

AMINOREX AND PULMONARY HYPERTENSION*

A Review

H. P. GURTNER

Section of Cardiology, Department of Internal Medicine, University of Bern,
Inselspital, Bern, Switzerland

SUMMARY

Gurtner, H. P. (Inselspital, Bern, Switzerland): *Aminorex and pulmonary hypertension. A review.* Cor Vasa 27 (2/3): 160—171, 1985.

There was an epidemic of chronic pulmonary hypertension in Austria, the Federal Republic of Germany and Switzerland, starting in 1967, peaking in 1968/69, and disappearing after 1972. The mechanism leading to pulmonary hypertension was chronic pre-capillary vascular obstruction due to plexogenic pulmonary arteriopathy. There was a close geographic as well as temporal relation of the epidemic to the marketing and intake of the appetite depressing drug aminorex fumarate (Menocil[®]). 10 years after the epidemic, half of the patients have died, usually of right heart failure. Of those surviving, half present a definite regression of the pulmonary vascular obstruction. Average survival after the initial diagnosis was 3.5 years in those patients who died. Their PA pressure (+22 %) and pulmonary arteriolar resistance (+40 %) was higher at the onset of the observation period if compared with the corresponding values of the survivors; also the incidence of right heart failure was significantly higher (84 vs. 58 %). Among the surviving patients, the only difference between those with an improved and those with a worsened haemodynamic situation was the age at the beginning of the weight-reducing treatment, those with a progression being 10 years older. The probability of survival after 10 years is considerably higher in chronic pulmonary hypertension of vascular origin (CPHVO) after aminorex than in "classical" primary pulmonary hypertension (CPHVO of unknown cause) and in CPHVO due to recurrent silent pulmonary thromboembolism. This difference in prognosis is an argument in favour of the identity of chronic pulmonary hypertension developing after the intake of the appetite depressing drug aminorex.

Key words: Pulmonary hypertension — Aminorex

Prof. H. P. Gurtner, Inselspital, CH 3010 Bern, Switzerland

1. History of the epidemic of pulmonary hypertension 1967—1972

Only 8 patients with chronic pulmonary hypertension of vascular origin (CPHVO) were studied in our "Kreislaflabor" during the 12-year period last-

* Dedicated to Professor Widimský on his 60th birthday

ing from 1955 until 1966. In the year 1967, however, there was a sharp rise in the prevalence of CPHVO which nobody had expected. Within 18 months the prevalence of patients with CPHVO (among all adults investigated by means of cardiac catheterization) rose from a previous 0.87 % to a remarkable 13.5 %, i. e. by a factor of 15. Similar observations were made in Basel, Geneva, Lausanne, Zurich and Vienna, and somewhat later and less marked, in a number of cardiology centres in the Federal Republic of Germany.

The random fluctuations of other congenital and acquired diseases of the cardiovascular system, diagnosed from 1958 until 1968 (end of June), were definitely smaller. There was no apparent change either in the composition and size of the patient population from which the disabled individuals with CPHVO had been extracted, or in the diagnostic accuracy of the practitioners referring their patients to the hospital, or finally in the diagnostic procedures employed in the cardiology centre. At this point we felt justified to rule out chance and altered diagnostic capacity as an explanation.

It was well-known from studies on CPHVO carried out prior to 1967 that recurrent silent pulmonary thromboembolism was responsible for the majority of cases. There was no reason, however, to suspect that the known conditions which have a tendency to be complicated by pulmonary thromboembolism should have increased in general. In fact, abdominal and pelvic surgery in the years preceding the onset of symptoms, fractures of the lower extremity, phlebothrombosis, stripping of varicose veins, clinically diagnosed pulmonary embolism, and a recent pregnancy, were rare features in the history of the 23 patients studied since the onset of the epidemic. In addition, only one patient gave a history of the use of oral hormonal contraceptives.

