 1997, a physician from MeritCare Medical Center (Fargo, N.D.) contacted the Mayo Clinic and inquired whether there was a recognized association between diet medications and valvular heart disease. The inquiry was precipitated by the physician's awareness that his echocardiographic sonographers had identified a cohort of 12 patients (Patients 2, 3, 6, and 10 through 18) with valvular heart disease who had a peculiar valvular mor-

phology. A further review of the patients' records revealed that all 12 patients had taken fenfluramine-phentermine. The patients' records and echocardiograms were sent to the Mayo Clinic. The echocardiograms disclosed valve lesions very similar to those noted in Patients 1 and 7. Excised valve tissue was obtained from two patients (Patients 2 and 3), and slides prepared with elastic-van Gieson stain were reviewed by a cardiac pathologist. Histopathological examination revealed features identical to those of ergotamine-induced and carcinoid valve disease.

March 1997

In March 1997, a surgeon at the Mayo Clinic was contacted by one of his patients (Patient 4) who had undergone mitral-valve repair in 1996. The patient informed him that she had aortic regurgitation and pulmonary hypertension. A review of the surgical records showed that the appearance of the valve was distinctly unusual and not consistent with a history of rheumatic heart disease. Further inquiry revealed that the patient had taken fenfluramine-phentermine for 12 months before mitral-valve surgery.

Also in March 1997, valve tissue from a cardiac surgical patient (Patient 5) operated on at another institution was received by the Mayo Clinic for a pathological opinion. The morphologic features of the explanted valve (Fig. 1) were identical to those of valves from Patients 1 and 4 at the time of surgical inspection. Gross pathological features included thickening of the leaflets and chordae and a glistening white appearance. The histopathological features were identical to those in Patients 2 and 3. Patient 5 had been treated with fenfluramine-phentermine for 11 months.

April 1997

In April 1997, a patient (Patient 8) with a six-month history of fenfluramine-phentermine use was evaluated for dyspnea by a Mayo Clinic cardiologist consulting in another city. Multivalvular heart disease and pulmonary hypertension were identified. The cardiologist, unaware of the previous cases, asked a colleague whether he knew of an association between fenfluramine-phentermine therapy and valvular heart disease. Echocardiography revealed valvular morphology similar to that noted in the other patients.

Seven other patients (Patients 9 and 19 through 24) with similar clinical histories and echocardiographic findings were identified during clinical evaluations at MeritCare Medical Center from January through April 1997.

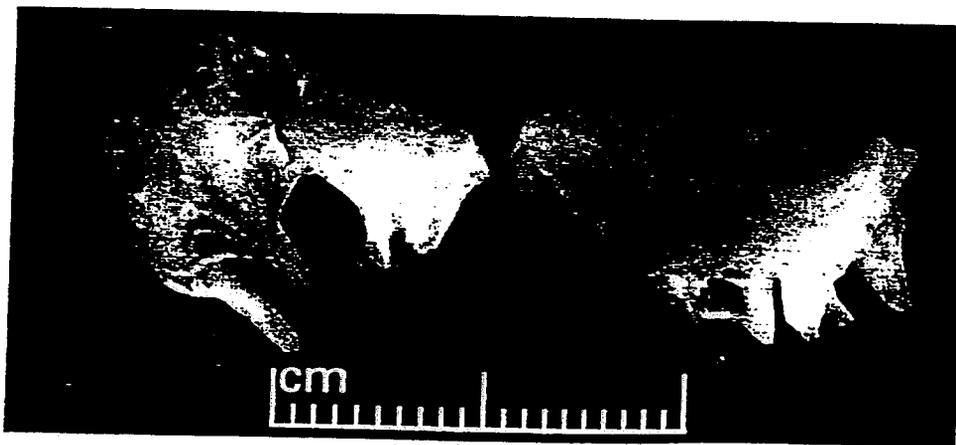


Figure 1. Explanted Mitral Valve from Patient 5, Demonstrating Glistening White Leaflets and Chordae with Mild-to-Moderate irregular but Diffuse Thickening.

CASE REPORTS

Patient 1

Patient 1 was a 41-year-old woman (body-mass index [the weight in kilograms divided by the square of the height in meters] before treatment with appetite suppressants, 39.7) who was referred to the Mayo Clinic for mitral-valve surgery three months after a systolic murmur was first noted. She had taken fenfluramine-phentermine (fenfluramine, 40 mg three times per day, and phentermine hydrochloride, 16 mg three times per day) for 25 months. Therapy had been discontinued one month before cardiac surgery because of the reported potentially catastrophic catecholamine-depleting effect of fenfluramine.¹¹ Echocardiography and cardiac catheterization confirmed the presence of severe mitral regurgitation.

