

# mykosen

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## Incidence Rate of Pulmonary Aspergillosis in the High Tatra Mountains Sanatoria for Tuberculosis and Respiratory Diseases of Adults

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The original idea that pulmonary aspergillosis is a primary disease caused by the bronchiectatic action of *Aspergillus* (1) has been replaced in the era of antibiotics by the view that pathogenetically the disease is a secondary phenomenon (2, 3). According to this viewpoint, pulmonary aspergillosis develops as a result of nidation of the ubiquitous *Aspergillus* in sites anatomically damaged by previous inflammations, or in organisms whose immunobiological resistance has been weakened by an affection of RES or the longtime administration of corticosteroids. In recent years reports have appeared which again admit of the primary development of some cases, in agreement with MONOD's original concept. These authors draw attention in discussing the pathogenesis of pulmonary aspergillosis, to the role of enhanced exposure to organic dust rich in *Aspergillus* spores (4, 5).

We have ourselves been seeking an answer to these open questions in recent years. Accordingly, a selected group of patients was investigated for the frequency of aspergillosis in relation to their anamnesis with particular reference to their professional exposure to organic dust and experience of pulmonary tuberculosis. We also concentrated on the relation to sex and average age. Within the framework of the total incidence of aspergillosis, we were also interested in the frequency of the individual *Aspergillus* species and their pathogenic importance in our country. We furthermore studied the effect of administration of broad-spectrum antibiotics and corticosteroids on the development and progress of pulmonary aspergillosis. Patients with a history of tuberculosis also interested us in terms of how soon after „debaecillization“ X-ray and clinical manifestations of aspergillosis became apparent. Finally, we observed the frequency of haemoptysis, and in this connection also explored the question whether and to what extent the intensity of *Aspergillus* growth on Sabouraud's medium and of the agar-gel precipitation reaction could serve as indices of the activity of the pathogenic process clinically manifested by haemoptysis.

### Material and Methods

The object of our study were 362 patients from five sanatoria in the High Tatra Mountains area for adults suffering from tuberculosis and respiratory diseases. These patients were selected on the basis that their sera had been submitted to the laboratory of the Sanatorium at Vyšné Hágy in 1967 and 1968 to be tested for antiaspergillus precipitin, their donors being suspected of aspergillosis accompanying chronic pneumopathy. These clinical suspicions were mostly based on the X-ray pictures of the patients' lungs showing chronic cavities of specific and nonspecific origin and in some cases also on other signs, e. g. increased expectoration without any demonstrable bacterial flora in the sputum or haemoptysis without detectable *Mycobacterium tuberculosis*.

Diagnosis of aspergillosis was primarily based on a positive *Aspergillus* precipitin reaction in the serum. Precipitins were detected by the method of double-diffusion precipitation in agar gel according to OUCHTERLONY (6). A patient's serum was placed in the central well in a Petri dish and tested against antigens of five *Aspergillus* species (*fumigatus*, *niger*, *nidulans*, *restrictus* and *flavus*). Each serum specimen was divided into two aliquots and tested in parallel at the Laboratory of the Sanatorium at Vyšné Hágy and the Laboratory for Medical Mycology, Hygiene

Medical Faculty, Charles University, Prague, where this method was originally introduced. Only agreeing results were evaluated. Using the same procedure, we obtained quite a good correspondence of results. Another advantage of this parallel testing was that, in contrast to other authors, we could take the weaker precipitation reactions into consideration as well.

Cultivation of aspergilli was performed on Sabouraud's glucose agar at 22° C and 37° C.

In agreement with the literature (2, 7, 8, 9), we assumed that enhanced exposure to organic dust is associated with the following professions: agriculture, textile factories, mining; we also included one painter and varnisher employed in a cellulose factory into the "exposed" group.

