

Mushroom allergy

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It is popular belief that mushrooms are capable of eliciting allergic symptoms. Studies on this subject are few and take no account of many of the important mushroom families, for example, in Scandinavia. Most mushrooms are universal, growing equally in northern and southern Europe and North America. Studies of mushroom allergy have mainly focused on the species from these regions.

There are 50,000–200,000 different species of fungi in the world, depending on the reference. Their taxonomy is based on different systems and undergoes constant revision. The relationship between the major taxonomical groups, together with the common names of various fungi are shown in Fig. 1.

The word mushroom refers mainly to macrofungi with edible fruiting bodies, while toadstool refers to those with poisonous fruiting bodies and other minor macrofungi. These fungi, with bolets and agarics as major classes, mostly belong to the Basidiomycotina: fungi producing basidiospores. Consequently, mushrooms and macrofungi are often called “basidiomycetes”, the word constituting a class description. However, mushrooms should not be limited to this one group, as morels, for example, such as false morel (*Gyromitra esculenta*), belong to the Ascomycotina: fungi producing ascospores. Mushroom is not a suitable designation for bracket fungi (Polyporaceae), puff balls (Lycoperdaceae) or jelly fungi (Tremellales), all of which are woodland macrofungi

spreading abundant basidiospores. The formation of spores is shown in Fig. 2.

Smuts (Ustilaginales) and rusts (Uredinales), which produce large quantities of spores in forests and fields, belong to the Basidiomycotina, but being microfungi cannot be called mushrooms. Mildews (*Erysiphe*) are very similar to rusts and smuts but belong to the Ascomycotina. Some of the slime moulds (Myxomycota) are macroscopically identical with the jelly fungi that belong to Basidiomycotina.

Mushroom allergenicity, often referred to as basidiospore or basidiomycetes, should not be confined to the Basidiomycotina. However, as basidiospores derive from both macro- and microfungi, Basidiomycotina microfungi are hard to exclude. Numerous spore-producing fungi exist in woodlands and fields, and in this study we review all macrofungi regardless of the type of spore formation. For aerobiological reasons mildews, rusts and smuts are also included. The word mushroom is used here in its widest sense. As the taxonomy is subject to continual review we have chosen to use the latest accepted latin name but mention in brackets the name used in the original article reviewed.

Aerobiology

The allergenic properties of outdoor airborne basidiospores were first suggested by Gregory & Hirst in 1952 (11). The year before Frankland

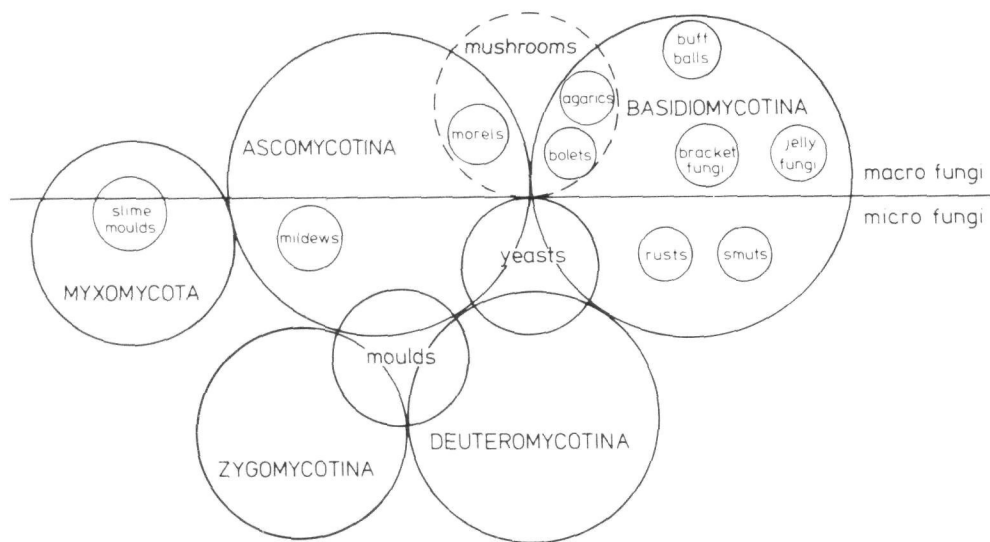


Fig. 1. The whole field of fungal allergy or mycoallergology.