During mitral-valve repair, unusual morphologic features were noted: the posterior and anterior leaflets were tethered, and the chordae were shortened. The valve was glistening white, had no rheumatic calcification or yellowish discoloration, and resembled valves affected by ergot alkaloid derivatives.¹ The patient had not used ergot preparations. Intraoperative transesophageal echocardiography demonstrated severe mitral regurgitation (Fig. 2) and mild tricuspid regurgitation.

After hospital discharge, symptomatic tricuspid valve regurgitation developed. Echocardiography demonstrated that the mitral-valve repair was intact without regurgitation. The tricuspid valve was thickened and failed to coapt; tricuspid regurgitation was severe. With medical management, symptoms of right ventricular failure improved despite the persistence of severe tricuspid regurgitation.

Patient 2

Patient 2 was a 44-year-old woman (pretreatment body-mass index, 35.5) who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for one year before dyspnea and a heart murmur were noted. Echocardiography demonstrated thickened aortic, mitral, and tricuspid valves with regurgitation. Because of progressive symptoms, mitral-valve and aortic-valve replacement and tricuspid-valve repair were performed at MeritCare Medical Center six months after fenfluramine-phentermine therapy was stopped. Histopathological examination of the resected mitral valve dem-

onstrated intact valve architecture, with a plaque-like process that extended along the leaflet surfaces and encased the chordae tendineae (Fig. 3). Lesions on the aortic valve were similar but less extensive.

Patient 3

Patient 3 was a 48-year-old woman (pretreatment body-mass index, 34.5) with no previous cardiac disease who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for nine months. Therapy was discontinued when a murmur was noted, and symptoms of edema and breathlessness were reported. At echocardiography, the mitral valve was thickened and severely regurgitant. Three months later, the patient underwent mitral-valve replacement at MeritCare Medical Center for symptomatic mitral regurgitation. Histopathological examination demonstrated intact valve architecture and plaque-like lesions of apparent myofibroblasts in an abundant extracellular matrix of glycosaminoglycans and collagen (Fig. 4).

Patient 6

Patient 6 was a 51-year-old woman (pretreatment body-mass index, 56.3) with normal findings on cardiac examination who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day in divided doses). Seven months after this treatment was initiated, dyspnea and edema developed and a new murmur was noted. Transthoracic and transesophageal echocardiography at MeritCare Medical Center demonstrated thickened valves with severe mitral regurgitation and moderate aortic-valve and tricuspid-valve regurgitation. Fenfluramine-phentermine therapy was discontinued, and medical therapy for heart failure was instituted. Echocardiography performed three months later demonstrated minimal improvement in the valvular disease. The patient continues to be observed medically and has persistent symptoms of dyspnea.

Patient 7

Patient 7 was a 44-year-old woman who began receiving fenfluramine-phentermine for a pretreatment body-mass index of 30.5. Two years earlier, echocardiography had revealed normal valves. The initial dose was 50 mg of fenfluramine per day in divided doses and 30 mg of phentermine per day. Under medical



Figure 2. Intraoperative Transesophageal Echocardiograms in Patient 1.

The image on the left shows a thickened mitral valve (MV) during diastole. With the addition of color flow, the image on the right demonstrates severe mitral regurgitation (MR) during systole. LA denotes left atrium, and LV left ventricle.