Apart from the observation that the patients studied in 1967 and 1968

- 1) differ from those investigated prior to 1967 with respect to a rare history of pulmonary embolism (13 % vs. 62 %), a number of other differences between the two patient populations could be noted:
- 2) The disease showed a rapid progression, the interval between the onset of complaints and hospital admission lasting only 10 months on the average in the "new patient sample" compared to 4 1/2 years in the "old series".
- 3) Whereas in 4 out of 6 cases of the "old series" pulmonary thromboembolism had been demonstrated on autopsy, lung biopsy in 4 patients of the "new series" (no autopsies were available at the time) failed to give evidence of thromboembolic or inflammatory pulmonary vascular lesions. Rather, histologic examination demonstrated the presence of a marked fibrosis and hyalinosis of the small pulmonary arteries and arterioles.
- 4) Half of the patients studied since 1967 were more or less overweight (>110 % of ideal weight) compared to 12 % in the "old series".
- 5) 18 out of the 23 patients (78 %) of the "new series" tried to get rid of their effective — or imaginary — overweight by means of appetite depressing agents. 17 admitted the intake of the anorectic drug aminorex fumarate (Menocil[®]) prior to the development of their first symptoms, i. e. usually dyspnoea on exertion, less often syncope or chest pain. (One patient had taken amphetamines apparently exclusively many years before the onset of symptoms). The patients

of the "new series" were carefully questioned about a possible exposure to dusts and vapours, sprays and plastic substances, solvents and other chemical compounds including herbicides and insecticides, commonly used in the household, workshop, farm or factory. This search for new ambient factors was negative — except for what has been said with respect to aminorex.

Aminorex (2-amino-5-phenyl-2-oxazoline) resembles adrenaline and ephedrine in its chemical structure and acts as a potent appetite depressing agent in most individuals and as a central stimulant in many of them. The drug which was developed and produced by the McNeill Laboratories, USA, was introduced on the Swiss market in November 1965, and was withdrawn in October 1968, i. e. 5 months after the communication of our findings at the annual cardiology meeting and 4 months after a recommendation sent to the Swiss dealer by the Interkantonale Kontrollstelle für Arzneimittel (IKS).

Let us now look at the development of the epidemic as it took place after the withdrawal of aminorex from the market. Figure 1 summarizes the pertinent data collected in our department up to the middle of 1978. The following conclusions can be drawn from this figure:

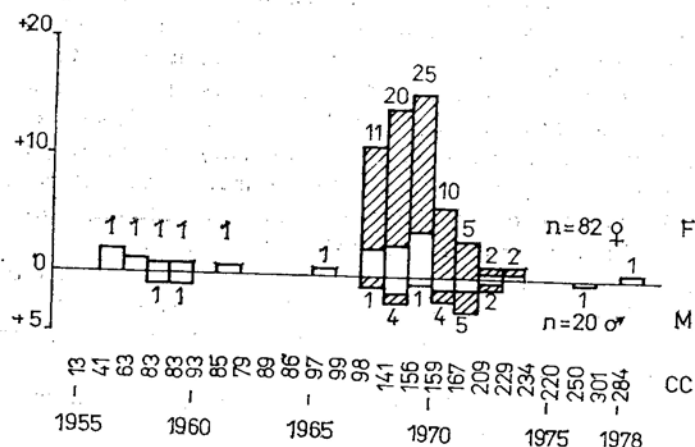


Fig. 1. Prevalence of adult patients with chronic pulmonary hypertension of vascular origin (CPHVO) in percent of individuals studied by cardiac catheterization, Bern, 1955 until of June, 1978. Aminorex was introduced on the Swiss market in November 1965, and its sale was stopped in October 1968 (Ordinate — % patients with CPHVO; above abscissa — women, below abscissa — men. Hatched part of columns — patients with a history of aminorex intake, $n = 71$; empty part of columns — patients without a history of aminorex intake, $n = 23$. Numbers above columns — number of cases of CPHVO in individual years; CC — total number of persons who underwent catheterization in individual years).

- 1) Women are affected about four times more frequently than men.
- 2) The prevalence of CPHVO rises abruptly in 1967, reaching a peak in 1968/1969. It starts falling equally abruptly in 1970. By 1972 it approaches the level which had been present prior to the epidemic.
- 3) 71 out of 92 patients (77 %) studied from 1967 until 1973 (end of June) gave

a positive history of aminorex intake preceding the onset of their symptoms, i. e. half of the males (8/17) and more than 4/5 of the females (63/75).