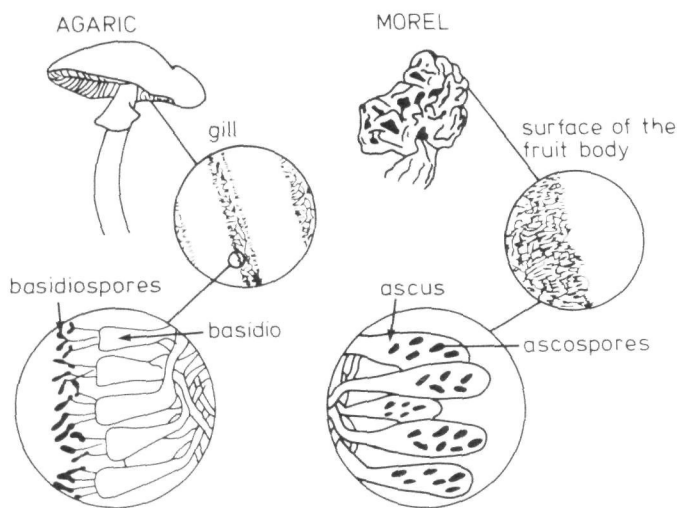


Fig. 2. The formation of basidiospores and ascospores with an agaric (Basidiomycotina) and a morel (Ascomycotina) as examples.

& Hay had shown sensitization to basidiospores of dry rot, *Serpula* (*Merulius*) *lacrymans* (9). Further evidence came from a study in New Orleans where basidiospore counts were compared with asthma admission rates in a local hospital. A positive correlation between high spore counts and asthma admission rates was shown (27). A similar phenomenon was reported from England where total daily spore counts from Derby correlated with daily asthma admissions in nearby Birmingham (4). Peak spore counts of *Sporobolomyces*, *Botrytis* and *Cladosporium* were reported after a thunder-

storm. The presence of basidiospores other than *Sporobolomyces* was not mentioned. However, based on aerobiological facts it is evident that after a thunderstorm in late July also basidiospore peaks occur (1, 35).

Studies of the mean spore and pollen counts for 1 year in Hamilton, Canada, show that basidiospore and mould spore counts are approximately equal and higher than ascospore counts (35). Continuous aerobiological surveys during 1976–86 produced similar findings in Finland, also a northern climate (7). Spore counts and pollen counts are not comparable as pollen are bigger than spores; however, the almost equal mean values for the total mass of individual pollen and spore indicates that basidiospores might be as potentially aeroallergenic as pollen or mould spores (35).

Data from various aerobiological studies on basidiospores are presented in Table 1. Spore counts in northern Europe and Canada show that basidiospores of Agaricales are in the air from June to November with peaks in August and September (1, 7, 35) The Finnish data from 1976 to 1986 (7) show that the easily identifiable spores of Boletaceae always occur from July to September and those of Russulaceae in September and October. In the years of abundant “mushrooming” the season starts 1 month earlier and lasts 1 month longer than in years with “poor mushrooming”. In maximum years the basidiospore counts of

Boletaceae and Russulaceae reach 9000 and 3000 per m³, respectively. These airspore amounts correspond to those of the well-known allergenic, *Cladosporium*. However, this is an example of an insufficiently studied area in inhalant allergy which could be as important as some previously investigated. The concentration of basidiospores is usually highest after midnight and during high humidity,

whereas concentrations of the spores of rusts and smuts are highest in summer and when the humidity is low (1, 35). In the southern climate of New Orleans the peak occurrence is similar but spores are distributed from March to December and show no diurnal variation, although occasional basidiospore showers may occur after midnight (26). Like basidispor es, most ascospores occur in high concentrations