Out of the total of 362 patients (Table 1), 282 were males (78%) and 80 females (22%). Distribution according to the various grouping criteria employed was fairly even within both sexes. There was a history of tuberculosis in 138 (48.9%) males and 37 (46.2%) females. Enhanced exposure to organic dust was assumed on professional grounds in 75 (26.6%) males and 23 (28.8%) females. The mean age of all the patients was 51 years. Males with a history of tuberculosis were on the average four years younger and females as much as twelve years younger than patients of the respective sexes without such a history. There were extreme differences in the female group, where in the subgroup of those exposed to organic dust the mean ages of those with and without tuberculosis in their anamnesis were 39 and 59 years, respectively.

Table 1

Patients, total	362 (51)				100%			
Sex	Males 282 (52) 78%				Females 80 (45) 22%			
Myco tb in anamnesis	+		-		+		-	
	138 (50) 38%	144 (54) 40%	37 (41) 10%	43 (53) 12%				
Professional exposure to organic dust	E	N	E	N	E	N	E	N
	36 (53) 10%	102 (49) 28%	39 (57) 11%	105 (51) 29%	10 (39) 3%	27 (44) 7%	13 (59) 4%	30 (51) 8%

Explanations:

- Brackets = average age
- + Myco tb = the organism was proved in anamnesis
- Myco tb = the organism was not proved in anamnesis
- E = professional exposure to organic dust
- N = no professional exposure to organic dust

Results

Table 2 shows the frequency of aspergillosis findings with respect to history of tuberculosis and professional exposure to organic dust. *Aspergillus* precipitins were detected

Table 2

Region	Patients, total				Tb in anamnesis				Tb not in anamnesis			
	E		N		E		N		E		N	
	A/T	%	A/T	%	A/T	%	A/T	%	A/T	%	A/T	%
East-Slovakia	16/50	32	5/103	5	13/25	—	5/49	—	3/25	—	—/54	—
Central-Slovakia	12/39	31	5/119	4	6/16	—	5/57	—	6/23	—	—/62	—
West-Slovakia	1/9	11	4/42	10	—/5	—	3/23	—	1/4	—	1/19	—
Slovakian Socialist Republik	29 (53) /98 (55)	29	14 (41) /264 (50)	5	19 (48) /46 (50)	42	13 (43) /129 (48)	10	10 (61) /52 (59)	19	1 (15) /135 (51)	1
	43 / 362 (49) (50)		12 %		32 / 175 (47) (48)		18 %		11 / 187 (57) (54)		6 %	

## Explanations:

- E = group exposed to organic dust  
 N = group not exposed to organic dust  
 A = absolute number of aspergillosis cases  
 T = total number of patients in respective groups  
 Brackets = average age of patients

in the sera of 43 patients, i. e. 12 % of the total. The frequency was higher among post-tuberculosis patients than the other group and among those professionally exposed to organic dust than in the nonexposed group. Out of the total of 29 aspergillosis patients who had been exposed to organic dust, 22 were employed in agriculture, four in mines, two in the textile industry and one was a painter and varnisher in a cellulose factory. The topographic distribution of aspergillosis according to district was even in the East Slovakia and Central Slovakia Regions. The West Slovakia Region was not evaluated in this respect, because the number of patients from that region hospitalized in these sanatoria was small.

Table 3 shows aspergillosis distribution by sex. The frequency was twice as high in women as in men. The proportion of aspergillosis between the two basic groups (history of tuberculosis and no tuberculosis) was the same in both sexes. With a single exception, a 15-year-old boy with inborn cystic bronchiectasis, all the aspergillosis cases without previous tuberculosis had been exposed to organic dust. Again with the exception of this adolescent, there were no major differences in age among the patients in the various subgroups.

