

The New England Journal of Medicine

© Copyright, 1996, by the Massachusetts Medical Society

VOLUME 335

AUGUST 29, 1996

NUMBER 9



APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

LUCIEN ABENHAIM, M.D., YOLA MORIDE, PH.D., FRANÇOIS BRENOT, M.D.,* STUART RICH, M.D., JACQUES BENICHO, M.D., XAVIER KURZ, M.D., TIM HIGENBOTTAM, M.D., CELIA OAKLEY, M.D., EMIL WOUTERS, M.D., MICHEL AUBIER, M.D., GÉRALD SIMONNEAU, M.D., AND BERNARD BÉGAUD, M.D.,
FOR THE INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY GROUP†

ABSTRACT

Background Recently in France, primary pulmonary hypertension developed in a cluster of patients exposed to derivatives of fenfluramine in appetite suppressants (anorexic agents), which are used for weight control. We investigated the potential role of anorexic agents and other suspected risk factors for primary pulmonary hypertension.

Methods In a case-control study, we assessed 95 patients with primary pulmonary hypertension from 35 centers in France, Belgium, the United Kingdom, and the Netherlands and 355 controls recruited from general practices and matched to the patients' sex and age.

Results The use of anorexic drugs (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension (odds ratio with any anorexic-drug use, 6.3; 95 percent confidence interval, 3.0 to 13.2). For the use of anorexic agents in the preceding year, the odds ratio was 10.1 (95 percent confidence interval, 3.4 to 29.9). When anorexic drugs were used for a total of more than three months, the odds ratio was 23.1 (95 percent confidence interval, 6.9 to 77.7). We also confirmed an association with several previously identified risk factors: a family history of pulmonary hypertension, infection with the human immunodeficiency virus, cirrhosis, and use of cocaine or intravenous drugs.

Conclusions The use of anorexic drugs was associated with the development of primary pulmonary hypertension. Active surveillance for this disease should be considered, particularly since the use of anorexic drugs is expected to increase in the near future. (N Engl J Med 1996;335:609-16.)

©1996, Massachusetts Medical Society.

PRIMARY pulmonary hypertension is a rare, often fatal disease that tends to occur with particular frequency in women during their third or fourth decade.^{1,2} The factors leading to its development remain enigmatic. The occurrence of familial primary pulmonary hypertension suggests a genetic susceptibility.³ Reports have also suggested that portal hypertension^{4,5} and recent pregnancy⁶ may have causative roles. Exogenous factors have been suspected as well, including cocaine use,⁷ infection with the human immunodeficiency virus (HIV),⁸ oral-contraceptive use,^{9,10} and the use of anorexic agents.¹¹⁻¹³ In the 1960s, there was an epidemic of primary pulmonary hypertension in Switzerland, Germany, and Austria in association with a particular anorexic agent, aminorex fumarate.¹¹ In the early 1990s, French investigators reported a cluster of cases among patients who had used derivatives of fenfluramine.¹³ Dexfenfluramine,

From the Centre for Clinical Epidemiology and Community Studies, McGill University and Sir Mortimer B. Davis-Jewish General Hospital, Montreal (L.A., Y.M.); the Pneumology Service, Antoine Bécclère Hospital, Clamart, France (F.B., G.S.); the Section of Cardiology, University of Illinois, Chicago (S.R.); the National Cancer Institute, Rockville, Md. (J.B.); the Pharmacology Laboratory, Pathology Institute, Centre Hospitalier Universitaire de Liège, Liege, Belgium (X.K.); the Section of Respiratory Medicine, University of Sheffield, Sheffield, United Kingdom (T.H.); the Department of Cardiology, Hammersmith Hospital, London (C.O.); the Department of Pulmonology, University Hospital Maastricht, Maastricht, the Netherlands (E.W.); the Pneumology Service, Bichat Hospital, Paris (M.A.); and the Centre for Pharmacovigilance, Pellegrin Hospital, Bordeaux, France (B.B.). Address reprint requests to Dr. Abenhaim at the Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis-Jewish General Hospital and McGill University, 3755 Côte Sainte-Catherine, Montreal, QC H3T 1E2, Canada.

*Deceased.

†Other contributing authors and the participants in the International Primary Pulmonary Hypertension Study Group are listed in the Appendix.

the main drug thought to be involved, is used to treat obesity.

We sought to assess the incidence of primary pulmonary hypertension and investigate the causative roles of various suspected risk factors, especially anorexic agents.¹⁴

METHODS

This was a prospective case-control study conducted in four countries (France, Belgium, the United Kingdom, and the Netherlands). The study included men and women 18 to 70 years of age who had lived in the country where they were studied for more than six months, were able to participate in the interview, and did not have another chronic, active, life-threatening disease.