Table 1
Aerobiological surveys depicting the amounts of spores per m³ in the air. New Orleans study gives the spores as a weekly mean count grains per cm²

	Cardiff 1958-61 (1) mean	New Orleans 1967-68 (26) limits	Ontario 1972 (35) mean	Turku 1976-86 (7) max
Basidiospores	1150	100 < > 2000		
Agaricales	760			
coloured	220			
<i>Ganoderma</i>			2000	
<i>Boletaceae</i>				-9000
<i>Hypholoma</i>				
<i>Corpinus</i>			200	
<i>Psilocybe</i>				
<i>Inocybe</i>				
<i>Nonalea</i>				
<i>Agaricus</i>				
<i>Entoloma</i>				
<i>Rhodophyllus</i>				
<i>Thelephora</i>				
hyaline	540			
<i>Polypores</i>				
<i>Tremellales</i>				
<i>Russulaceae</i>				-3000
<i>Armillaria</i>				
Lycoperdales	0.5			
Sporobolomycetaceae	290			
<i>Sporobolomyces</i>	270		150	
<i>Tilletiopsis</i>	20			
Rusts	7	50 < > 200		
Smuts	85	> 3000	150	
Ascospores	550	50 < > 4000		
hyaline	470			
coloured	76			
<i>Erysiphe</i>	4			
Fungi imperfecti	1360			
<i>Cladosporium</i>	1200	50 < > 3000	1200	
<i>Penicillium</i> /				
<i>Aspergillus</i>	50	100 < > 2000	50	
<i>Alternaria</i>	8		150	
<i>Botrytis</i>	30		50	
<i>Epicoaccum</i>	15		100	
<i>Pullularia</i>	27			

in the air from late summer to autumn and mainly when it is wet. The occurrence of the ascospores of mildews resembles that of rusts and smuts with peaks in summer and dry weather. Basidiospore counts are higher in woodlands than in cities, whereas spore counts of moulds and phycomycetes and ascospores are about equal in these areas (2).

The problem with basidiospores in aerobiological studies is that most species or even genera cannot be distinguished microscopi-

cally. It is therefore important to know the fruiting times of the different species. Those genera producing distinguishable basidiospores are *Ganoderma*, *Boletus*, *Rhodophyllus*, *Thelephora*, *Russula* and *Lactarius*. Most of the spores can be categorized by colour or shape, or as spores of Tremellales or Polyporaceae. In Britain *Coprinus* spores form about half of the brown basidiospores, *Hypholoma fasciculare* spores about 40 %, and *Agaricus* spores about 10 % of the olive-coloured basidiospores (2).

Table 2
Number of skin prick tests with mushroom and other allergen extracts in allergic populations

	London	Cambridge	Cardiff		Phoenix	New Orleans		Ontario
	1951	1963	1966	1969	1975	1976	1982	1979
	(9)	(5)	(12)	(13)	(10)	(19)	(17)	(35)
Number of patients	100	20	200	19	78	25	82	294
Extract A:		15						
<i>Meripilus giganteus</i>								
<i>Ganoderma applanatum</i>			3 < > 30	6				24
<i>Stereum hirsutum</i>								
Extract B:		15						
<i>Trametes versicolor</i>								
<i>Piptoporus betulinus</i>								
<i>Heterobasidion annosum</i>								
<i>Armillaria mellea</i>			3 < > 30	11				
<i>Serpula lacrymans</i>	20		3	6				
<i>Polyporus squamosus</i>			24	8				
<i>Agaricus bisporus</i>			3	5				
<i>Coprinus micaceus</i>			32	11				
<i>comatus</i>						15	7	
<i>Hypholoma fasciculare</i>			3 < > 30	10				
<i>sublateritium</i>						15	5	
<i>Cantharellus cibarius</i>						17	8	
<i>Pleurotus ostreatus</i>						12	7	
<i>Xylobolus frustulatus</i>						17	12	
<i>Dacrymyces stillatus</i>						13	9	
<i>Chlorophyllum molybdites</i>					11		6/19	
<i>Podaxis pistillaris</i>					10			
<i>Stemonitis ferruginea</i>					12			
<i>Fuligo septica</i>					12			
<i>Lycogala epidendrium</i>					12			
<i>Sporobolomyces</i>		18		11				
<i>Tilletiopsis</i>						16		
Smuts		19			11			
Rusts		16			16			
Ascomycetes		16						
<i>Aspergillus</i>		14				13		
<i>Cladosporium</i>		15						
<i>Penicillium</i>		12				17		
Grasses		8						
House dust		16						