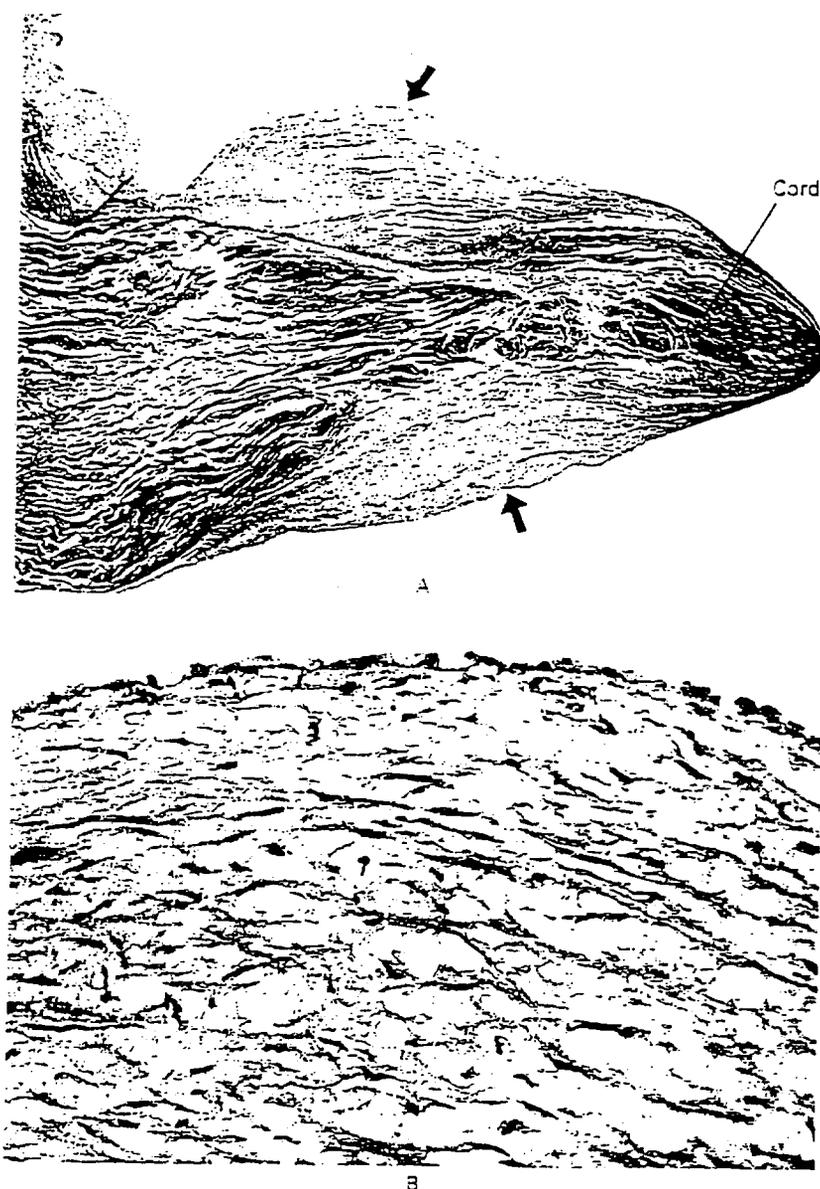


Figure 3. Photomicrographs of Resected Mitral Valve from Patient 2. In Panel A, a low-power view (elastic-van Gieson stain, $\times 36$) shows intact valve architecture with "stuck-on" plaques (arrows). In Panel B, a high-power view (hematoxylin and eosin, $\times 360$) shows proliferative myofibroblasts in an abundant extracellular matrix.

direction, the daily doses were gradually increased to 220 mg of fenfluramine and 60 mg of phentermine.

Twelve months after fenfluramine-phentermine treatment was initiated, dyspnea developed on exertion. Echocardiography demonstrated a thickened tricuspid aortic valve with moderate regurgitation. Pulmonary-artery systolic pressure measured by cardiac catheterization was 75 mm Hg. Treatment with fenfluramine-phentermine was discontinued.

RESULTS

Table 1 summarizes the clinical features of the patients. Except for systemic hypertension, all of the

patients were thought to be free of cardiovascular disease at the onset of weight-reduction therapy. The physicians who prescribed the anorectic agents for the patients were not the ones who evaluated the cardiovascular changes. The patients were evaluated a mean (\pm SD) of 12.3 ± 7.1 months after the initiation of fenfluramine-phentermine treatment. The actual durations of drug therapy are shown in Table 1. Twenty patients presented with cardiovascular symptoms, and four patients had only a new murmur.