Three hundred six cardiology and pulmonary-medicine centers at large or university-based hospitals, public and private, were contacted in France, Belgium, the United Kingdom, and the Netherlands, and 220 of them agreed to participate. The centers were provided with stamped, preaddressed postcards with which to report cases of primary pulmonary hypertension to local research teams. The centers were also contacted every two to three months by mail or telephone, or they were visited. The medical records of the patients identified were screened at each site by trained specialists who, in almost all instances, were not affiliated with the reporting centers. During the site visits, the diagnostic and reporting process at the centers was reviewed to identify patients with primary pulmonary hypertension who might have been overlooked and assess potential biases in reporting. In Belgium, regular contact was established with each of 71 centers where primary pulmonary hypertension might have been diagnosed. This contact allowed us to calculate the annual incidence of the disease in the Belgian population.

Patients

We recruited patients with primary pulmonary hypertension diagnosed from September 1, 1992, through September 30, 1994, at the time of the patient's first right-heart catheterization. The diagnosis required both that pulmonary hypertension be documented and that the following secondary causes be absent: congenital abnormalities of the lungs, thorax, or diaphragm; congenital or acquired valvular or myocardial disease; pulmonary thromboembolism; obstructive lung disease; interstitial lung disease; pulmonary-artery or pulmonary-valve stenosis; pulmonary venous hypertension; central hypoventilation with hypoxemia and hypercapnia; parasitic disease affecting the lungs; sickle cell anemia; the acquired immunodeficiency syndrome (AIDS); and collagen vascular diseases. An international panel of reviewers assessed abstracted medical data, cardiac-catheterization reports, chest radiographs, perfusion lung scans, and echocardiographic images or reports for patients qualifying for the study. The panel, whose members had no knowledge of any patient's exposure to anorexic drugs, classified the patients in three groups: patients with definite primary pulmonary hypertension, those with probable primary pulmonary hypertension, and those who were not considered appropriate for the study. The first two groups were included in the case-control analysis. The reproducibility of the classifications, as verified by a second review of 10 randomly selected files, was excellent (all the decisions to include or exclude patients were confirmed). The results of autopsy or biopsy were obtained for nine patients who underwent transplantation or died soon after their inclusion in the study, and they all had plexogenic pulmonary arteriopathy, regardless of their status with respect to anorexic-drug use.

Controls

Four control patients were sought for each patient with primary pulmonary hypertension. The controls were randomly selected from lists of consecutive patients seen by the same general

practitioner as the patient with primary pulmonary hypertension. The general practitioner was identified by the patient and defined as the physician the patient consulted for usual care. If this physician was unavailable (usually because he or she refused to participate in the study), other general practitioners were contacted who practiced in the region where the patient lived. One third of the controls were recruited in this manner. The controls were individually matched to the case patients with respect to age (within five years), sex, and the number of visits to the physician per year (<2 or ≥2). The following data were recorded for all the visits made during a one-week period: the patient's name, age, sex, and the number of visits made by that patient per year. All visits of patients who met the matching criteria were identified, and four controls were randomly selected by the local coordinating center. The general practitioner was contacted again for the names and telephone numbers of the patients selected. The same criteria for inclusion and exclusion were used in selecting the controls that were used in selecting the case patients, except for the diagnosis of primary pulmonary hypertension.

Exposure to Anorexic Drugs

Each patient underwent a thorough, face-to-face interview conducted by a specially trained interviewer who had no medical background and was unaware of the study's main hypotheses. The patients were asked about demographic characteristics; their medical, surgical, and obstetrical histories; and exposure to drugs. Data on such exposures were recorded chronologically on a calendar-like data sheet. The recording of exposures reported to have occurred after August 1, 1989, was more detailed than that of earlier exposures. The presence of HIV infection and the diagnosis of cirrhosis were determined by a review of the medical charts. Drug use was established by three methods: spontaneous reporting by the patient; the presentation to the patient of lists of approximately 80 trade names chosen from among the most commonly prescribed drugs in 17 therapeutic classes (the individual products varied slightly from country to country); and the presentation to the patient of a visual display showing 35 selected packages, tablets, or both. Only exposure to antihypertensive drugs, oral contraceptives, thyroid extracts, and anorexic agents (also called appetite suppressants) was analyzed. The following anorexic agents were considered: derivatives of fenfluramine (fenfluramine and dexfenfluramine), amphetamine-like anorexic agents (diethylpropion [amfepramone], clobenzorex, fenproporex, mazindol, and phenmetrazine), and compound preparations of appetite-suppressant drugs and other drugs taken to lose weight. Special preparations used in order to lose weight, with no reference to appetite suppression, were not considered anorexic agents. Each patient was given a special questionnaire assessing his or her use of illicit drugs (intravenous drugs, cocaine, hashish, and marijuana). The data-collection process was identical in all the countries studied.