Skin and provocation tests

Table 2 presents the numbers of patients with positive skin tests and Table 3 those with positive bronchial provocation tests to mushroom extracts in studies with allergic patients. Studies are few and mostly concern different species. However, the percentage of positive reactions is undoubtedly high compared with the percentage for mould or other inhalant allergens.

In the early sixties Bruce (5) studied skin and bronchial reactivity in asthmatics to different allergen extracts comprised of basidiospores: extract A included species *Meripilus (Polyporus) giganteus*, *Ganoderma applanatum*, both bracket fungi, and *Stereum hirsutum*, and extract B species *Trametes (Polystictus) versicolor*, *Piptoporus (Polyporus) betulinus*, *Heterobasidion (Fomes) annosus*, all bracket fungi, and *Armillaria mellea*. Reactivity to both extracts was seen with bronchial challenge test and intradermal skin test.

The present study included also basidiospore extracts of *Sporobolomyces*, a common yeast in air particularly in England, a smut *Ustilago nuda*, and rusts from the family Puccinia, as well as ascospore extracts of *Xylaria polymorpha* and a mildew, *Erysiphe graminis*. All these extracts produced both skin and bronchial reactivity. Basidiospore extracts gave a higher frequency of positive reactions to bronchial provocations than extracts of house dust, and pollen or spores of rusts, smuts, or moulds (*Cladosporium herbarum*, *Penicillium expansum* and *Aspergillus flavus*). In skin tests the reactions were frequent but smaller than those with moulds or common allergens.

Herxheimer et al. (12) tested 200 asthmatics in the mid-sixties with basidiospore extracts. These were prepared from basidiospores of *Agaricus bisporus*, *Armillaria mellea*, *Coprinus micaceus*, *Hypholoma fasciculare*, *Ganoderma applanatum*, *Serpula lacrymans*, *Polyporus squamosus*

Table 3

Bronchial provocation tests with mushroom and other allergen extracts. When not all patients have been tested the number of patients tested is mentioned

	Cambridge 1963 (5)	Cardiff 1966 (12)	Cardiff 1969 (13)
	Number of positive reactions among		
	20 asthmatics	42 asthmatics	19 asthmatics
Extract A:	12		
<i>Meripilus giganteus</i>			
<i>Ganoderma applanatum</i>		3/3	6/14
<i>Stereum hirsutum</i>			
Extract B:	14		
<i>Trametes versicolor</i>			
<i>Piptoporus betulinus</i>			
<i>Heterobasidion annosum</i>			
<i>Armillaria mellea</i>		8/9	9/18
<i>Serpula lacrymans</i>		3/3	7/16
<i>Polyporus squamosus</i>		4/6	7/16
<i>Agaricus bisporus</i>		6/7	7/15
<i>Coprinus micaceus</i>		18/26	15/20
<i>Hypholoma fasciculare</i>		6/9	10/18
<i>Sporobolomyces</i>	10	8/12	9/18
Smuts	8		
Rusts	14		
Ascomycetes	6	3/3	
<i>Aspergillus</i>	7		
<i>Cladosporium</i>	8		
Grasses	5		
House dust	0		

and *Sporobolomyces* and from ascospores of *Daldinia concentrica*. *Coprinus micaceus* extract gave the greatest number of positive reactions (in 16 % of the patients), whereas *Agaricus bisporus* and *Merulius lacrymans* extracts gave positive reactions in only 1.5–1.6 % of the tested. 42 patients were selected for bronchial challenge tests and 19 of these were taken for follow-up (13). During 5 years of follow-up eight patients had a status asthmaticus attack during high basidiospore counts. Among the 19 follow-up patients the most important allergens, according to skin and bronchial challenge tests, were *Armillaria*, *Coprinus* and *Hypholoma*.

