Fungal Hypersensitivity: Pathophysiology, Diagnosis, Therapy

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I. Introduction

The comments contained herein are those of a clinical immunologist whose major professional activity is patient care. Over the last several years, as the general awareness of fungal exposure as a cause of illness has grown, more and more patients have been presenting themselves for diagnosis and treatment after exposure to homes and offices heavily contaminated by fungi. The Internet has come to play a major role in the dissemination of good, and some not so good, information about fungal diseases, and the number of patients has mushroomed. Most American trained physicians have had little instruction in mycology and tend to dismiss or minimize the possibility of fungal illness except for certain generally accepted special situations. These would include immunologically deficient patients, *Candida* infections in women, thrush in newborns, skin infections such as ringworm and athlete's foot, and lung infections in areas endemic for histoplasmosis

or coccidioidomycosis. Even allergists who limit themselves to skin tests for diagnosing hypersensitivity ignore patients complaining of serum sickness–like symptoms (e.g., headaches, rash, malaise, joint pain, etc.) following exposure to moldy environments and often refer them for psychiatric care (Terr, 2001). The unfortunate patient has nowhere to turn except to those few physicians who have listened to their patients, believe what they say, and accept the challenge to try to help. These physicians have gone to the Internet or the medical literature and developed scientifically inspired diagnostic and treatment programs that have proven to be helpful to their patients. I stand among these physicians, and I would vigorously defend the scientific basis and efficacy of my approach to the diagnosis and treatment of patients suffering from exposure to high ambient levels of fungi in indoor environments. My best thoughts on the subject are offered herein.

II. Health Effects of Fungi

There is much about the health effects of fungi that is not understood. Exposure to high ambient fungal spore levels in a water-damaged home or building is, more likely than not, a mixed bag. Not only are more than one fungal genus likely to be present, but bacteria such as *Legionella* or *Actinomyces* may be present in sufficient quantities to add complexity to the resulting symptoms (Fink, 1984). Endotoxins are frequently found in abundance when Gram-negative bacteria abound, as when sewage is the source of the water (Rylander, 2002). In addition, insects such as mosquito larvae or other mold-feeding insects (mites) may be contributing to the airborne organic particle burden. Even large rodent populations have been discovered in older, run-down, water-damaged homes and buildings. All of these can contribute to the disease patterns seen in patients exposed to ''fungi'' in water-damaged structures.

A. INNATE AND ADAPTIVE IMMUNITY

Fungal exposure itself can produce a confounding array of symptoms as different elements of the body's defense systems are triggered. Early in the course of exposure, the innate immune system can be activated as endotoxins or fungal elements enter the body tissues. This inflammation can proceed without any involvement of the adaptive immune system with its antibodies and activated T-cells (Kauffman *et al.*, 2000).

However, after a few days or weeks of antigen presentation on an inflamed mucosa, the adaptive system is likely to become involved as antibodies and T-cells specifically reactive to fungal antigens are generated. This will add to the inflammation of the affected tissues. Finally, fungal elements become directly involved if mycotoxins or other inflammatory triggers are formed that can cause toxic injury to specific organ systems. One need only be reminded of such fungal compounds as alcohol, lysergic acid (LSD), antibiotics, cyclosporin, or mushroom toxins to appreciate the ability of such organic molecules to cause symptoms.

Physicians who treat patients with mold-related problems are often challenged by the variations in the disease symptoms and the multi-organ involvement that are presumably the result of exposure to environments heavily contaminated with fungi. They may accept the likelihood that fungal exposure is the cause of their patient's symptoms but not understand the underlying pathophysiology. Still, an attempt is made to treat the patient, essentially by utilizing various programs that remove the patient from the fungi. Over time, they learn that the clinical patterns seen in such patients are consistent, the diagnosis can be accurately made, and the response to therapy is very good.

There are other physicians who deny that fungi as encountered in homes or office-type work spaces are capable of causing illness. These physicians generally are not primary caregivers and can dismiss the patient's complaints because of their apparent complexity without a consequence. They are better designated as theorists who base their negativity on arguments that the lack of sufficient evidence-based proof of a causal relationship of fungal exposure to human disease proves that such a relationship is not possible. They dismiss all case reports (Marinkovich *et al.*, 1975) (Fink *et al.*, 1971), epidemiological studies (Dearborne, 2002) (Etzel *et al.*, 1998), and clinical observations of experienced clinicians as worthless and such patients as malingerers or psychiatrically disturbed (Hardin *et al.*, 2003). They seem to lack the vision to accept the challenge of the possibility that injury to multiple organ systems may result from exposure to large amounts of fungus-derived materials (such as spores and/or mycotoxins) in a home or office environment. They are wrong, and they can do a great deal of harm. First in denying the patient's symptoms, and second by blocking disability requests from such patients injured by exposure to fungi in their workplaces. They are guilty of using poor scientific logic because it is closed-minded. Such

thinking has no place in a medical setting where there are sick patients who need help.

