This is Exhibit H referred to in the affidavit of Dr. John Granton, sworn before me, this 24th day of September, 2004.

A Commissioner for Taking Affidavits, etc.

SUSAN ALLISON PHILLIPS, a
Commissioner, etc., City of Toronto, for
Rochon/Genova, Barristers and Solicitors.
Expires November 27, 2005.

Primary Pulmonary Hypertension Associated With the Use of Fenfluramine Derivatives*

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Fenfluramine derivatives (Fds) are a well-established risk factor for primary pulmonary hypertension (PPH). We compared 62 Fd-PPH patients (61 women) evaluated in our center between 1986 and 1997 with 125 sex-matched PPH patients nonexposed to Fd referred during the same period (control PPH). In the Fd-PPH group, 33 patients (53%) used dexfenfluramine alone, 7 patients (11%) used fenfluramine alone, and 5 patients (8%) used both drugs. In 17 cases (27%), Fd use was associated with that of amphetamines. Most of the exposed patients used Fd for at least 3 months (81%). The interval between the onset of dyspnea and that of drug intake was 49±68 months (27 days to 23 years). At the time of diagnosis, Fd-PPH and control PPH were similar in terms of New York Heart Association functional class and symptoms. The two groups significantly differed only in terms of age (50±12 vs 40±14 years) and body mass index (28±6 vs 23±4). The two groups displayed similar severe baseline hemodynamics (total pulmonary vascular resistance: 32±12 vs 31±12 IU/m^2), but the percentage of responders to acute vasodilator testing was higher in control PPH (27% vs 10%, $p<0.01$). As a result, more patients were treated with oral vasodilators in the control PPH group (36% vs 16%, $p<0.01$) and long-term epoprostenol infusion was more frequently used in the Fd-PPH group (52% vs 31%, $p<0.01$). Overall survival was similar in the two groups with a 3-year survival rate of 50%.

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Primary pulmonary hypertension (PPH) is a rare but devastating disorder of unknown etiology. However, there is increasing evidence that some triggers or expression factors can cause or hasten the development of this disease. Recent reports have indicated that portal hypertension,[1] HIV infection,[2,3] and anorexic drugs[4] may have causative roles. When exposed to these supposed risk factors, only a minority of patients develop pulmonary hypertension (PH), suggesting that genetic predisposition is likely to play an important part. In the 1960s, the medical community was first alerted to the problem of an epidemic of PH related to the intake of the appetite-suppressant drug, aminorex.[5] Recently, due to the widespread use of another class of anorexic drugs, the fenfluramine derivatives, this old problem has been revisited.

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Anorexigens and PPH: A Historical Review

Aminorex PPH

Between 1967 and 1972, in Austria, Germany, and Switzerland, the incidence of cases of severe PH increased sharply.[6] Among the 582 cases of PH observed in these countries during this period, 62% of affected patients had a history of aminorex intake (alone or in association with other anorexic drugs). In this epidemic of severe PH, the role of aminorex was very quickly suspected because of the evidence of a close geographic as well as temporal relationship between the intake of aminorex and the increased incidence of cases of PH. The epidemic started about 2 years after the introduction of the drug into the market and suddenly disappeared 2 years after aminorex was withdrawn. Among aminorex users, it was estimated that only about 1/1,000 developed PPH. This is an estimated odds ratio of about 500 for the development of PH in aminorex users. In patients with aminorex-related PPH, clinical, hemodynamic, and histologic findings were similar to those of patients with spontaneous PPH. About 30% of patients with aminorex-related PPH showed a signif-

icant clinical improvement after discontinuing treatment with the drug. Such a spontaneous improvement is almost never observed in PPH and probably explains the trend toward better survival in the group with aminorex-related PPH as compared with those with spontaneous PPH.[6]