4) The overall prevalence of CPHVO augmented from 0.87 % in 1955—1966 to 8.74 % during the epidemic in 1967/1973 (end of June), i. e. by a factor of 10.

I do not believe that anybody, when looking at this figure, will deny the existence of a true epidemic of CPHVO. By the same token I suppose that most readers will agree that there is at least a close temporal association between the sale of aminorex and the epidemic. We shall attempt to show that there is more to this association than mere sequence in time.

2. Clinical and functional findings in patients with CPHVO after aminorex

CPHVO was identified in all patients by means of right heart catheterization, blood gas analysis and pulmonary function studies. Thus, left-to-right shunts, alveolar hypoventilation, pulmonary parenchymal disease and pulmonary venous congestion could be ruled out as pathogenetic mechanisms. Without going into the details of additional diagnostic procedures such as pulmonary arteriography and scintigraphy, determination of the diffusing capacity for oxygen, additional lung biopsies and postmortem examinations, let us quickly run through the patients' history, symptoms, signs and functional findings. A comparison is made between patients with a positive history of aminorex intake ($n = 71$) and patients without it ($n = 29$); the χ^2 and the Student's t -test for unpaired samples were used for statistical analysis.

History and symptoms: The two groups do not differ from each other except for the higher incidence of a history of pulmonary embolism in the aminorex-free group. Dyspnoea on exertion is the leading symptom (98 %), followed by angina pectoris (45 %) and syncope (38 %).

The *clinical findings* are, for all practical purposes, identical in the two groups. Central cyanosis (81 %) and signs of right ventricular failure (67 %) occur frequently, relative pulmonary regurgitation is rare. A loud and often palpable second sound in the 2nd left intercostal space is an important clue for the clinical diagnosis (94 %). The same is true for the marked right axis deviation of QRS ($+109 \pm 44^\circ$).

Miscellaneous parameters: As should be expected, the average percentage overweight is higher in the aminorex positive group (+15 vs. -3 %). Arterial O₂ saturation at rest is but slightly diminished (91 ± 4 %), whereas arterial P_{CO₂} is definitely below normal (33 ± 3 mmHg), thus reflecting alveolar hyperventilation. Residual volume (in % of total lung capacity) is practically normal (31 ± 6 %), and so are vital capacity and the forced expiratory volume in the 1st second, thereby explaining the absence of airways obstruction.

Haemodynamics: There is evidence of right ventricular failure, with both the P_{RAm} (10 ± 5 mmHg) and the P_{RVed} (15 ± 7 mmHg) reaching abnormally high levels. Above all there is marked pulmonary hypertension of the vaso-obstructive type (50 ± 12 mmHg), the PA wedge pressure not exceeding its normal range on the average (9 ± 4 mmHg). The cardiac index is reduced by one third

of its normal value (2.2 ± 0.7 l/min.m²). Therefore, pulmonary arteriolar, i. e. precapillary resistance is grossly increased by a factor of more than 15 (960 ± 392 dyn.s.cm⁻⁵).

Thus, identification of the "new" disorder was simple in terms of deranged function, i. e. pathophysiology, the common denominator being chronic precapillary vascular narrowing not due to shunts, hypoventilation or pulmonary parenchymal disease. Its identification with respect to aetiology, however, presented as a major challenge.

3. Identification of the aetiology of CPHVO after aminorex intake

This discussion will centre around the following 4 topics: epidemiology, pharmacology, morphology, and long-term follow-up.

Epidemiology: In a cooperative retrospective study, 23 centres from Austria, West Germany and Switzerland contributed to a collection of a total of 582 cases with CPHVO (Greiser et al., 1973).