All patients underwent comprehensive two-dimen-

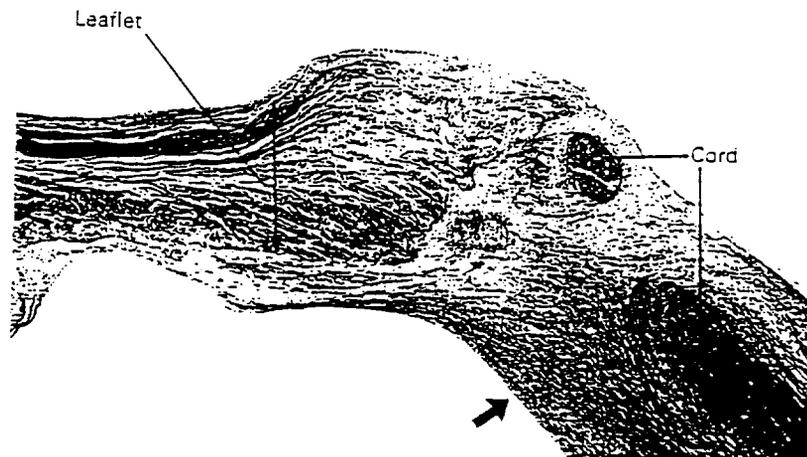


Figure 4. Photomicrograph of Resected Mitral Valve from Patient 3. A low-power view (elastic-van Gieson stain, $\times 36$) shows intact leaflet and tendinous cord, with encasement by proliferative plaque (arrow).

sional echocardiography, pulsed- and continuous-wave Doppler imaging, and color-flow examination according to previously described techniques.¹¹⁻¹³ Valve morphology was noted by two examiners to be atypical for rheumatic, congenital, or degenerative lesions. The mitral and aortic valves exhibited echocardiographic features similar to those seen in patients with chronic rheumatic involvement; however, there was no evidence of valve obstruction. Thickening and diastolic doming of the anterior mitral leaflet, with preserved mobility and thickening, and immobility of the posterior leaflet were typical findings (Fig. 2). Subvalvular involvement was characterized by thickening and shortening of the chordae tendineae, causing tethering of the posterior leaflet. The combination of abnormalities resulted in malcoaptation and central regurgitation. The aortic valve was characterized by thickening and mild retraction of the leaflets. With tricuspid-valve involvement, the septal leaflet was thickened and variably fixed to the septum. The anterior leaflet appeared thickened and exhibited decreased mobility, diastolic doming, and loss of coaptation visible on two-dimensional imaging. Color-flow imaging demonstrated variable degrees of regurgitation in all patients. The echocardiographic appearance of the valves was similar in the medically treated and the surgically treated patients.

Eight patients had Doppler echocardiographic or catheter evidence of pulmonary hypertension (right ventricular systolic pressure, >50 mm Hg; range, 52 to 93) that had not been documented previously. Tricuspid regurgitation of moderate or greater severity was present in five of the eight patients with pulmonary hypertension.

DISCUSSION

Fenfluramine is a sympathomimetic amine that has an anorectic action mediated through the activation of serotonergic pathways in the brain. Fenfluramine promotes the rapid release of serotonin, inhibits its reuptake, and may have receptor-agonist activity,¹⁴ thus making serotonin more susceptible to metabolism and breakdown. The *d*-isomer of fenfluramine, dexfenfluramine, appears to be relatively selective for the central serotonergic system. Phentermine is a noradrenergic agent. Commonly used doses of these medications are 20 to 120 mg of fenfluramine per day and 18.75 to 37.5 mg of phentermine resin per day or 15 to 30 mg of phentermine hydrochloride per day.

Patients with malignant carcinoid syndrome have high levels of circulating serotonin. Associated cardiac disease is characterized by fibroplasia that involves primarily the valvular endocardium on the right side of the heart.^{10,15} The mechanism of valve injury in patients with carcinoid syndrome has not been determined but is believed to be serotonin-mediated, because such patients have higher circulating levels of serotonin than do their counterparts without cardiac involvement.¹⁰ The predilection for right-sided valve disease in carcinoid syndrome is most likely related to the serotonin-rich blood that enters the right atrium directly from the liver and the subsequent partial pulmonary degradation of serotonin. In our patients both left-sided and right-sided valvular lesions were seen, and multiple valves were often involved in individual patients.

The pathophysiologic mechanism in patients with ergot-alkaloid-induced valve disease has not been established, but the similar chemical structures of se-

rotonin, methysergide, and ergotamine may provide a clue.¹⁰ Ergotamine-induced and carcinoid valve disease are microscopically identical, with fibrotic endocardial changes.³ The pathological, surgical, and echocardiographic features of carcinoid and ergotamine-induced valve disease are indistinguishable from the features noted in our patients.

Fenfluramine alters serotonin metabolism in the brain.¹⁴ Phentermine interferes with the pulmonary clearance of serotonin, which may explain its association with primary pulmonary hypertension.¹⁷ Although serotonin levels were not measured in our patients, we postulate that the combination of fenfluramine and phentermine may potentiate the effect or concentration of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome or in those taking ergot preparations. However, the precise process by which this might occur is not known. No studies examining the effect of the combination of fenfluramine and phentermine in animals have been reported. Five of the 24 patients included in this series were taking either sertraline or fluoxetine while receiving fenfluramine-phentermine.