III. Clinically Relevant Characteristics of Fungi

Fungi are nature's recyclers. They are extremely abundant in nature, carrying the mandate to reduce all organic matter to its basic constituents. The organisms are armed with several features that allow them to satisfy this mandate. They are microscopic cells that are numerous in all climates where temperatures are above freezing; they exist in two forms: an active, growing form and a dormant, hardy, drought-resistant and easily wind-borne form (the spore, also known by the scientific name of conidia). They are superbly versatile and can grow on virtually any wet surface. They secrete their digestive enzymes (Kurup, 2003), digest their environment, and absorb their necessary foodstuffs from their immediate, digested environment. Among the products of digestion are toxins (known as *mycotoxins* because they are derived from fungi), which help them control the potential intrusion of competing organisms into their space. Each of these characteristics plays a role in the disease patterns seen in fungal illness.

The job of fungal spores is to broadcast the organism widely in the environment. They are tiny, lightweight, and easily airborne. They are in all natural environments the most prevalent particles in the air at all times. Even at the height of a pollen season, the pollen particles are outnumbered 10 to 1 by fungal spores. The human body is marvelously equipped to deal with such large numbers of potentially infectious particles in the air. The filtering capacity of the nasal mucosa easily removes the larger spores, greater than 10 microns in diameter, from the inspired air. Once trapped on the mucosa, the tiny hairs on mucosal surfaces (cilia) move the particles toward the throat where they are swallowed and destroyed by the acid in the stomach. Some of the smaller spores, less than 10 microns in diameter, may be inhaled into the lungs (Geiser *et al.*, 2000). However, even here the normal self-cleansing functions of the lung, which includes its own cilia and mucus production, are mobilized, and particles are moved upward and swallowed. A small subset of the tiniest spores, less than 3 microns in diameter, may be inhaled and trapped in the alveoli and terminal bronchioles beyond the reach of the cilia. They are handled by the scavenger cells in the lungs, the alveolar macrophages.

This is extremely important to understanding the pathophysiology of fungal exposure, because once the fungal elements have reached

the alveoli they have entered the tissue space from which they can be absorbed into the blood stream.

IV. Diagnosis

The diagnosis of fungal hypersensitivity syndrome rests on four criteria: exposure to an identified heavily contaminated source, appropriate symptoms temporally related to exposure, high serum-specific IgG levels to molds, and finally, a positive response to therapy. IgE antibodies are usually not involved in hypersensitivity phenomena secondary to exposure to high-dose antigen such as fungi, foods, and occupational exposures to organic matter (Fink, 1984). Skin tests are therefore of little if any value. The fourth criterion for diagnosis is an essential feature of all medical therapy—namely, the clinical improvement resulting from a fungal avoidance regimen. When this condition is not met, the diagnosis must be revisited. Either avoidance is inadequate, therapy is insufficient, or the diagnosis is wrong.

A. Antibodies or Lack Thereof

Everyone is exposed to fungi in daily living, and therefore antibodies to fungi are found in nearly everyone. They have been shown to be protective, except for patients whose immune systems are inadequate in response. These patients are extremely susceptible to fungal infection. In such cases—for example, AIDS patients, cancer patients (especially if on chemotherapy), transplant recipients on immunosuppressive drugs, and patients with acquired or congenital immune deficiency, especially involving cellular immunity—fungal colonization can be life threatening. In most healthy individuals, the constant exposure to ambient fungal spore levels is handled easily by normal mucosal cleansing mechanisms and the ever-vigilant immune system. Ill effects do not generally occur in the normal population. However, this statement is not true for all otherwise ''healthy'' individuals. The extreme example of this is seen in certain occupational fungal diseases—for example, farmer's lung (Emanuel *et al.*, 1964), malt workers pneumonitis (Riddle *et al.*, 1968), etc—where enormous exposures occur on a daily basis and virtually everyone can be symptomatic. In such cases the inflammatory changes produced in the lungs can cause severe destruction of lung tissue, extensive colonization of lungs with fungi and bacteria, and slow progression to respiratory deficiency and death (Pepys, 1969). Such patients must be treated aggressively with complete cessation of further exposure, high doses of systemic and

inhaled antifungals (Nark *et al.*, 2003; Stevens *et al.*, 2000), and the judicious use of systemic steroids to reduce inflammation and arrest the progressive damage or remodeling of the lungs (Kaltreider, 1993). Steroids actually encourage fungal growth by suppressing the inflammatory reaction, and their use must be carefully monitored to walk the tightrope between too much steroid, encouraging fungal growth, and too little, allowing progressive destruction of lung tissue.