Anatomic lesions in the lungs, which in some patients amounted to advanced fibrosis with cavities, were matched by functional pulmonary damage that was objectified by testing vital capacity (VC) and one-second vital capacity (FEV<sub>1</sub> sec). A ventilation disorder of the obstructional or mixed type was detected in 80 % of the aspergillosis

Table 3

Aspergillus patients, total	A/T	43 / 362 (49) (51)						12 %
Sex	Males				Females			
	A/T	28 / 282 (50) (52)		15 / 80 (47) (45)				10 % 19 %
Mycob in anamnesis	+		-		+		-	
	A/T	21 / 138 (50) (50) 15 %	7 / 144 (54) (54) 5 %	11 / 37 (42) (41) 30 %	4 / 43 (61) (53) 9 %			
Professional exposure to organic dust	E		N		E		N	
	A/T		A/T		A/T		A/T	
	15 (51) /36 (53) 42 %	6 (42) /102 (49) 6 %	6 (61) /39 (57) 15 %	1 (15) /105 (51) 1 %	4 (38) /10 (38) 40 %	7 (44) /27 (44) 26 %	4 (61) /13 (59) 31 %	— (30) /51 (51) — %
	42 %		6 %		15 %		1 %	

## Explanations:

- E = professional exposure to organic dust  
 N = no professional exposure to organic dust  
 A = aspergillus patients  
 T = total number of patients in respective groups  
 Brackets = average age of patients

Table 4

	Aspergilloma		other forms of aspergillosis	Total	
	typical	atypical		absol. No	%
Aspergillus fumigatus	30	7	—	37	86 %
Aspergillus flavus	—	1	3	4	9 %
Aspergillus niger	—	—	2	2	5 %
Total	30	8	5	43	
	88 %		12 %	100 %	

patients. Advanced changes (VC below 50 % of normal values and FEV/1 sec below 50 % VC) were ascertained among 32 % of posttuberculosis patients and 43 % of patients without a history of tuberculosis.

By far the most frequent *Aspergillus* species isolated in our set was *Asp. fumigatus*, which was present in 86 % of cases, invariably in the form of typical or less typical aspergillomas (Table 4). Of the other species, *Asp. flavus* was detected four times and *Asp. niger* twice. These species did not manifest themselves morphologically, except one instance involving *Asp. flavus*; this organism was probably derived from an atypical inclusion in a tuberculous cavity in a female diabetic.

Table 5 presents the frequency data for haemoptysis associated with aspergillosis, in relation to medical history and aspergillosis morphology. The overall frequency of haemoptysis (symbol He in Table 5) was 21/43, i. e. haemoptysis was present in 49 % of the aspergillosis cases. Haemoptysis was more frequent in the cases with (53 %) than in those without (36 %) a history of tuberculosis. Haemoptysis was associated with aspergillomas, which, as already mentioned, were almost exclusively due to *Asp. fumigatus*. Haemoptysis was not encountered in cases elicited by other *Aspergillus* species. In 15 patients, i. e. 35 % of all cases, haemoptysis appeared as the initial sign and was conducive to the detection of the disease (bracketed in Table 5).

Table 5

	Aspergilloma				Other forms of aspergillosis		Total	
	typical		atypical					
	Hae/T	%	Hae/T	%	Hae/T	%	Hae/T	%
TB	14 (11) / 24	58 %	3 (1) / 5	60 %	— / 3	—	17 (12) / 32	53 %
No TB	3 (3) / 6	50 %	1 / 3	33 %	— / 2	—	4 (3) / 11	36 %
Total	17 (14) / 30	57 %	4 (1) / 8	50 %	— / 5	—	21 (15) / 43	49 %

## Explanations:

- Hae = number of persons with haemoptysis in anamnesis  
 bracket = number of persons with haemoptysis at detection of disease  
 T = total number of patients in respective groups  
 TB = tb in anamnesis  
 No TB = no specific anamnesis

The frequency of haemoptysis (Table 6) was in our material directly proportionate to both the intensity of *Aspergillus* growth on Sabouraud's medium and the intensity on agar-gel precipitation reactions. If haemoptysis is a manifestation of the activity of aspergillosis, this activity was reflected by our laboratory indices.