For each case patient and that patient's matched controls, the index date used in the study of risk factors corresponded to the date of onset of the case patient's symptoms (usually dyspnea). Patients were classified as having been exposed to a given risk factor if the exposure occurred before the index date (a "definite exposure"). Exposures reported to have occurred at an indeterminate time or during the same month as the index date were classified as "possible exposures." Patients in whom the exposure began after the index date were considered unexposed to that risk factor. Definite exposure to anorexic agents was categorized further, depending on whether the exposure occurred in the 12 months before the index date ("recent use") or had ended more than 12 months earlier ("past use"). Because of the design of the calendar data sheet, this categorization could be used only for 65 case patients and 234 matched controls whose index dates were later than August 1, 1989.

Statistical Analysis

All the odds ratios presented here were obtained through conditional logistic regression. All the models included exposure to

appetite suppressants (categorized as none, possible, or definite, as defined above), weight-related confounding variables, and other variables thought to be possible risk factors. The weight-related variables consisted of the patient's highest lifetime body-mass index (calculated as the weight in kilograms divided by the square of the height in meters and dichotomized as <30 and ≥30, a cut-off point selected a priori); behavior aimed at losing weight (categorized as present or absent, with the former defined as a report of unstable weight; the use of diuretics, laxatives, or phytotherapy for weight loss; or episodes of anorexia); and the use of thyroid extracts (yes or no). The other variables thought to be risk factors were the use of cocaine, intravenous drugs, or both (yes or no); treatment for systemic hypertension (present or absent); and smoking (yes or no). In separate analyses conducted of women, oral-contraceptive use (yes or no) and pregnancy during the year before the index date (yes or no) were also considered, and adjustment was made for them. Variability in sampling associated with the estimated odds ratios was assessed by two-sided 95 percent confidence intervals. All the analyses were performed with the SAS statistical package, version 6.13 (Unix), and Egret, version 026.6. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

One hundred thirty-five patients with primary pulmonary hypertension met the criteria for inclusion in the study. An additional 26 patients were already dead or were too sick to be interviewed. Twenty-three of the 135 patients were considered by the review panel not likely to have primary pulmonary hypertension, 2 were lost to follow-up, 2 declined to participate, and 13 could not be interviewed, or their data reviewed, before the final analysis. The remaining 95 patients (80 with definite and 15 with probable primary pulmonary hypertension), who were retained in the case-control study, were identified at a total of 35 specialized centers (Table 1). A national referral center for primary pulmonary hypertension in France (Antoine Béclère Hospital)¹⁵ contributed 35 patients; the other centers each contributed 1 to 6 patients (mean, 1.7). The mean (±SD) age of the case patients was 44.7±12.3 years, and that of the controls was 45.1±12.6 years. Among the case patients, the female:male ratio was 2.3:1 (Table 1). Among the controls, the rate of participation was 85.3 percent in France, 92.1 percent in Belgium, 81.8 percent in the United Kingdom, and 100 percent in the Netherlands.

The clinical characteristics of the patients with primary pulmonary hypertension are shown in Table 2. Dyspnea was the initial symptom in 91 percent, and it was severe (New York Heart Association class III or IV) in two thirds at the time of diagnosis. In almost two thirds of these patients, the diagnosis was not established until more than a year had passed after the appearance of symptoms.

The case patients and the controls were very similar with regard to both occupation and 24 broad classes of preexisting morbidity, as defined in the *International Classification of Diseases, Ninth Revision*. The case patients and the controls had taken an almost identical number of drugs (4.4±4.5 and

TABLE 1. CHARACTERISTICS AND COUNTRIES OF THE STUDY POPULATION.

COUNTRY	NO. OF CENTERS	CASE PATIENTS (N=95)	CONTROLS (N=355)
		no. (%)	
France	18		
National referral center		35 (36.8)	117 (33.0)
Other 17 centers		29 (30.5)	115 (32.4)
Belgium	7	13 (13.7)	59 (16.6)
United Kingdom	6	11 (11.6)	36 (10.1)
The Netherlands	4	7 (7.4)	28 (7.9)
All	35		
Women		66 (69.5)	265 (74.6)
Men		29 (30.5)	90 (25.4)
Mean (±SD) age — yr		44.7±12.3	45.1±12.6

TABLE 2. CLINICAL, FUNCTIONAL, AND PULMONARY HEMODYNAMIC VARIABLES IN THE 95 PATIENTS WITH PRIMARY PULMONARY HYPERTENSION.

VARIABLE*	VALUE†
Initial symptoms (% of patients)	
Dyspnea	91
Chest pain	16
Syncope	14
Edema	9
Time from onset of symptoms to cardiac catheterization (% of patients)	
≤12 mo	37
12–35 mo	39
≥36 mo	20
Unknown	4
Severity of dyspnea at diagnosis (% of patients)	
NYHA class I or II	34
NYHA class III or IV	66
Cardiac-catheterization findings (mm Hg)	
Pulmonary arterial pressure	
Systolic	88±21
Diastolic	39±10
Mean	57±13
Pulmonary-capillary wedge pressure	9±3
Right atrial pressure	11±6
Pulmonary-function tests (% of predicted value)	
Forced vital capacity	98±15
Total lung capacity	97±13
FEV ₁	91±16
DLCO	79±22
Blood gas measurements	
PaCO ₂ (mm Hg)	31±5
PaO ₂ (mm Hg)	76±20
SaO ₂ (%)	94±4

*NYHA denotes New York Heart Association, FEV₁ forced expiratory volume in one second, DLCO single-breath diffusing capacity for carbon monoxide, PaCO₂ partial pressure of arterial carbon dioxide, PaO₂ partial pressure of arterial oxygen, and SaO₂ arterial oxygen saturation.