B. Individual Variations in Response

The levels of fungi in contaminated homes and office buildings may be quite high but are generally not nearly as high as those encountered in the special occupational situations previously mentioned above. Still, they are high enough to cause serious illness in non-immuno-compromised individuals (Burr, 2001). A considerable variation in response to moldy homes among members of the family is common. In some cases all members of the family are affected, with some small variations in severity and in the organs infected (e.g., skin, lungs, sinuses, gastrointestinal tract, headaches, etc.). In other instances the variation in severity of illness can be considerable among family members; one person at one extreme may be quite ill, even disabled, while another at the other extreme has little to show for the exposure. This is understandable in that not all rooms in the house may be equally contaminated and those sleeping in the rooms with highest levels of contamination are likely to have more severe symptoms. Variations may be seen in the amount of time each individual spends at home. And then there is genetic polymorphism, where each individual is endowed with his own unique immune responsiveness and two individuals in the same family or bloodline may respond quite differently to the same exposure. In studies done with serum sickness in which normal, healthy individuals were given different volumes of horse serum intravenously, some individuals developed symptoms (Von Pirquet, 1951) with relatively low volumes of serum while others required 10 times more serum to show the same symptoms. The conclusion of these studies was that everyone was susceptible but that there is a dose-dependent susceptibility among different individuals.

Sustained exposure to airborne fungal spores at levels far below the occupational disease levels in otherwise normal healthy individuals will produce symptoms in some percentage of patients. The exact percentage of susceptible individuals is likely to be low, perhaps under 1% of the population. But with the widespread contamination of homes and workplaces in this country—with perhaps 30% of the

schools, homes, and offices involved—the actual number of affected individuals can easily reach 1 million. One percent of the population is about 3 million individuals, and a third of these would be 1 million. This is an epidemic. Unfortunately, many of these cases are not recognized by the medical community and go undiagnosed and untreated. Thanks to the Internet and the media publicizing the results of litigation involving mold cases, the public's awareness of the problem has grown. Hopefully, this will induce more health caregivers to learn about fungal illness.

C. HYPERSENSITIVITY

The human immune response, part of the body's system of adaptive immunity, can be amazingly sensitive. A person allergic to cats can sense the presence of cat dander in a room months after the cat has departed. And rarely, one reads of a sudden death from anaphylaxis provoked by exposure to a tiny amount of antigen such as vespid venom from a single bee sting or the steam rising from a fish stew, or tiny particles of peanut contaminating a package of almonds processed on machinery previously used to process peanuts (Samson, 1992). The extreme sensitivity potential of the immune system is rarely seen but frightening when it occurs. When the number of individuals exposed to such spore levels is very high—as seems to be the case today in homes, schools, and workplaces—a significant number of cases will occur. To deny this is akin to denying the existence of significant pollen or cat allergies because the great majority of people do not show such symptoms on exposure. Genetic polymorphism is the basis for a considerable number of differences within the human population, and the immune response, based on the same mechanisms, shows the same wide variations in response among individuals.

V. Symptoms

While the symptoms seen in patients exposed to high ambient levels of fungal elements can vary a great deal among different individuals, a fairly consistent pattern of illness is seen in patients presenting with sufficient symptoms to warrant seeing a physician. Most patients describe a progression of symptoms beginning a few months to a few years after the onset of exposure (e.g., moving into a mold-infested house). Initially the complaints are nasopharyngeal (sore throats, hoarseness, stuffy nose, transient hearing loss) or pulmonary (cough, wheezing, shortness of breath). With time, symptoms progress to

include headaches, fatigue, rashes, vertigo, muscle and joint pain, fever, recurrent sinus or ear infections, etc. (Rylander, 1994). Many of these symptoms are the result of an overactive immune system trying desperately to overcome what it perceives to be an overwhelming infection. The immune system generates antibodies to the absorbed materials (or antigens). These antibodies react with the antigens to form immune complexes, which is all part of the body's normal immune elimination function. These complexes are quickly taken up by scavenger cells, which remove the complexes from the circulation, thus limiting their inflammatory effects. When complex formation continues over a long period of time, this clearing mechanism can become overloaded. The complexes then remain in the blood stream, causing myriad symptoms, known to clinical immunologists as *serum sickness* or *immune complex disease* (Cochrane *et al.*, 1973). To the patient, the symptoms appear to be a severe, unrelenting flu syndrome. When one looks up in the older literature the classical symptoms seen in serum sickness, they are exactly those symptoms the patients with fungal illness describe to their physician (Von Pirquet, 1951).