Fig. 2 shows the prevalence of patients with CPHVO among individuals studied by cardiac catheterization from 1960 until 1972. Black bars refer to pa-

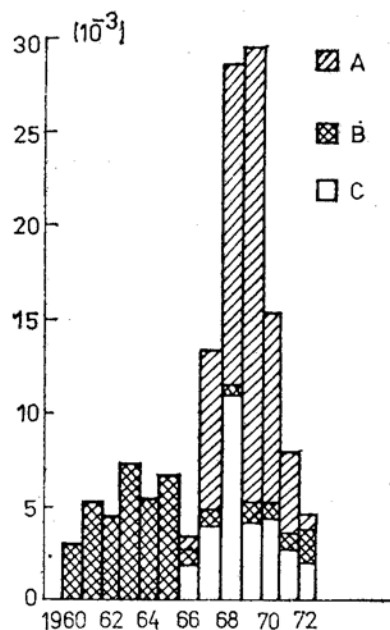


Fig. 2. Prevalence of patients with CPHVO among individuals studied by cardiac catheterization in 23 cardiological centres from Austria, the Federal Republic of Germany and Switzerland 1960–1972. Total number of patients: 582. Adapted from Schüren, 1979, after Greiser et al., 1973. (Vertically — prevalence, 10^{-3} ; horizontally — years; A — patients using anorectic drugs; B — diagnosed as idiopathic pulmonary hypertension (IPH) without further data; C — IPH of unknown origin).

tients who had taken aminorex alone or in combination with other anorectic drugs. Again there is no doubt: A true epidemic of pulmonary hypertension did occur in the 3 West European countries, starting in 1967, culminating in 1968/69, and tapering off in the subsequent years.

Which clues with respect to aetiology can be derived from the epidemiological evidence? First, there is a geographic association. The epidemic is limited to those countries where aminorex has been on sale. In countries without marketing of the drug, such as the United Kingdom, Italy and the USA, the prevalence of CPHVO failed to show a more than random fluctuation from 1965 until 1972.

Second, there is a remarkable temporal correlation. For instance, in Bern the onset of the typical symptoms of pulmonary hypertension used to follow the beginning of the anorectic treatment by an average of 8.6 months (6 to 12 months). In the FRG, a similar phase shift could be demonstrated between the market (wholesale) of aminorex and the relative incidence of CPHVO.

These fairly strong associations should not blind the eye to the following two features: a small, albeit consistent rise in the incidence of patients with CPHVO but with a negative history of aminorex intake during the epidemic, and the occasional use of anorectics other than aminorex.

Pharmacology: In his early experiments with dogs, Yelnosky (1966) found that the drug increased the heart rate and the systemic arterial blood pressure; the effect on the lesser circulation was not studied. After 1968, new and more thorough studies were undertaken. Aminorex was given to open- and closed-chest dogs, rats, monkeys, pigs and calves, either as a single dose, repeatedly, or in the form of a chronic, up to two years' administration. Without going into details, the essence of the results of these painstaking experiments can be summarized as follows:

- 1) Acute and subacute administration of aminorex leads to a marked but transient rise in PA-pressure and pulmonary arteriolar resistance in most of the species tested. This work was done mainly in Vienna by the group of Kraupp (1969).
- 2) It has not been possible, however, to induce chronic pulmonary hypertension or plexogenic pulmonary arteriopathy in any of the animal experiments after chronic administration of the drug.

What is the relevance of these results for the resolution of our problem? Several arguments make us believe that it is minimal, indeed:

- 1) The number of animals used was too small. Since the probability of acquiring pulmonary hypertension after aminorex was minimal, namely around 1 out of 1000 individuals exposed, the number of animals needed would have been extremely high.
- 2) There are marked differences in transport mechanisms and metabolism of drugs between animals and man, among animals of different species, and even among different breeds of the same species.
- 3) In general, whereas "positive" animal experiments may favour a positive aetiological or conditioning correlation between study factor and study disease, "negative" experiments will never have the power of an exclusive proof.

In short, pharmacology and animal experimentation were of little or no help in defining the role of aminorex for the European epidemic of CPHVO. *Morphology:* On the other hand, histologic examination of lung tissue, be it biopsy or/and autopsy, from patients with CPHVO after aminorex, resulted in a rather unexpected finding. It was observed as early as 1968 that the morphologic changes of the pulmonary vasculature in such patients were not at all compatible with the assumption of recurrent thromboembolism.