This description of patients is limited by the absence of pathological confirmation in the majority of cases. Many of the patients continue to be treated medically and have not undergone invasive or interventional procedures. Consequently, neither direct inspection nor histopathological evaluation has been carried out in most of the patients. Because no patient had symptomatic or clinical evidence of cardiovascular disease before the initiation of therapy with appetite suppressants, no routine pretreatment echocardiographic base-line studies were obtained. Only one patient had had an incidental echocardiographic study two years before treatment, and it showed no abnormalities. In the aggregate, however, these patients and those who underwent operative intervention had similar clinical and echocardiographic features. The mean age at the initiation of treatment, body-mass index, and duration of treatment before symptoms developed were similar in the medically and surgically treated groups.

In the absence of a control group or a case-control study, definitive statements about a true association of valvular disease with fenfluramine-phentermine therapy cannot be made. However, the appearance of clinically significant left-sided regurgitant valvular heart disease in a population less than 50 years old is rare.¹⁸ Thus, the association of valvular regurgitation with fenfluramine-phentermine treatment is not likely to be due to chance. Moreover, the unusual echocardiographic morphology of the lesions further diminishes the likelihood of a coincidental observation.

These cases should arouse concern that this combination of appetite suppressants has important implications regarding valvular heart disease. Prospective studies of this association will be required to validate the possibility that this combination of medications may cause valvular heart disease. The mechanism of valve injury and the frequency of the association have yet to be determined. Candidates for fenfluramine-phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease.

We are indebted to Pam Ruff, B.S., R.D.C.S., for identification of the patients, to Jeanne Beare, R.N., for data acquisition, and to Julie Kiernmensen and Ann McCullough, M.D., for assistance in the preparation of the manuscript.

REFERENCES

- Weintraub M, Hasday JD, Muslin AI, Lockwood DH. A double-blind clinical trial in weight control: use of fenfluramine and phentermine alone and in combination. *Arch Intern Med* 1984;144:1143-8.
- Langreth R. Critics claim diet clinics misuse obesity drugs. *Wall Street Journal*, March 31, 1997:38.
- Brenot F, Herve P, Penepret R, Parent F, Duroux P, Simonneau G. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993;70:557-61.
- McMurray I, Bloomfield R, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986;292:239-40.
- Heuer L. Pulmonary hypertension. *Chir Prax* 1978;23:497.
- Abenhaim 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.
- Weir EK, Reeve HL, Huang JM, et al. Anorectic agents aminorex, fenfluramine, and dexfenfluramine inhibit potassium current in rat pulmonary vascular smooth muscle and cause pulmonary vasoconstriction. *Circulation* 1996;94:2216-20.
- Redfield MM, Nicholson WJ, Edwards WD, Tajik AJ. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992;117:50-2.
- Pelikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;87:1188-96.
- Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease: correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation* 1995;92:790-5.
- Beckett AH, Saimon JA. Pharmacokinetics of absorption, distribution and elimination of fenfluramine and its main metabolite in man. *J Pharm Pharmacol* 1972;24:108-14.
- Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification, and validation. *Mayo Clin Proc* 1973;53:271-305.
- Nishimura RA, Miller FA Jr, Calahan MJ, Benassi RC, Seward JB, Tajik AJ. Doppler echocardiography: theory, instrumentation, technique, and application. *Mayo Clin Proc* 1985;60:321-43.
- Mitchell R, Smythe G. Hormonal responses to fenfluramine in depressed and control subjects. *J Affect Disord* 1990;19:43-51.
- Thorson AH. Endocardial sclerosis and other heart lesions in the carcinoid disease. *Acta Med Scand Suppl* 1958;334:99-119.
- Redfield MM. Ergot alkaloid heart disease. In: Hurst JW, ed. *New types of cardiovascular diseases: topics in clinical cardiology*. New York: Igaku-Shoin Medical, 1994:63-76.
- Morita T, Menendaie HM. Effects of chlorphentermine and phentermine on the pulmonary disposition of 5-hydroxytryptamine in the rat in vivo. *Am Rev Respir Dis* 1983;127:747-50.
- Klein AL, Burstow DJ, Tajik AJ, et al. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 113 volunteers. *J Am Soc Echocardiogr* 1990;3:54-63.