Fenfluramine PPH

Fenfluramine derivatives are sympathomimetic amines exhibiting an anorexic action through the activation of serotonin pathways in the brain. Fenfluramine and dexfenfluramine have been widely used in Europe and especially in France in the 1980s and in the early 1990s. In April 1996, the Food and Drug Administration approved dexfenfluramine for use in the United States. The first cases of fenfluramine-associated PPH were reported in 1981.[7] These observations were particularly demonstrative because PH markedly decreased in both patients after discontinuing treatment with the drug. Moreover, in one case, rechallenge with fenfluramine was associated with a rapid deterioration in exercise tolerance. In 1993, Brenot et al[8] reported 15 cases among a population of 73 patients with PPH. A scientific demonstration of a strong association between the risk of PPH and the use of anorexic drugs (mainly fenfluramine derivatives) was provided by the prospective International Primary Pulmonary Hypertension Study[4] conducted in 35 centers in Europe, including France, Belgium, the Netherlands, and the United Kingdom. In this case-control study, 95 patients with PPH were enrolled and compared with 355 control subjects recruited from the same general practitioner and matched to the patient's sex and age. Among all the different supposed risk factors for PPH, only the odds ratio for anorexigen use was found to be statistically significant; definite use of anorexigens had been reported by 30 of the 95 PPH patients (31.6%) but by only 26 of 355 control subjects (7.3%); this is an odds ratio of 6.3 (95% confidence interval, 3.0 to 13.2); when anorexic drugs were used for a total of >3 months, the odds ratio was 23.1 (95% confidence interval, 6.9 to 77.7). In this study, fenfluramine derivatives and especially dexfenfluramine were the most commonly used drugs, since only two patients and three control subjects reported the use of amphetamine-like anorexic agents alone.

In France, the regulations regarding the prescription of anorexic agents have been changed as early as June 1995 leading to a major restriction of their use. In September 1997, fenfluramine and dexfenfluramine were recalled from global world market.

Fenfluramine Derivatives-Associated PPH: A 12-Year Clinical Experience of a National Referral Center in France

Patients and Methods

From 1986 to September 1997, 62 patients with fenfluramine-associated PPH were evaluated in our center for pulmonary vascular disease. Pulmonary hypertension was defined as a mean resting pulmonary artery pressure >25 mm Hg during right heart catheterization, with a mean pulmonary wedge pressure <12 mm Hg. Secondary causes of PH were excluded. We also excluded patients with PPH and associated portal hypertension and HIV infection. All the fenfluramine-associated PPH patients had a history of intake of fenfluramine derivatives (fenfluramine or dexfenfluramine), alone or in combination with amphetamine-like anorexic agents. If the exposure to fenfluramine derivatives began after the onset of the symptoms related to PPH (mainly dyspnea), patients were considered unexposed to that risk factor and were not included in this study. These 62 patients with fenfluramine-associated PPH were compared with a control group of 125 sex-matched patients with PPH unrelated to the use of fenfluramine derivatives. Patients with portal hypertension and HIV infection were also excluded from this control group. All patients were tested with IV epoprostenol or inhaled nitric oxide to identify responders to acute vasodilator testing. An acute vasodilatory response was defined by a decrease in pulmonary vascular resistance of at least 20% associated with a fall in mean pulmonary arterial pressure of at least 20% of the mean of two or three baseline measurements.

Results

The main clinical characteristics of the two groups of patients with PPH are shown in Table 1. Patients

Table 1—*Clinical Characteristics

	Control PPH (n=125)	Fenfluramine-Associated PPH (n=62)	p Value
Sex, female:male†	30:1	30:1	
Age, yr	40±14	50±12	<0.01§
Body mass index	23±4	28±6	<0.01§
Symptoms, No. (%)			
NYHA functional class			
I or II	34 (27)	18 (29)	
III or IV	91 (73)	44 (71)	
Syncope or near syncope	57 (46)	20 (32)	
Right heart failure	34 (28)	24 (39)	
Duration of symptoms, mo‡	25±35	18±18	
Associated conditions, No. (%)			
Raynaud's phenomenon	29 (23)	15 (24)	
Antinuclear antibody titre >1/80	11 (10)	8 (13)	

*Values are expressed as mean±SD. NYHA=New York Heart Association.