Two years later and based on more material, our pathologist concluded that the microscopic changes of the muscular pulmonary arteries ($\varnothing$ 100–1000 μ) were identical with those described by Heath and Edwards in 1958 in children with pulmonary hypertension due to large congenital left-to-right shunts. These conclusions were confirmed by Heath (Liverpool), and Wagenvoort (Amsterdam), to whom we had sent some material, and by Widgren (Geneva).

In 1977 Widgren published a detailed report on the morphologic findings in 37 patients who had developed pulmonary hypertension after the intake of aminorex. The autopsy material was provided by 8 Swiss pathology institutes. The clinical and autopsy findings in these patients were as follows: 34 females, 3 males; mean age 50 years; duration of aminorex treatment 271 days; total dose of aminorex 249 tablets (14 mg each tablet); mean PA pressure 52 mmHg; pulmonary arteriolar resistance 1258 dyn.s.cm⁻⁵; heart weight 427 g; thickness of right ventricle 7.7 mm. Right ventricular failure was the cause of death in 26 out of 35 patients. The results of Widgren are best summarized in his own words: "Histologic examination of muscular pulmonary arteries from 100–1000 μ diameter showed lesions entirely comparable to those described by Heath and Edwards in cases of pulmonary hypertension secondary to cardiac malformations. They were in no significant way different from the lesions we observed in cases of (classical) primary or (hyperkinetic) secondary pulmonary hypertension." These lesions were given the name "plexogenic pulmonary arteriopathy" during a WHO-meeting in Geneva in 1973/75 by Heath and Wagenvoort. They include:

- medial hypertrophy of the muscular pulmonary arterioles;
- onion-skin intimal proliferation and necrotizing arteritis of muscular pulmonary arteries;
- organization of the fibrin liberated during fibrinoid necrosis into dilated thin-walled branches of the parent arteries;
- formation of a plexiform pattern of fibrillary cells, the so-called plexiform lesion.

Widgren put forward the following hypothesis with respect to the possible action of aminorex (1977): "A direct or indirect action of aminorex... causes an increase in the tone of the muscular arteries, which is followed by vasospasm. This induces an endothelial lesion on which fibrinoid material is deposited, producing intimal proliferation. This proliferation in which myointimal cells, then smooth muscle cells, are abundant, contributes to the aggravation of the pulmonary hypertensive disease..."

The impact of the morphologic findings, however, can be judged adequately in the context of the long-term course of the disease.

Long-term course of CPHVO after aminorex (Bern 1967–1979/80)

What has been said so far when considering the differential diagnosis of the aetiology of the epidemic of pulmonary hypertension, is summarized in Fi-

figure 3 which shows the various mechanisms leading to pulmonary hypertension together with the multiple causes underlying each mechanism.

The three conditions of chronic pulmonary hypertension which the clinician is unable to differentiate further with his clinical tools and which are the