†Plus-minus values are means ±SD.

4.3±4.4, respectively). Two case patients reported a family history of primary pulmonary hypertension; three had HIV infection (eight with AIDS were excluded from the study at the screening stage); more case patients than controls were alcohol drinkers (72.6 percent vs. 64.0 percent), but not significantly more ($P=0.13$); and seven case patients reported a history of cirrhosis, which could be confirmed in four from the medical chart. None of these diseases were reported by any of the controls.

Table 3 shows the frequency of appetite-suppressant use and the adjusted odds ratios for primary pulmonary hypertension with all the confounding variables and other risk factors. Thirty case patients (31.6 percent) and 26 controls (7.3 percent) reported using appetite suppressants before their index date, yielding a crude (matched) odds ratio of 7.1 (95 percent confidence interval, 3.7 to 13.9) and an adjusted odds ratio of 6.3 (95 percent confidence interval, 3.0 to 13.2) (Table 3). The odds ratio associated with recent use (in the year before the index date) was 10.1 (95 percent confidence interval, 3.4 to

29.9), and the odds ratio associated with past use was 2.4 (95 percent confidence interval, 0.7 to 8.2). The odds ratio increased sharply with the duration of exposure (use for three months or less, 1.8; use for more than three months, 23.1). The total intake of anorexic drugs was estimated by totaling the reported number of months of use. Figure 1 shows the distribution of such intake for the patients with primary pulmonary hypertension and the controls. Very few controls (0.6 percent) used anorexic agents for a total of 12 months or more, as compared with 12.6 percent of case patients.

When the case patients with cirrhosis, familial pulmonary hypertension, HIV infection, or intravenous drug use and their matched controls were excluded from the analysis, the adjusted odds ratio associated with anorexic-drug use increased to 8.6 (95 percent confidence interval, 3.8 to 19.5). There was no change in the effects of anorexic drugs or other risk factors for primary pulmonary hypertension when alcohol intake was included in the logistic model (odds ratio, 6.3). Among female subjects, 27 patients with primary pulmonary hypertension (40.9 percent) and 25 controls (9.4 percent) had used anorexic drugs (adjusted odds ratio, 7.9; 95 percent confidence interval, 3.5 to 17.5), as compared with 3 male patients with primary pulmonary hypertension (10.3 percent) and 1 male control (1.1 percent) (adjusted odds ratios were not defined for men).

Table 3 also shows the individual drugs used by the case patients and the controls. Dexfenfluramine and fenfluramine were the most commonly used: 22 patients (23.2 percent) and 23 controls (6.5 percent) had used at least one of them; of these subjects, 16 patients (16.8 percent) and 18 controls (5.1 percent) reported not using any other anorexic drug. Amphetamine-like anorexic agents (diethylpropion, clobenzorex, fenproporex, phenmetrazine, or a combination of these) had been used by eight case patients (8.4 percent) and eight controls (2.3 percent), among whom only two case patients and three controls did not also report using a fenfluramine derivative before the index date. Seven patients with primary pulmonary hypertension (7.4 percent) and no controls reported exposure to compound preparations. The content of the compound preparations used by three patients was learned: one contained dexfenfluramine, one contained an amphetamine-like anorexic agent and possibly fenfluramine, and one contained both an amphetamine-like anorexic agent and dexfenfluramine; the preparations also typically contained diuretics, phytotherapy products, thyroid extracts, or a combination of these. Most of the exposure to appetite suppressants occurred in France (22 patients and 22 controls) and Belgium (6 patients and 4 controls). One patient each from the United Kingdom and the Netherlands had used ap-

TABLE 3. USE OF APPETITE SUPPRESSANTS AND ADJUSTED ODDS RATIOS FOR THE RISK OF PRIMARY PULMONARY HYPERTENSION.