†Control PPH patients were sex matched with fenfluramine-associated PPH patients.

‡Duration of symptoms indicates the time between the onset of symptoms and first hemodynamic evaluation (echocardiography and/or right heart cathterization).

§Statistical analysis used the Student's *t* test. A p value <0.05 was considered as significant.

were mostly women, with a female:male ratio of 30:1 in the two groups. This was in sharp contrast with the 1:1.7 sex ratio reported in the National Institutes of Health Registry[9] and in our cohort.[10] Patients with fenfluramine-associated PPH and control PPH were very similar in terms of New York Heart Association functional class, symptoms, and associated conditions. Fenfluramine-associated PPH patients significantly differed from control PPH patients only with respect of age (50±12 years vs 40±14 years, respectively) and body mass index (28±6 vs 23±4, respectively). Thirty-two percent of PPH patients with fenfluramine use had a body mass index of ≥30 compared with only 9% in the control PPH group.

In the fenfluramine-associated PPH group, 33 patients used dexfenfluramine alone (53%), 7 patients used fenfluramine alone (11%), and 5 patients used both drugs (8%). In 17 cases, the use of fenfluramine derivatives was associated with that of amphetamine-like anorexic agents (diethylpropion hydrochloride [amfepramone], clobenzorex, fenproporex). The duration of fenfluramine use before the onset of symptoms is shown in Figure 1; most of exposed patients used fenfluramine derivatives for at least 3 months (81%). The interval between the onset of drug intake and that of symptoms related to PPH showed marked individual variations, with a mean of 49±68 months, a minimum of 27 days, and a maximum of 23 years. Baseline hemodynamic variables of the two groups at diagnosis are shown in Table 2; the two groups showed similar hemodynamic characteristics of severe PH. The percentage of responders to acute vasodilator testing was significantly higher in the control PPH group than in the fenfluramine-associated PPH group (27% vs 10%, respectively). As a result, the percentage of patients treated with long-term oral vasodilator therapy was higher in the control group (Table 3); however, the percentage of patients treated with long-term epoprostenol infusion was higher in the fenfluramine-associated PPH group.

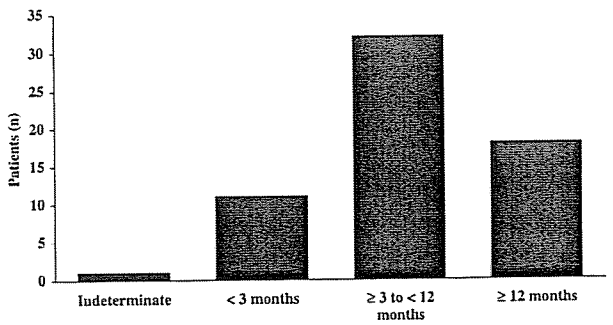

FIGURE 1. Duration of fenfluramine use before onset of symptoms.

Table 2—*Hemodynamic Data at Diagnosis

	Control PPH (n=125)	Fenfluramine-Associated PPH (n=62)	p Value
Right atrial pressure, mm Hg	10±5	12±6	
Mean pulmonary artery pressure, mm Hg	65±5	63±12	
Pulmonary wedge pressure, mm Hg	9±3	10±3	
Cardiac index, L/min/m^2	2.3±0.6	2.2±0.6	
Total pulmonary resistance index, U/m^2	31±12	32±12	
Mixed venous oxygen saturation, %	59±13	56±10	
Acute vasodilator response, No. (%)†	31 (27)	6 (10)	<0.01‡

*Values are expressed as mean±SD.
†Acute vasodilator response was defined by a decrease in total pulmonary vascular resistance of at least 20% associated with a fall in mean pulmonary arterial pressure of at least 20% of the mean of two or three baseline measurements.
‡Statistical analysis used the Student's *t* test. A p value <0.05 was considered as significant.