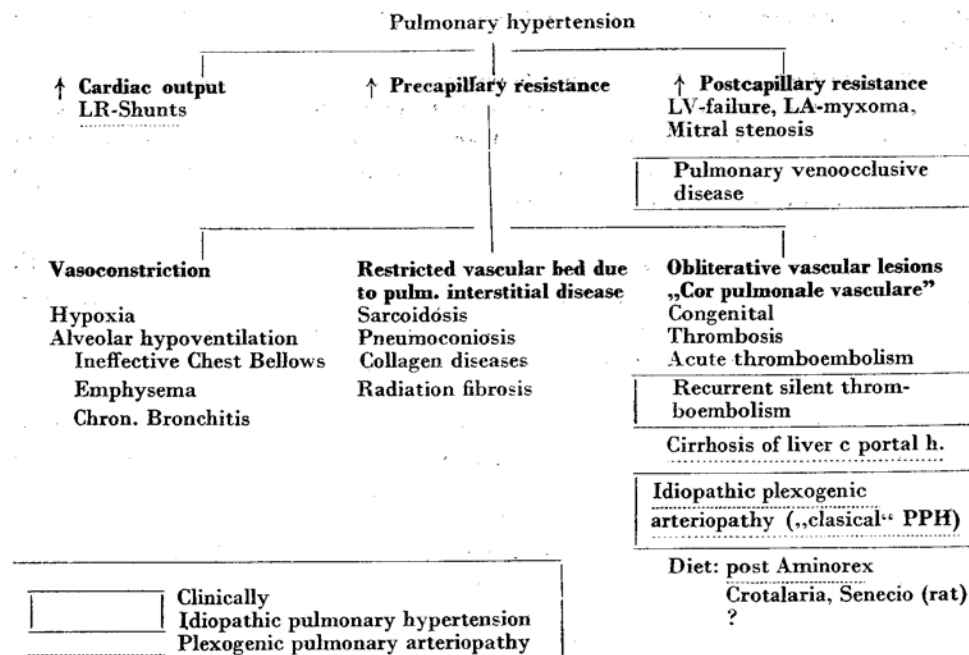


Fig. 3. Aetiology and pathogenesis of pulmonary hypertension (LV — left ventricle, LA — left atrium, c portal h. — with portal hypertension; PPH — primary pulmonary hypertension).

referred to as “clinically idiopathic pulmonary hypertension” include pulmonary veno-occlusive disease, recurrent silent thromboembolism, and classical primary pulmonary hypertension.

Veno-occlusive disease, an extremely rare condition, was ruled out on the basis of the morphological findings. So was, together with the results of angiography, recurrent silent thromboembolism. In addition, the two conditions can be cancelled from our list due to their inexorably poor prognosis. Looking at the differential diagnosis from this angle, we are therefore left with the task of distinguishing between “classical primary pulmonary hypertension” and pulmonary hypertension after aminorex.

Looking at the problem from the point of view of morphology, plexogenic pulmonary arteriopathy is — apart from post-aminorex pulmonary hypertension — characteristic of, but not specific for, left-to-right shunts, cirrhosis of the liver with portal hypertension, and — again — “classical primary pulmonary hypertension”. There were no shunts in the patients studied, nor was there cir-

rhosis of the liver. Again, therefore, the only competitor in differential diagnosis is "classical primary pulmonary hypertension".

If a patient with "classical primary pulmonary hypertension" is compared with a patient suffering from pulmonary hypertension which developed after the intake of aminorex, there is, at first sight, no way to distinguish between the two since the clinical, functional, angiographic and histologic findings are identical.

What turned out to be different, however, is the prognosis. Let us, therefore, look at a follow-up study which was carried out in the years 1979/80. Between 1967 and 1973 72 patients with CPHVO after aminorex intake were studied in Bern [(64 f, 8 m; mean age 49 years; average consumption of aminorex 150 tablets of 14 mg (10 to more than 600 tablets); mean pulmonary artery pressure 50 mmHg (26 to 76)].

By October 1979, 34 of the 72 patients had died at an average age of 53 years and after an average survival of 3.5 years (3 months to 10.5 years) following the correct initial diagnosis. Out of the 38 survivors 20 representative patients (19 f, 1 m) were followed-up and studied a second time, on the average 10.5 years (7.7 to 12.7 years) after the original investigation. In 12/20 patients there was a marked improvement of both the clinical and the haemodynamic conditions with a rise of the cardiac index (+50 %) and a fall of the mean pulmonary artery pressure (-50 %) and pulmonary arteriolar resistance (-67 %). In the remaining 8/20 patients, however, there was a deterioration of the haemodynamics (mean PA pressure + 23 %, pulmonary arteriolar resistance + 44 %), even though, clinically, half of this group felt improved. This observation is important since it demonstrates that a follow-up study is subject to error if it is based merely on an evaluation of symptoms.

The only difference between the two groups relates to the fact that the improved patients had been 10 years younger when starting their weight reducing treatment than those with a progression of their pulmonary hypertension. Their body lean mass, lung function and pulmonary haemodynamics as well as the total amount of aminorex ingested, however, had been equal.