In Phoenix, Arizona, a group of 78 allergics were investigated for mushroom allergy in the mid-seventies (10). The intradermal and scratch tests done by Giannini et al. included spore extracts of slime moulds *Stemonitis ferruginea*, *Lycogala epidendrum*, and *Fuligo septica*, each of which produced positive reactions in 15 %. *Puccinia cynodontis*, a rust, gave a positive reaction in 20 % and *Ustilago maydis*, a smut, in 14 %. North American basidiomycetes *Chlorophyllum molybdites* and *Podaxis pistillaris* gave reactions in 14 % and 13 %, respectively.

Dialysed extracts of *Agaricus campestris*, *Coprinus micaceus*, *Lycoperdon perlatum*, *Scleroderma lycoper-*

doides, *Fuligo septica*, *Ustilago maydis* and sooty mould were tested for immediate and delayed skin reactivity in Connecticut and Maryland. Tests were performed on 62 patients with asthma and 75 patients with rhinitis, both groups having symptoms in October and November. The asthmatic group showed more immediate reactions than the rhinitis group, whereas the converse applied with delayed reactions. Results for individual extracts have not been published and are thus not presented in Table 2 (28).

Since the work in Cardiff in the sixties, the evaluation of basidiospore allergy has focused mainly in New Orleans, where the role of high basidiospore counts in the air as a cause of asthma has been studied since the early seventies (16, 17, 19, 27, 36). In two different studies (17, 19) skin reactivity was seen with extracts of *Tilletiopsis minor*, *Dacrymyces stillatus (deliquescens)*, *Xylobolus frustulatus (Stereum frustulatum)*, *Pleurotus ostreatus*, *Hypholoma (Naematoloma) sublateritium*, *Cantharellus cibarius*, *Coprinus comatus* and *Chlorophyllum molybdites*. Results are shown in Table 2.

Immunological studies

In the earlier works basidiospore allergenicity was assessed by skin and provocation tests only,

Table 4
Immunological studies with somatic mycelium extracts, unless otherwise stated

	Number of antigens		RAST	Number of allergens CRIE
	IE (19)	CIE		
<i>Tilletiopsis minor</i>	5			
<i>Dacrymyces stillatus</i> (17)				
metabolic extract		11		3
somatic extract	8	21	+	13
<i>Xylobolus frustulatus</i> (17)				
metabolic extract		16		3
somatic extract	3	26	+	2
<i>Pleurotus ostreatus</i>				
metabolic extract (17)		11		3
somatic extract (17)	7	33	+	13
spore extract (36)		27		5
<i>Hypholoma sublateritium</i>	4			
<i>Cantharellus cibarius</i> (19)	10		+	
<i>Coprinus comatus</i> (16)	4	23		7
<i>Ganoderma applanatum</i> (35)				
spore extract			+	

but in New Orleans immunological methods were also used. Basidiospore antigenicity in man was studied with counterimmunoelectrophoresis (IE) and in rabbit with Ouchterlony's double-diffusion, counterimmunoelectrophoresis and crossed immunoelectrophoresis (CIE). RAST and crossed radioimmunoelectrophoresis (CRIE) was used to study allergenicity in man.