In the group with fenfluramine-associated PPH, only six patients reported a clinical improvement after discontinuing treatment with the drug. The overall survival rate was similar in the two groups (Fig 2) with a 3-year survival rate of 50%. The annual incidence of fenfluramine-associated PPH in our institution is shown in Figure 3. Annual incidence markedly increased from 1986 to reach a maximum in 1994 and 1995 (10 cases each year). Since the beginning of 1997, the incidence has dropped sharply, with only one case of fenfluramine-associated PPH diagnosed during the first 9 months.

MECHANISMS OF FENFLURAMINE-ASSOCIATED PPH: THE SEROTONIN HYPOTHESIS

The pathogenetic mechanisms of PPH associated with fenfluramine is unknown. However, it appears

Table 3—*Outcome*

	Control PPH (n=125)	Fenfluramine-Associated PPH (n=62)	p Value
Epoprostenol continuous infusion, No. (%)	39 (31)	32 (52)	<0.01*
Oral vasodilator, No. (%)	45 (36)	10 (16)	<0.01*
Transplantation, No. (%)	24 (19)	12 (19)	
Conventional therapy alone, No. (%)	50 (40)	20 (32)	

*Statistical analysis used the Student's *t* test. A p value <0.05 was considered as significant.

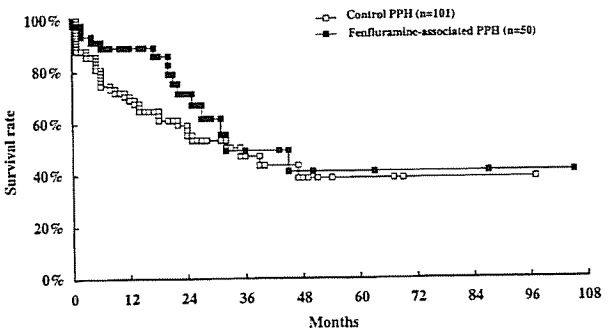

FIGURE 2. Overall survival rates.

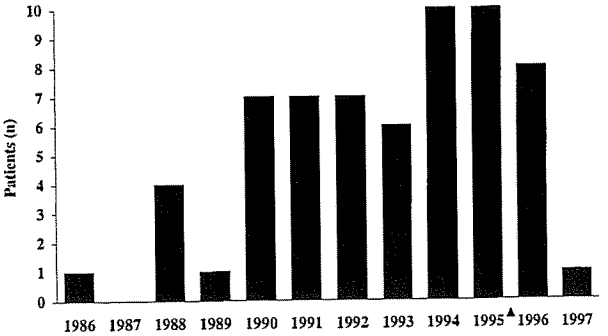

FIGURE 3. Annual incidence of fenfluramine-associated PPH cases at Paris-Sud University.

that alteration of the serotonin (5-hydroxytryptamine [5-HT]) pathway might be a common denominator of fenfluramine- or amphetamine-associated PPH. Serotonin is known to be a powerful pulmonary vasoconstrictor and can induce platelet aggregation.[11] Moreover, recent studies indicate that serotonin is also a potent factor stimulating pulmonary smooth muscle proliferation.[12] Clinical and experimental evidence supports the hypothesis that fenfluramine may contribute to PPH by increasing serotonin availability in blood and/or by interacting with serotonin (5-HT) receptors, thereby promoting pulmonary vascular smooth muscle proliferation, pulmonary arterial vasoconstriction, and local microthrombosis.