Since hypersensitivity states develop only after relatively long exposure times, normal children under 10 years of age do not have significant antibody titers to fungi. However, when children experience very high exposure levels in the home or school, measurable antibody levels appear rather quickly—that is, within a few months of exposure. Normal mature adults living in temperate or tropical climates commonly show antibody activity toward fungi and experience symptoms following unusual exposures. The onset of symptoms often follows exposures by 1 or 2 days, the symptoms are not recognized for what they are, and the symptoms are likely to be diagnosed as a virus infection.

VI. Mycotoxins

Mycotoxins are the most respected of fungal products for their potential to cause serious illness through their direct biochemical action on key body functions (Croft *et al.*, 1986; Johanning *et al.*, 1996; Leino *et al.*, 2003). The immune system is not involved. One of these, aflatoxin, is known to be among the most potent of carcinogens. Another group, trichothecenes, are toxins released by the fungus *Stachybotrys atra* (also known as *chartarum*) as well as others. There is controversy regarding the role of trichothecene mycotoxins in pulmonary hemosideroisis (Dearborn *et al.*, 1999). Other toxins can affect various hormonal, neurological, and other body functions to produce serious health effects (Sorenson, 1999). They are so effective in certain

biological activities that they have been harnessed by the pharmaceutical and food industries for commercial use such as antibiotics, immune suppressants to control graft rejection, medicine for cholesterol control, and enzymes used in food processing and preservation. Mycotoxins are produced by fungi under specific growth conditions, and their role in human illness is not well understood. Exposure to certain mycotoxins producing organisms such as *Stachybotrys* seem to cause neurological damage seen as short-term memory loss, cognitive dysfunction, inability to concentrate, and ''fuzzy thinking.'' There are common complaints of patients with fungal illness. The changes seem to be reversible, at least in part, but they can take years to resolve. Hyperactive immune systems responding to the influx of fungal antigens following chronic exposures are much more likely to be a cause of symptoms in most individuals.

VII. The Role of IgE and Non-IgE Mechanisms

Allergists have accepted the role that fungal spores can play in eliciting allergy symptoms in susceptible individuals. This is akin to the effects of other airborne organic particles such as pollen, animal dander, and insect dust. The illness affects only individuals programmed genetically to make large quantities of specific IgE antibodies on exposure to relatively small amounts of allergen. This is type I immunopathology, as defined by Gell and Coomb (Gell *et al.*, 1964) and involves the release of pre-formed histamine and other biologically active cytokines from sensitized mast cells and basophils. Symptoms include watery nasal discharge, sneezing paroxysms, and itching of the naso-oro-pharyngeal mucosa and tearing eyes and can be significantly disabling. Symptoms disappear quickly on cessation of exposure, leaving little or no residual effects. It has been suggested that perhaps 5 percent of the population may be affected in this way by fungi, although those numbers will vary in different climates (e.g., more in Florida than New Mexico). The great majority of patients presenting with symptoms of fungal illness do not show IgE antibody to the fungus (Fink, 1984). This may be the result of isotype switching from IgE to IgG production as stimulation of the immune system increases. When this happens, far more elaborate and damaging immune responses can be generated by the body following exposure to large amounts of fungal particles, especially when the exposure is chronic. These illnesses were originally described in association with various occupational exposures in unprotected workers such as farmer's lung, bagassosis in sugar cane workers, and many others. More recently such conditions

have been identified and studied in office workers whose workplace is contaminated by fungi (especially in buildings with closed ventilation systems [Fink, 1984]), in individuals exposed to swamp coolers (Marinkovich *et al.*, 1975) or contaminated air conditioners in the home (Banaszak *et al.*, 1970), and in many other school, home, and workplace exposures, generally as case reports involving a few patients per report (Cakmak *et al.*, 2002; Dales *et al.*, 1991; Hodgson *et al.*, 1998). These symptoms can occur in all individuals with normal immunity because they are ultimately manifestations of a robust immune response to a heavy unrelenting airborne fungal load with consequential overload of clearing mechanisms or macrophages and the activation of inflammatory processes.