More than half of the posttuberculosis cases (Table 7) developed within the first three years of „debacillization“. It should also be borne in mind that many of the cases which were detected later after debacillization could have existed asymptotically already before. Interesting was a group of six patients where *Aspergillus* and *M. tuberculosis* grew simultaneously on the respective cultivation media. Most of the patients

Table 6

Aspergillus growth on Sabouraud's medium	Precipitin bands		Precipit. reaction total	
	1	2 or more		
	Hae/T	Hae/T	Hae/T	%
none	1/7	3/6	4/13	31 %
medium	1/7	7/9	8/16	50 %
heavy	4/5	5/9	9/14	64 %
Total	6/19 32 %	15/24 63 %	21/43	49 %

## Explanations:

Growth intensity: medium = growth in more than 1 culture on at least 1 of 3 consecutive media  
 heavy = grown in 3 consecutive cultures or heavy growth on 1 medium

Table 7

Interval after debacillization	Aspergillomas		Other forms of aspergillosis	Total	
	typical	atypical			
None — aspergilloma contemp. with Myco. tb.	4	—	2	6	} 66 %
1 year	3	2	—	5	
2 years	3	1	—	4	
3 years	5	1	—	6	
4 or more years	9	1	1	11	34 %
Total	24	5	3	32	100 %

alike with and without a history of tuberculosis had received antibiotics and some of them also corticoids for an unequal period of time prior to the detection of aspergillosis. However, a direct relationship between this therapy and the development of aspergillosis could not be demonstrated, although in some cases aspergillosis followed very closely upon the administration of these drugs. We had the impression that in five patients exhibiting aspergillomas in whom we could observe the origin and development of the process during treatment in the sanatorium, antibiotics and corticosteroids stimulated the growth of *Aspergillus* and were thus conducive to the enlargement of aspergilloma that was atypically or latently present in the lungs already prior to their administration. We

inferred the presence of *Aspergillus* already in anamnesis from previous documentation and in some cases from the presence of haemoptysis in anamnesis.

### Statistical Evaluation

In the group of 362 patients, 43 cases of aspergillosis were demonstrated. Sex-specific frequency was the first point analyzed. The frequency of the disease was statistically significantly lower in males than females, the respective rates being 9.9 % (28 out of 282 cases) and 18.8 % (15 out of 80 cases). This difference was examined by the  $\chi^2$  test.  $\chi^2 = 4.64$ , i. e.  $P < 0.05$ . The frequency of this disease in females is accordingly almost twice as high as in males (the difference being significant at a 5 % level).

We next analyzed the frequency of the disease in respect of two other features, viz. "accompanying tuberculosis" (TB) and "exposure to organic dust" (OD):

Group	TB	OD	Males	Females
1.	+	+	15/36 = 41.7 %	4/10 = 40.0 %
2.	+	—	6/102 = 5.9 %	7/27 = 25.9 %
3.	—	+	6/39 = 15.4 %	4/13 = 30.8 %
4.	—	—	1/105 = 0.95 %	0/30 = 0 %

A significant difference in sex-specific frequency of the disease remains only in group 2. Accordingly, this group is responsible for most of the difference in the sex-specific incidence of aspergillosis ( $\chi^2 = 7.50$ , i. e.  $P < 0.01$ ).

In view of the very low frequency of the disease in group 4, we could analyse the other aspects regardless of sex.

Frequency was higher in the "OD" group (29/98 = 29.6 %) than in the nonexposed group (12/264 = 5.3 %) ( $P < 0.01$ ). However, the frequency of the disease was twice as high in exposed persons with a history of tuberculosis (19/46 = 41.3 %) as in exposed persons without tuberculosis in their anamnesis (10/52 = 19.2 %) ( $\chi^2 = 5.73$ ,  $P < 0.025$ ).