A comparison between surviving and non-surviving patients with a positive history of aminorex intake is presented in Table I. Again the two groups are comparable with respect to age, weight and risk factors for pulmonary thromboembolism at the time of the initial investigation. However, mean PA pressure (+22 %) and pulmonary arteriolar resistance (+40 %) were higher in the non-survivors, and so was the incidence of right heart failure (84 % vs. 58 %).

For the group of aminorex consumers as a whole a correlation between the total amount of the anorexigen ingested and mortality could not be demonstrated. Only if two extreme groups are compared, such a correlation could be suspected (subgroup with an intake of less than 40 tablets: mortality 22 %; subgroup with an intake of more than 400 tablets: mortality 80 %).

Finally we were interested in the mortality and survival of patients with CPHVO if patients with a positive history of aminorex intake are

Table I. Comparison of the characteristics of surviving and non-surviving patients with a positive history of aminorex intake, from the total number of 72 patients with chronic pulmonary hypertension of vascular origin developing after consumption of the appetite depressing drug (Bern 1967—1978).*

	Dead	Alive
N	34	38
Mean survival (years) after diagnosis	3.5	
1st investigation: age, body mass, risk factors of pulmonary thromboembolism	idem	
Mean PA pressure (mmHg)	55 (+22%)	45
PA resistance (dyn. s. cm ⁻⁵)	1100 (+40%)	785
Right heart failure (incidence)	84%	58%
Mortality and total amount of aminorex consumed:		
— whole group (n=72): no correlation		
— subgroups: less than 40 tabl. (n=9): 22% mortality		
above 400 tabl. (n=5): 80% mortality		

compared with patients free of anorexigens. Table II summarizes the pertinent data. The statistics relate to all patients with CPHVO studied in Bern from 1955 until 1978 (86 f, 22 m). In the 36 patients without appetite depressing treatment the mechanism of CPHVO was considered to be in most instances recurrent silent pulmonary thromboembolism or classical primary pulmonary hypertension, as judged on the basis of the clinical course and the haemodynamic findings; pulmonary arteriography and an autopsy were available in a number of cases.

Whereas age, the severity of pulmonary hypertension and the incidence of risk factors for pulmonary thromboembolism are comparable in the two

Table II. Mortality and survival in patients with chronic pulmonary hypertension of vascular origin with a positive and a negative history of aminorex intake (Bern 1955—1978).

	Aminorex	
	positive	negative
n	72	36
Median survival (years) after diagnosis (catheterization)	12	4.5
Probability of survival after 10 yrs.	53%	34%
1st investigation: age	idem	
mean PA pressure (mmHg)	50	52
Duration of symptoms prior to cardiac catheterization (months)	14	40
Incidence of risk factors of pulmonary embolism	idem	
Long-term anticoagulation treatment	87%	67%
— subgroup with long-term anticoagulation and cardiac catheterization 10 or more yrs. ago: survival for 10 yrs.	25/45	1/13

groups, median survival after diagnosis is almost 3 times longer and the probability of survival after 10 years considerably higher in the aminorex-positive groups, median survival after diagnosis is almost 3 times longer and the probability in the aminorex-positive group. For, if two subgroups are compared whose initial diagnosis lay back at least 10 years and who had been practically on continuous anticoagulation, the difference in prognosis favouring the anorexigen-positive group is even more conspicuous.

Our finding of a relatively benign long-term course of aminorex-associated CPHVO and of a considerable incidence of a regression of its severity is therefore in contrast to the gloomy outlook in classical primary and in chronic thromboembolic pulmonary hypertension. We feel that this difference in prognosis between aminorex-related and classical primary pulmonary hypertension supports the hypothesis according to which plexogenic pulmonary arteriopathy, their common histopathological denominator, is a non-specific way of reaction of the small muscular pulmonary arteries in the presence of different and mostly unknown (one exception: aminorex) noxious factors. Depending on the type of such a factor, the duration of its activity, possibly its dosage and, maybe most important, the patient's individual reactivity, the severity and the extent of the lesions arising in the pulmonary vasculature, the degree of their reversibility, and thereby the prognosis may vary.