Tilletiopsis minor, *Dacrymyces stillatus*, *Xylobolus frustulatus*, *Pleurotus ostreatus*, *Hypholoma sublateritium*, *Cantharellus cibarius* and *Coprinus comatus*, were used in the immunological studies and the antigens and allergens of these species are best known (16, 17, 19, 36). As atopic and non-atopic sera were tested against these precipitins, *Pleurotus ostreatus* were found in all tested sera, and occasional precipitin lines were found against *Dacrymyces*, *Hypholoma* and *Tilletiopsis* (19). Data from these and other studies are presented in Table 4. Immunoelectrophoretic techniques were used to compare different mushroom fractions (17, 36). RAST studies are in accordance with skin tests and show that hypersensitivity is IgE-mediated (16, 17, 19).

Quality of allergen extracts

The most essential problem in mushroom allergy studies is the source of allergen. The air contains large quantities of mushroom spores but to gather them and prepare reliable, pure extracts is almost impossible. Most of the studies mentioned above were done with spores gathered either by scraping or shaking the fruiting body or from the spore print. The problems are: defining the species and above all contamination of the spores with pollen, bacteria and mould spores. Not one of the studies cited mentions who had defined the species, a task requiring considerable skill. Microscopical evaluation of the spore material was reported in two works (17, 30). On the other hand, total evaluation by microscope is too laborious. The surface of the fruiting bodies is contaminated, but mycelium obtained aseptically from the inside is clean and reliable; however, this was used only in one study (36).

The problem of contamination was solved in

New Orleans by culturing the mycelium *in vitro* under sterile conditions (16, 17, 19). However, this raised another problem: neither fruiting bodies nor spores are produced *in vitro*. As it is not known which part of the fungus: mycelium, fruiting body or spores, contains allergens, whether they are produced or not *in vitro*, remains unclear. Spores are spread in the air in the autumn but many allergic patients in Finland get symptoms as soon as the snow disappears, before the mould or pollen season. This might be due to the allergens from decomposed fruiting bodies or mycelium.

Allergens from the mycelium, fruiting body and spores of *Pleurotus ostreatus* have been compared by crossed immunoelectrophoresis (36). It is shown that mycelium, fruiting body and spores share common allergens, but the spores also have their own specific allergens. Metabolic and somatic antigens could be studied and compared by using *in vitro* cultures of mycelium (17). CIE analysis showed that *Xylobolus frustulatus*, *Dacrymyces stillatus* and *Pleurotus ostreatus* had about twice as many somatic as metabolic antigens. CRIE showed that allergen amounts were virtually equal except in *Pleurotus*, which had four times as many somatic allergens as metabolic. The significance of somatic and metabolic allergens in nature is unclear, metabolic allergens are possibly excreted from mycelium onto the soil from where they become airborne.

Skin reactions have usually been frequent but small (5). This might be due to inadequate disruption of mycelium or spores and low protein concentration. Sonication is hardly enough for chitin-containing cell walls.

Symptoms

Basidiospores and other spores of woodland fungi are small (most of them less than 10 µm in diameter) and capable of entering the lower respiratory tract. Thus, the main symptoms could be asthmatic. Most of the studies on mushroom allergy have concerned the etiology of asthma. Sporadic cases of work-related allergic rhinitis caused by puff balls (18) and contact dermatitis caused by *Suillus luteus* have been described (8), but the whole extent of

mushroom-related symptoms is not known. Some idea may be deduced from the reports given by parents of our asthmatic children (Table 5). According to these, 5 to 30 % of the children have symptoms which could be associated with inhalant mushroom allergens.

Reports of gastrointestinal exposure are few, although quite a number of people report symptoms after eating mushrooms (Table 5). A case was reported of peroral exposure to *Ramaria flava* which led to anaphylaxis and death. The postmortem showed a positive RAST to *Ramaria flava* (Tony Foucard, personal communication). The paxillus syndrome, named after *Paxillus involutus*, is a complement-mediated immunohaemolytic reaction caused by peroral antigen exposure to *Paxillus involutus*, *Suillus luteus* and possibly *Gyromitra esculenta* (8).