VARIABLE	CASE PATIENTS (N=95)	CONTROLS (N=355)	ADJUSTED ODDS RATIO (95% CI)*
	no. (%)		
Definite use of appetite suppressants	30 (31.6)	26 (7.3)	6.3 (3.0–13.2)
Duration of use			
≤3 mo	7 (7.4)	12 (3.4)	1.8 (0.5–5.7)
>3 mo	18 (19.0)	5 (1.4)	23.1 (6.9–77.7)
Indeterminate	5 (5.3)	9 (2.5)	2.6 (0.5–12.6)
Products reported as used†			
Dexfenfluramine	18 (18.9)	22 (6.2)	—
Fenfluramine	6 (6.3)	4 (1.1)	—
Diethylpropion	3 (3.2)	2 (0.6)	—
Clobenzorex	3 (3.2)	6 (1.7)	—
Fenproporex	2 (2.1)	1 (0.3)	—
Phenmetrazine	2 (2.1)	0	—
Compounds	7 (7.4)	0	—
Possible use	3 (3.2)	2 (0.6)	
Use after index date	3 (3.2)	17 (4.8)	
Timing of use‡			
Recent	14 (21.5)	7 (3.0)	10.1 (3.4–29.9)
Past	7 (10.8)	14 (6.0)	2.4 (0.7–8.2)

*Odds ratios were adjusted for systemic hypertension, use of cocaine or intravenous drugs, smoking status, high body-mass index, weight-loss behavior, use of thyroid extracts, and possible exposure to anorexic agents. CI denotes confidence interval.

†Categories shown are not mutually exclusive because patients may have had multiple concomitant or serial exposures.

‡Data are based on appetite-suppressant use in 65 case patients and 234 matched controls. Recent denotes anorexic-drug use within the 12 months before the index date, and past denotes use that ended more than 12 months before the index date.

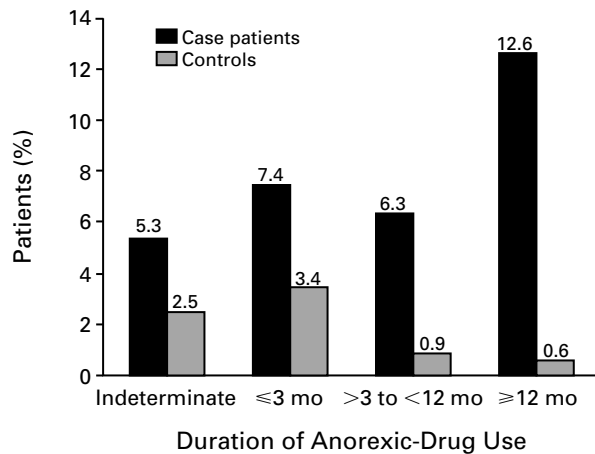


Figure 1. Duration of Exposure to Anorexic Drugs in the Study Patients before the Onset of Symptoms of Primary Pulmonary Hypertension.

petite suppressants. The matched crude odds ratios associated with the use of appetite suppressants were 10.7 in Belgium and 5.9 in France (these ratios could not be calculated in the Netherlands or the United Kingdom). All the patients from the national referral center in France and several Belgian patients were followed, and there was no marked improvement in the condition of those who had used anorexic agents after that use had stopped.

Table 4 shows the frequency of the weight-related confounding variables and the other variables thought to be risk factors for primary pulmonary hypertension, with their corresponding odds ratios (after adjustment for each other and for the use of anorexic agents). High body-mass index, treated systemic hypertension, the use of cocaine or intravenous drugs (in patients without HIV infection), and pregnancy in the year before the onset of symptoms were more frequent in the patients with primary pulmonary hypertension than in the controls, but not significantly so. The case patients used thyroid extracts less often than the controls, but not significantly so. Although smoking was reported significantly more often by case patients than by controls, it was not associated with an increased risk of primary pulmonary hypertension when other covariates were controlled for. The use of oral contraceptives, hashish, and marijuana (data not shown) did not differ between the patients and the controls. When the case patients with HIV, cirrhosis, familial pulmonary hypertension, or intravenous drug use and their matched controls were excluded from the analysis, the effect of the risk factors shown in Table 4 did not differ notably between groups. The adjusted odds ratio associated with obesity was 1.6 (95 percent confidence interval, 0.7 to 3.7) in women.

Incidence Study

In the study of the annual incidence of primary pulmonary hypertension in Belgium, 24 patients were identified over a 24-month period (13 were included in the case-control study and 11 either had died or were identified too late to be included). There were approximately 7 million inhabitants of Belgium 18 to 70 years of age at the time of the study. The annual incidence of primary pulmonary hypertension in this population was 1.7 per million (95 percent confidence interval, 1.0 to 2.4).

DISCUSSION

Our most striking findings concern the use of appetite suppressants as a risk factor for primary pulmonary hypertension, especially use lasting more than three months (odds ratio, 23.1). This is especially important because dexfenfluramine, the main drug involved in this study, was recently approved by the Food and Drug Administration for the long-term treatment of obesity. The risk of primary pulmonary hypertension seems to increase steadily with the quantity of appetite suppressants used, but there has been very little experience with their long-term use in Europe.