A selection of the bibliography used for this paper can be obtained from the author.

R É S U M É : En 1967 commença en Autriche, en République fédérale d'Allemagne et en Suisse une épidémie d'hypertension pulmonaire chronique (HPC) qui culmina en 1968—1969 et disparut après 1972. Le mécanisme de la genèse de HPC consistait dans l'obstruction vasculaire provoquée par l'artériopathie pulmonaire plexogène. L'épidémie était en connexion temporelle et géographique étroite avec la vente et l'utilisation d'un médicament diminuant l'appétit, le fumarate d'aminorex (Menocil R). 10 ans après l'épidémie, 50 p. c. des malades étaient morts, le plus souvent par suite d'insuffisance du coeur droit. Chez la moitié de ceux qui ont survécu, on peut observer que l'obstruction vasculaire pulmonaire recule. Chez ceux qui sont morts, la durée de survie était en moyenne 3,5 ans après le premier diagnostic. Chez les personnes qui moururent, la pression artérielle pulmonaire et la résistance artérielle pulmonaire au début de l'observation étaient plus élevées (22 p. c. et 40 p. c.) que chez les survivants; également l'incidence de l'insuffisance du coeur droit était significativement plus élevée que chez les survivants (84 p. c. vs 58 p. c.). L'unique différence entre les malades ayant survécu, dont les indices hémodynamiques vont s'améliorant, et ceux, chez lesquels les perturbations hémodynamiques progressent, consistait dans l'âge qu'ils avaient au début du traitement par l'aminorex: les malades avec progression avaient dix ans de plus. La probabilité de survie après 10 ans est considérablement plus élevée chez les malades avec HPC d'origine vasculaire (HPCOV), provoquée par l'aminorex que chez les malades avec HPCOV d'origine inconnue (HP primaire "classique") et chez les malades avec HPCOV provoquée par des thromboembolies pulmonaires occultes répétées. Cette différence dans le pronostic est un des critères confirmant l'identité de HCP provoquée par l'aminorex.

ZUSAMMENFASSUNG: Im Jahre 1967 kam es in Österreich, der Bundes-

republik Deutschland und der Schweiz zu einer Epidemie der chronischen Pulmonalhypertonie (CPH), die in den Jahren 1968—1969 ihren Gipfel erreichte und nach 1972 verschwand. Der Entstehungsmechanismus beruhte auf einer präkapillaren Gefäßobstruktion, die durch eine plexogene Pulmonalarteriopathie hervorgerufen wurde. Die Epidemie hing zeitlich und geographisch mit dem Verlauf und der Einnahme des appetitbremsenden Medikaments Aminorex Fumarat (Menocil®) zusammen. 10 Jahre nach der Epidemie war die Hälfte der Betroffenen gestorben, meistens an rechtsseitiger Herzinsuffizienz. Bei den Überlebenden war ein Rückgang der pulmonalen Gefäßobstruktion bemerkbar. Die durchschnittliche Überlebenszeit betrug bei den verstorbenen Patienten 3,5 Jahre. Bei den Verstorbenen war der pulmonale Arteriendruck und die pulmonale arterielläre Resistenz am Anfang der Beobachtung höher (+22 % bzw. 40 %) als bei den Überlebenden; auch die Inzidenz der rechtsventrikulären Insuffizienz war bei ihnen signifikant höher (84 % vs. 58 %). Der einzige Unterschied zwischen den überlebenden Patienten mit den verbesserten hämodynamischen Indikatoren und der Kranken mit progredienten Störungen betraf das Alter am Anfang der Aminorexeinnahme: die Kranken mit Progression waren 10 Jahre älter. Die Überlebenschance nach 10 Jahren ist bei den Kranken mit CPH vaskulären Ursprungs (CPHVU) nach Aminorexeinnahme wesentlich höher als bei den Kranken mit CPHVU, die durch wiederholte Pulmonalthromboembolien hervorgerufen wurde. Dieser Unterschied in der Prognose stellt ein Kriterium dar, das die Identität der durch Aminorex hervorgerufenen CPH bestätigt.