Cases of allergic alveolitis similar to farmer's lung have been described; these were due to exposure to spores of *Lycoperdon* (34) and cultivated mushrooms and will be discussed in detail later. Mushroom antigens are known to produce allergic reactions of the Gell and Coombs types, I, II, III and IV.

Mushroom worker's lung

Mushroom worker's lung, for the first time described by Bringhurst et al. 1951 in Puerto Rican mushroom workers, is analogous to farmer's lung of uncertain etiology (3). Thermophilic actinomycetes *Micropolyspora faeni* and *Thermoactinomyces vulgaris* were proposed as etiological factors by Sakula (24). Serum precipitins to these species have been shown in other studies, which have also indicated a possi-

ble role of other microbes in the mushroom compost (15).

In the mid-seventies Schulz et al. (29) presented a similar illness in Bavarian mushroom workers, and proposed *Pleurotus florida* spores to be the cause. The patients had an immediate skin reaction to an extract of *Pleurotus* spores and serum precipitins to *Pleurotus* antigen on analysis with Ouchterlony's gel diffusion. At the same time Stewart & Pickering (33) reported respiratory symptoms in workers cultivating *Agaricus hortensis*. These workers had precipitins to *Agaricus hortensis* but not to thermophilic actinomycetes. Skin and provocation tests to both these species were negative. In Nanjing, China, 92 % of workers on a farm cultivating *Pleurotus ostreatus* had cough, high mucus production, and dyspnoea (37). Of these 79 % had immediate skin reactivity to spore extract of *Pleurotus ostreatus*.

Thermophilic actinomycetes undoubtedly play a role in the etiology of mushroom worker's lung, but not invariably. Mushroom spores and mycelium should be considered as etiological factors. In all the studies of mushroom worker's lung the problem has been the purity of spore extracts. As pure spore or mycelium extracts were not obtained, the etiology of mushroom worker's lung has remained obscure. Apart from *Agaricus* and *Pleurotus*, work-related allergy is presumed to be caused by *Flammulina velutipes*, *Stropharia rugosoannulata*, *Lentinus edodes*, *Volvariella volvacea* and *Kuehneromyces mutabilis* (8).

Summary

The overall extent of mushroom allergy is not known. It may be very slight (1 %) from eating, but could, alternatively, be as prevalent as pollen and mould allergy (10-30 % of an allergic population). Aerospora of mushrooms and other woodland fungi, mostly basidiospores, occur in temperate zones in June to November, reaching maximum in August and September in quantities comparable to pollen and mould spores. There are large local and annual variations in species and spore concentrations in different milieus. In SPT and BPT studies about two dozen of these species have been associated with inhalant type I allergy. All spe-

Table 5

Mould allergy in asthmatic children. Questionnaire sent to 929 patients and answers obtained from 800

Question	Answer		
	Yes	Possibly	No
Positive SPT/RAST to moulds	146	69	533
Symptoms in forest	102	148	501
Symptoms on handling mushrooms	37	73	641
Symptoms from eating mushrooms	13	24	715

cies studied so far have yielded positive results. Mushroom allergens have been explored in only two studies. These show that mushrooms are antigenically rich and that a species can have more than one allergen.

The difficulties of mushroom allergen research are very substantial because one usually has to rely on naturally growing mushrooms, where allergenic contamination by other allergen sources is frequent. Choice and recognition of species is also difficult. Virtually all known allergenic mushrooms and fungi are universal, growing equally well in Europe and North America (14, 20, 21, 22, 31). The genus *Chlorophyllum* occurs only in North America, but its close relatives of the genus *Macrolepiota* are common also in Europe. *Podaxis* grows only in desert regions near the equator and is not found in Europe. The majority of the large and more common universal mushroom families has not yet been investigated. The allergenicity of families Cortinariaceae, Russulaceae, Lactariaceae and Boletaceae is totally obscure even though they produce large quantities of spores in the air, particularly in northern Europe.

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