### Discussion

Although a detailed comparison of the frequency of aspergillosis in our material with that reported in other sets is impossible because of different criteria used in selecting the basic populations, we can nevertheless say on the basis of our experience that aspergillosis is not rarer in Czechoslovakia than the other parts of Europe that lie at the same latitude and have similar climatic conditions.

An 18 % incidence of aspergillosis among patients with residual posttuberculosis pulmonary lesions approximates to the data of the Research Committee of the British Tuberculosis Association reported in 1968 (10), where the criteria for selecting patients into the basic population were stricter than ours.

In our group of aspergillosis patients, advanced anatomic and functional changes in the lungs were searched for both in those with and those without a history of tuberculosis.

Aspergillosis was clearly a secondary disease in posttuberculosis patients, whereas in patients without a history of tuberculosis this question so far remains unresolved, since it was not clear whether the pulmonary lesions were primarily elicited by aspergillosis or whether the pulmonary tissue had been altered by some nonspecific previous inflammations and had thus become accessible to *Aspergillus* nidation. However, the influence of enhanced exposure to organic dust on the frequency of pulmonary aspergillosis cannot be neglected in either of the groups, as the statistical evaluation indicates. This factor had a decisive influence on the development of aspergillosis in patients without a history of tuberculosis in our set, where, with a single exception, all patients had enhanced professional exposure to organic dust in their anamnesis.



The higher average age in both sexes in the group of persons without a history of tuberculosis could suggest that the anatomic changes which are decisive for *Aspergillus* nidation in the lungs develop later in this group than in tuberculosis patients. In tuberculosis it is not age but the extent of the original finding and mode of treatment with antitubercotics that are decisive for the development of residual pulmonary lesions, whereas in nonspecific pulmonary diseases similar lesions apparently only develop in later age and their development is possibly supported by the effect of long-term exposure to organic dust.

In accordance with the literature, we demonstrated *Aspergillus fumigatus* in the great majority of cases by cultivation and serological methods; this organism most often grows in the form of intracavitary aspergillomas and by the effect of its metabolites on the cavity wall it elicits pathological lesions that lead to haemoptysis. Aspergillosis cases due to other species of *Aspergillus* gave weak precipitation reactions, yielded isolated *Aspergillus* growth on Sabouraud's medium and did not exhibit haemoptysis. Our material displayed a relatively close correspondence between the activity of the process and haemoptysis on the one hand and the intensity of *Aspergillus* growth on Sabouraud's medium and of agar-gel precipitation reaction on the other hand.

In contrast to British authors (10), we observed nidation of *Aspergillus* in posttuberculosis lesions rather sooner, in most cases within three years of "debaecillization". In six cases we observed *Aspergillus* growth on Sabouraud's medium simultaneously with the growth of *M. tuberculosis* on Löwenstein's medium. These instances are interesting from the point of view of the antagonism and symbiosis of these two pathogenic organisms.

## Summary

In 1967 and 1968, we examined for the presence of antiaspergillus precipitins the sera of 362 patients suspected of pulmonary aspergillosis who were hospitalized in five sanatoria for tuberculosis and respiratory diseases of adults in the High Tatra Mountains area. All the tests were performed in parallel in two serological laboratories. Precipitins were demonstrated in 43 patients, i. e. 12% of the group under study. The respective rates among patients with and without a previous history of tuberculosis were 32 out of 175 (18%) and 11 out of 187 (6%). Rather extensive anatomic changes in the lungs amounting to fibrosis with cavities were probably a prerequisite for the nidation of *Aspergillus* in both of these basic groups, but especially among the posttuberculosis patients.

Professional exposure to organic dust was a factor which could not be neglected in either of these basic groups; in both of them the frequency of the disease was statistically significantly higher among patients who had had this exposure. The dependence on professional exposure was especially marked in the group of nontuberculous patients, where 10 out of 11 aspergillosis patients had professional exposure in their anamnesis. Susceptibility to aspergillosis was twice as high in females as in males in both of the basic groups. Patients with a history of tuberculosis suffered from aspergillosis at younger age than patients with nonspecific diseases.