We conducted additional analyses to identify potential sources of bias. We investigated whether patients exposed to anorexic agents could have been preferentially included in the study. This phenomenon may not be significant in the United Kingdom and the Netherlands, where anorexic agents were rarely used, or in Belgium, where the number of patients in the incidence study was very close to the

TABLE 4. FREQUENCY OF WEIGHT-RELATED AND OTHER VARIABLES AND ADJUSTED ODDS RATIOS FOR THE RISK OF PRIMARY PULMONARY HYPERTENSION.

VARIABLE	CASE PATIENTS (N=95)	CONTROLS (N=355)	ADJUSTED ODDS RATIO (95% CI)*
	no. (%)		
All patients			
Body-mass index ≥30	34 (35.8)	65 (18.3)	1.9 (1.0-3.6)
Weight-loss behavior	57 (60.0)	178 (50.1)	1.1 (0.6-2.0)
Thyroid-extract use	2 (2.1)	11 (3.1)	0.5 (0.1-2.5)
Systemic hypertension	11 (11.6)	21 (5.9)	2.1 (0.7-6.0)
Use of cocaine or intravenous drugs	4 (4.2)	4 (1.1)	2.8 (0.5-15.7)
Smoking	42 (44.2)	112 (31.5)	1.4 (0.8-2.4)
Female patients†			
Recent pregnancy	5 (7.6)	14 (5.3)	1.9 (0.6-6.0)
Oral-contraceptive use	47 (71.2)	174 (65.7)	1.3 (0.6-3.1)

*Odds ratios are adjusted for appetite-suppressant use. CI denotes confidence interval.

†Data shown are based on 66 case patients and 265 matched controls.

number expected on the basis of earlier figures.¹⁴ In France, only two thirds of the centers contacted agreed to participate in the study. We think it very unlikely that at these centers a significant number of patients, if any, with diagnosed primary pulmonary hypertension might not have been reported, considering all the verification procedures we used. There is no reason to believe that the proportion of patients exposed to anorexic agents would differ in the centers that did not participate. We have been informed that at least five cases of primary pulmonary hypertension diagnosed during the study period in patients who were exposed to derivatives of fenfluramine were reported to the manufacturer by non-participating centers. Among the participating centers, the exposure to anorexic agents was similar in the patients originally identified at the national referral center (31 percent) and those identified at all the other French centers combined (37 percent). Also, we obtained data on exposure to anorexic drugs in the 13 patients identified too late to be included in the study and found that it was 31 percent — close to the proportion reported for the patients who were included. Sixty-two percent of the patients did not report any use of anorexic agents, as is consistent with the fact that anorexic agents are obviously not the only possible cause of this disease.

There could be another selection bias if persons with primary pulmonary hypertension who used anorexic agents were more likely to have their disease recognized than other patients. To explore this potential bias, we examined the time between the appearance of the first symptoms and the diagnosis and found that it did not differ significantly between the case patients who used anorexic agents and those who did not (16.8 and 17.6 months, respectively). We also compared the degree of dyspnea at the time of diagnosis and found that it was more often severe (New York Heart Association class III or IV) in case patients who used anorexic agents (89.7 percent) than in those who did not (56.6 percent), whereas the reverse would be expected if there were a preferential bias based on the diagnosis. (This study was done only among patients whose index dates were later than August 1, 1989.)

We also examined potential sources of misclassification of the exposure to anorexic agents. Patients with primary pulmonary hypertension might be more likely to remember using anorexic agents than controls (recall bias). On the basis of sales figures, we estimated a priori that 5 percent of the controls would have exposure to a derivative of fenfluramine,¹⁴ and we found that 6.2 percent actually had such exposure. The accuracy of the index date was another source of concern, since the development of dyspnea is often insidious. To explore this matter, we recalculated the odds ratios with the index dates moved back to 12 months before the reported dates

and found that the odds ratio associated with the use of anorexic agents was 7.4 — higher than the original odds ratio (6.3). Exposure after the original index date was slightly less frequent in the case patients than in the controls. All this rules out a “protopathic” (reverse causality) bias. We could not verify the actual content of most of the so-called appetite-suppressant compound preparations, but in the three instances in which we could do so, we found that they did contain anorexic agents. “Possible exposure” to anorexic agents was more often found in case patients than in controls.

We considered whether the association between the use of appetite suppressants and primary pulmonary hypertension could be explained by the confounding effect of obesity or that of any hidden factor associated with obesity. The odds ratio for anorexic agents was similar whether or not the logistic-regression models were adjusted for high body-mass index. The odds ratio for the interaction between obesity and appetite-suppressant use was 1.0 (95 percent confidence interval, 0.2 to 3.5). Therefore, the effect of anorexic agents was the same whether patients had a high body-mass index or not. Neither weight-loss behavior of another type nor the use of thyroid extracts was positively associated with the risk of primary pulmonary hypertension, as would have been expected if obesity accounted for the odds ratio observed for anorexic agents.