Effect of Fenfluramine on Serotonin Availability

Under normal conditions, the lung vascular bed is not exposed to excessive serotonin levels, because of the ability of platelets to store large amounts of serotonin. By interacting with the serotonin transporter, fenfluramine releases serotonin from platelets and inhibits its reuptake into platelet and pulmonary endothelial cells.[13] As a consequence, blood-free serotonin concentration increases with fenfluramine treatment.[14] Evidence indicates that such a defect in platelet serotonin storage is a trigger factor in the development of PPH in susceptible patients. (1) A decrease in platelet serotonin storage with enhanced blood concentration of free serotonin has been reported in sporadic cases of PPH,[15] and in numerous disorders occasionally associated with PPH,[15] including portal hypertension, Raynaud's phenomenon, collagen vascular disease, amphetamine-derived anorexigen exposure such as aminorex and phentermine,[11,16] and platelet storage pool disease.[17] (2) Platelet serotonin storage remains impaired in PPH patients after heart-lung transplantation,[15] whereas it is normal in patients with secondary PH,[18] indicating that this platelet dysfunction is not secondary to the pulmonary vascular disease. (3) The fawn-hooded rat, which has a genetic defect in serotonin platelet storage, develops severe PH upon exposure to modest hypoxia.[19] (4) Fenfluramine in association or not with phentermine has been shown recently to induce valvular heart disease very similar to that observed after exposure to serotonin-like drugs such as ergotamine and methysergide, and with increased serotonin levels associated with carcinoid disease.[16] Interestingly, one third of these patients with valvular heart disease had coexisting PH.[16] All these observations suggest that fenfluramine may trigger PPH by aggravating or inducing an impairment in the platelet serotonin storage.

Effect of Fenfluramine on Serotonin (5-HT) Receptors

The effects of the selective serotonin reuptake inhibitor (SSRI) drugs such as fluoxetine on platelet serotonin uptake are very similar to those of fenfluramine.[20] However, despite a large worldwide utilization, to our knowledge, no case of PPH or valvular heart disease has been reported yet with fluoxetine and the other SSRI drugs. By contrast, with fenfluramine derivatives (and the amphetamine-derived anorexigens) that are 5-HT receptor agonists in the brain, the SSRI drugs do not seem to stimulate 5-HT receptors.[13,20,21] This suggests that the increase in serotonin availability is not the unique mechanism of fenfluramine-associated PPH, and that fenfluramine might interact also with 5-HT receptors located in the pulmonary arterial wall, thereby promoting pulmonary artery smooth muscle proliferation and contraction. The mechanism of smooth muscle cell contraction induced by fenfluramine or serotonin is similar.[22-24] Fenfluramine as well as aminorex and serotonin inhibit potassium currents in the artery smooth muscle cells.[22,23] This inhibition of potassium channel produces smooth muscle cell membrane depolarization that permits the entry of calcium through voltage-gated calcium channels and causes contraction. This inhibition of potassium channel

accounts for the pulmonary vasoconstriction in isolated rat lungs and the potentiation of hypoxic vasoconstriction in dogs observed with fenfluramine and serotonin administration.[22-25] Because inhibition of potassium channel by serotonin is mediated by stimulation of a 5-HT receptor,[23] the possibility exists that fenfluramine also causes pulmonary vasoconstriction through a direct 5-HT receptor stimulation.

Only a minority of patients exposed to fenfluramine derivatives may develop PH, suggesting that a subset of patients may have a genetic susceptibility. Recently, two American groups have simultaneously localized the gene of familial PPH on chromosome 2q.[26,27] Whether the same genetic abnormality is present in the patients with fenfluramine-associated PPH has to be determined. Because the inhibition of the nitric oxide synthase markedly potentiated the vasoconstrictor effect of fenfluramine in isolated rat lung, Weir et al[22] speculated that the patients who develop PPH while taking an anorexic agent could have a preexisting diminished nitric oxide activity.

In conclusion, the use of fenfluramine derivatives is an established risk factor for PPH. The relative risk is low but does increase markedly in some situations such as long-term use. Therefore, a widespread uncontrolled use of these drugs can lead to an epidemic of PPH. The pathophysiologic link between fenfluramine derivative intake and the development of PPH remains unclear. However, accumulating evidence suggests a possible role for serotonin. Unfortunately, the absence of experimental animal models is an important limitation for a better understanding of this condition.

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