*Aspergillus fumigatus* was demonstrated in 37 patients, *Asp. flavus* in four and *Asp. niger* in two. Only *Asp. fumigatus* proved to be clinically offensive, producing typical and atypical aspergillomas and being the cause of haemoptysis, which developed in half the cases. The intensity of *Aspergillus* growth on Sabouraud's medium and the intensity of agar-gel precipitation reactions were good indicators of the activity of the process. Parallel testing of sera in two laboratories permitted us, where corresponding results were obtained, to take into consideration also the weaker positive reactions.

In the posttuberculosis cases, pulmonary aspergillosis usually developed within three years of the "debaecillization". In five patients in whom we had the possibility to observe the development of aspergillomas in the course of hospitalization, we witnessed the sup-

porting effect of antibiotics and corticosteroids on the growth and development of aspergillomas. In respect of domicile, the cases were distributed evenly throughout the territory of the Slovakian Republic, but the West Slovakia Region was represented by only a small number of instances in our material.

### Závěry

U 362 nemocných, hospitalizovaných v pěti léčebnách pro tuberkulosu a respirační nemoci dospělých v oblasti Vysokých Tater, jsme v letech 1967 a 1968 provedli vyšetření na přítomnost antiaspergilových precipitinů v seru pro podezření na plicní aspergilosu. Všechna vyšetření byla provedena paralelně na dvou serologických pracovištích. Precipitiny jsme dokázali u 43 nemocných, t. j. u 12 % všech vyšetřovaných. Z toho u 32 ze 175 (t. j. u 18 %) nemocných s tuberkulosou v anamnése a u 11 ze 187 (t. j. u 6 %) nemocných bez tuberkulosy v anamnése. Rozsáhlejší anatomické změny na plicích ve smyslu fibrosy s dutinami byly pravděpodobně předpokladem pro nidaci *Aspergillu* u obou těchto základních skupin, především však u nemocných s tuberkulosní anamnézou.

V obou těchto základních skupinách však nebylo možno přehlédnout ani vliv profesionální expozice organickému prachu na četnost aspergillosy. U nemocných s touto expozicí v anamnése byla frekvence onemocnění v obou skupinách statisticky významně vyšší než bez ní. Závislost na profesionální expozici se zvláště zřetelně ukázala ve skupině netuberkulosních onemocnění, kde z 11 nemocných s aspergillosami 10 mělo v anamnése prašnou expozici. U žen byla vnímavost vůči aspergillosám v obou základních skupinách dvakrát vyšší než u mužů. Nemocní s tuberkulosní anamnézou měli aspergillosy v mladším věku než nemocní s nespecifickými onemocněními.

*Aspergillus fumigatus* byl prokázán u 37 nemocných, *Asp. flavus* u 4 a *Asp. niger* u 2 nemocných. Jako klinicky ofensivní se ukázal jen *Aspergillus fumigatus*, který vytvářel typické a atypické aspergillomy a byl příčinou hemoptys, které se objevily u poloviny všech aspergillos. Intensita růstu *Aspergillu* na Sabouraudově půdě a intensita agarprecipitačních reakcí byly dobrými ukazateli aktivity procesu. Paralelní vyšetření ser na dvou pracovištích dovolovalo nám při shodě výsledků brát v úvahu i reakce o slabší intenzitě positivity.

Po pro dělané tuberkulose se plicní aspergillosy objevovaly ve většině případů do 3 let po debacilisaci. U pěti nemocných, kde jsme měli možnost sledovat vznik aspergillomů během ústavní léčby, jsme zaznamenali podpurný vliv antibiotik a kortikosteroidů na růst a rozvoj aspergillomů. Podle bydliště nemocných byly aspergillosy rozmístěny rovnoměrně po celém území Slovenské republiky, avšak západoslovenská oblast byla v našem materiálu zastoupena jen malým počtem pozorování.

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