We believe that the association between anorexic agents and primary pulmonary hypertension is due to neither bias nor chance. Our findings are consistent with observations in the 1960s of an association of primary pulmonary hypertension with the use of aminorex fumarate¹¹ and of more recent associations with fenfluramine derivatives, other anorexic agents, or related products.^{11-13,16-18} The consistency of our observations with previous findings, the strength of the association, the fact that it increases with longer use, and the fact that it is stronger with recent use than with past use all favor a causal relation. It is also worth noting that cases have been described in which the disease regressed after exposure to fenfluramine ended.¹⁷ Susceptibility factors are also likely to play a part, considering the rarity of primary pulmonary hypertension. The results apply mainly to derivatives of fenfluramine, which were used by 90 percent of the subjects who named an individual anorexic agent and were contained in all the preparations whose actual content was determined. The role of other amphetamine-like anorexic agents is unclear, and such agents were rarely used alone.

How fenfluramine and dexfenfluramine may lead to pulmonary hypertension is unknown. Hypotheses have been put forward that implicate serotonin,¹⁹ a pulmonary vasoconstrictor, a direct vasoconstrictor effect through potassium-channel blockade²⁰ (an effect that has also been shown to occur with amino-

rex), and pulmonary vasoconstriction,²¹ but these hypotheses remain speculative.

This international epidemiologic study of primary pulmonary hypertension confirms the clinical features of the disease as described in the National Registry of Primary Pulmonary Hypertension² and several case series.^{15,22} The severity of dyspnea at the time of diagnosis was consistent with the long delay between the first symptoms and diagnosis, a finding similar to that observed in the registry.² Efforts to shorten the delay could be valuable, since treatment has recently been shown to be effective in some patients.^{23,24}

Our results also confirm the role of several previously described risk factors for pulmonary hypertension, including HIV infection^{8,25} and cirrhosis.^{4,5} Because of simultaneous or multiple exposures, the role of intravenous drug use could not be examined separately from that of cocaine use, but both were used more frequently by the patients with primary pulmonary hypertension than by the controls. Primary pulmonary hypertension has previously been observed in infants born to mothers with a history of cocaine abuse⁷ and in users of related drugs.^{26,27} Pulmonary hypertension associated with intravenous drug use may also be due to the embolism of talc or other foreign substances. Recent pregnancies⁶ and treated systemic hypertension appeared to be more frequent in the case patients than in the controls, but the study did not have sufficient power to be conclusive in this regard. We could not confirm the previously reported suspicion of an association with oral contraceptive use.^{9,10} Obesity, which was marginally associated with the risk of primary pulmonary hypertension in this study, has not been previously reported as a risk factor. A subject's report of obesity may have been associated with use of anorexic agents that the subject did not report. If so, the appearance of an effect of obesity on the risk of primary pulmonary hypertension simply reflects the harmful effects of small amounts of unrecorded drug use.

In conclusion, the annual incidence of primary pulmonary hypertension estimated from this study is very low — on the order of 1 case per 500,000 inhabitants. The corresponding absolute risk for obese persons who use anorexic agents for more than three months would be more than 30 times higher than for nonusers. It is not known to what extent the risk continues to increase with longer use, because the experience with long-term use of anorexic agents has been extremely limited. We recommend active surveillance of the use of these drugs, especially if long-term use is planned.

Supported by a grant (9404 UO 27203-UI-A) from the Industry Program of the Medical Research Council of Canada, by the Institut de Recherches Internationales Servier, and by the Ministry of Public Health and Environment of Belgium.

We are indebted to Drs. Michael Kramer and John Esdaile for their valuable comments; to Ms. Linda Carfagnini for her administrative assistance throughout the project; to Dr. Bernadette Rains for reviewing the anatomical and pathological slides; and to Mr. Luc Lalonde for assistance with the statistical analysis.

APPENDIX

Robert Naeije, M.D., William Dab, M.D., David Langleben, M.D., Anicet Chaslerie, M.D., Bruno Stricker, M.D., Thierry Ducruet, M.Sc., Cees Wagenvoort, M.D. (deceased), Maurits Demedts, M.D., Emmanuel Weitzenblum, M.D., Marion Delcroix, M.D., Denise Walckiers, M.Sc., Claudine Peiffer, M.D., David Dutka, M.D., Ellen Pouw, M.D., Miriam Sturkenboom, Ph.D., Michael McGoan, M.D., and Lewis Rubin, M.D., were contributing authors of this paper.

Investigators at the participating centers: France — P. Achkar, S. Adnot, D. Anthoine, A. Arnaud, P. Assayag, P. Bareiss, J.-P. Bassand, A. Beardt, J. Beaume, P. Bernadet, Y. Bernard, B. Blaive, J.P. Bonhomme, M. Bory, J. Brune, I. Caubarrere, F. Chabot, A. Chavaillon, J. Clementy, L. Couraud, L. Desfossay, A. Didier, C. Dromer, G. Ducloux, P. Duroux, J.M. Fauvel, E. Ferrari, J.-L. Fincker, I. Gandjbakhch, G. Gebrac, P. Geslin, F. Guérin, A. Haloum, P. Hervé, A. Heulin, B. Housset, R. Kessler, P. Lemoigne, P. Leophonte, J. Lerousseau, P. Meyer, A. Michaud, A. Millaire, P. Morand, J.-F. Mornex, J.-F. Muir, M. Noirclerc, R. Pariente, S. Pham, J.-M. Polu, J.-C. Potier, M. Reynaud-Gaubert, J. Rochemaure, A. Sacrez, P. Scanu, M. Stern, A.B. Tonnel, E. Tuchais, P. Vacheron, P.-E. Valere, and C. Vinti; Belgium — E. Balthazar, Y. Bogaerts, R. Broux, P. Clement, J.-C. Debaisieux, S. Degre, L. Delaunois, M. DePauw, W. Elinck, M. Estenne, V. Legrand, M. Mairesse, P. Mengeot, M. Radermacker, J.-L. Vachiery, B. Van de Maele, P. Van Den Brande, J. Van Haecke, W. Van Mieghem, D. Van Renterghem, and J. Vanwelden; the Netherlands — F. Beaumont, G.J. Bosman, M. Cheriex, C. Jansveld, G.P.M. Mannes, M. van Rossum, J. van Stigt, F.J. Visser, and A. Welling; United Kingdom — A. Mitchell, A. Peacock, M. Ryan, and N. Uren.

REFERENCES

1. Rubin LJ. Primary pulmonary hypertension. *Chest* 1993;104:236-50.
2. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987;107:216-23.
3. Langleben D. Familial primary pulmonary hypertension. *Chest* 1994; 105:Suppl:13S-16S.
4. Hadengue A, Benhayou MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991;100:520-8.
5. McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? *Am Rev Respir Dis* 1983;127:437-41.
6. Dawkins KD, Burke CM, Billingham ME, Jamieson SW. Primary pulmonary hypertension and pregnancy. *Chest* 1986;89:383-8.
7. Collins E, Hardwick H, Jeffery H. Perinatal cocaine intoxication. *Med J Aust* 1989;150:331-2.
8. Legoux B, Piette AM, Bouchet PE, Laudau JF, Gepner P, Chapman AM. Pulmonary hypertension and HIV infection. *Am J Med* 1990;89:122.
9. Kleiger RE, Boxer M, Ingham RE, Harrison DC. Pulmonary hypertension in patients using oral contraceptives: a report of six cases. *Chest* 1976; 69:143-7.
10. Masi AT. Pulmonary hypertension and oral contraceptive usage. *Chest* 1976;69:451-3.
11. Gurtner HP. Aminorex and pulmonary hypertension. *Cor Vasa* 1985; 27:160-71.
12. Douglas JG, Munro JF, Kitchin AH, Muir AL, Proudfoot AT. Pulmonary hypertension and fenfluramine. *BMJ* 1981;283:881-3.
13. Brenot F, Herve P, Petitpretz P, Parent F, Duroux P, Simonneau G. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993;70: 537-41.
14. Abenheim L. The International Primary Pulmonary Hypertension Study (IPPHS). *Chest* 1994;105:Suppl:37S-41S.
15. Brenot F. Primary pulmonary hypertension: case series from France. *Chest* 1994;105:Suppl:33S-36S.
16. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986;293:51-2.

17. Pouwels HM, Smeets JL, Cheriex EC, Wouters EF. Pulmonary hypertension and fenfluramine. *Eur Respir J* 1990;3:606-7.
18. Fahlen M, Bergman H, Helder G, Ryden L, Wallentin I, Zettergren L. Phenformin and pulmonary hypertension. *Br Heart J* 1973;35:824-8.
19. Hervé P, Launay J-M, Scrobohaci M-L, et al. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 1995;99:249-54.
20. Michelakis ED, Archer SL, Huang JMC, Nelson DP, Weir EK. Anorexig agents inhibit potassium current in pulmonary artery smooth muscle cells. *Am J Respir Crit Care Med* 1995;151:Suppl:A725. abstract.
21. Naeije R, Wauthy P, Maggiorini M, Lecman M, Delcroix M. Effects of dexfenfluramine on hypoxic pulmonary vasoconstriction and embolic pulmonary hypertension in dogs. *Am J Respir Crit Care Med* 1995;151:692-7.
22. Oakley CW. Primary pulmonary hypertension: case series from the United Kingdom. *Chest* 1994;105:Suppl:29S-32S.
23. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol): results of a randomized trial. *Ann Intern Med* 1990;112:485-91.
24. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76-81.
25. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. *Circulation* 1994;89:2722-7.
26. Russel LA, Spehlmann JC, Clarke M, Lillington GA. Pulmonary hypertension in female crack users. *Am Rev Respir Dis* 1992;145:Suppl:A717. abstract.
27. Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long-term inhalation of "crank" methamphetamine. *Chest* 1993;104:614-6.