Although the general immune response to a heavy fungal antigen exposure may consist of all the immunoglobulin isotypes (IgA, IgM, IgG, IgD, and IgE) plus sensitized lymphocytes or T-cells, specific IgG is the most efficient single marker of generalized immune responses. Specific IgG antibody levels to fungi are not diagnostic when taken alone. However, antibody levels to fungi are directly proportional to levels of exposure in any individual, and generally high exposure levels result in high antibody titers. These antibody levels drop when the patient's exposure to the offending fungi ends. When elevated, they are helpful in arriving at the presumptive diagnosis, and repeat measurements at 4- to 6-month intervals help verify compliance with the fungal avoidance program and help monitor the success of therapy.

A. Immune Complexes

The presence of antibody in the serum is not pathologic in itself. All the immunoglobulins normally present in the tissues, with possible rare exceptions, are antibodies, and they contribute to the immune state. It is only when antigens combine with antibodies that immune complexes are formed and a potentially pathologic state is initiated. Immune complexes are not stable, since the union is one of complimentary surface configurational attraction between two or more molecules produced by Van der Wall forces. The complexes can easily be disrupted as the conditions in solution change. Changes in temperative, relative numbers of reacting molecules, their nature, the epitope specificity of the reacting antibodies, etc., can all effect changes in the size, shape, surface charges, and solubility of the complex. These factors are the ones that determine the inflammatory potential of the complexes formed and whether the complexes will tend to be deposited in kidneys, joints, blood vessel walls, skin, lungs, etc. (Cochrane

et al., 1973). Because of the inherent instability of immune complexes in tissue and serum, they are difficult to study. Interest in understanding immune complexes was very high in the 1950s and 1960s and quickly dissolved when IgE was discovered (Ishizaka *et al.*, 1966) and the attention of the immunological research teams was attracted to the newly defined antibody responsible for classical allergy symptoms, Type I of Gell and Coombs.

There are sound scientific reasons why specific IgG antibodies to fungi are not always diagnostic. Some individuals with high antibody levels to fungi remain symptom free during re-exposure. Such individuals may be less likely to produce the toxic immune complexes required to induce symptoms by virtue of the fungal antigen epitopes to which they respond. They may respond to minor epitopes that allow measurement of the antibody but which do not engage in the formation of toxic immune complexes. Other individuals may have a vast scavenger system, which can rapidly take up and extinguish all immune complexes generated before symptoms can ensue. Other individuals may satisfy the high exposure and the appropriate symptom requirements and have relatively low total specific antibody levels to fungi. They may be poor antibody responders with an even lower capacity to deal with immune complexes. The observation that they can still experience flu-like symptoms following fungal exposure demonstrates that a relatively low antibody level can still produce significant, disabling symptoms. Mold toxins can be powerful immune suppressors. It is sobering to remember that there would be no organ transplant program without the availability of fungal toxins (e.g., cyclosporin). It is possible and even likely that the fungal exposure of some patients will include exposure to immune suppressive mycotoxins. Another cause for low antibody levels in a symptomatic patient could be iatrogenic. Many patients develop arthritic symptoms and present themselves to rheumatologists who may choose to use an immunosuppressive drug such as methotrexate to treat the arthritis. Such a drug will certainly depress the immune response and relieve the severity of arthritic symptoms while masking what could be the real trigger for the arthritis.

VIII. Therapy

The therapy of all hypersensitivity diseases must be based on avoidance. In the case of fungi, it is important to recognize that there are three sources of exposure: The airborne particles, mostly spores, which result from water intrusion at home, school, and work; ingestion (as in the enormous amounts and types of fungal products used by the food

industry); and colonization of skin, lung, sinuses, and other mucosal surfaces.

A. ENVIRONMENTAL MOLDS

A moldy environment must be remediated or destroyed. All sources of water intrusion have to be discovered and sealed. All wetted surfaces must be completely dried (e.g., both sides of sheet rock), and any surfaces showing fungal proliferation must be replaced, including walls, floors, carpets and pads, cabinets, furniture, etc. In many cases of fungal hypersensitivity, the affected individual may not be able to return to the remediated space because his sensitivity is too great for the level to which remediation may reduce fungal efflux. There is a simple canary-in-the-mine parallel. No amount of surveying the remediated site can assure that the patient will be able to tolerate the reduced fungal levels. More times than not, they cannot. Avoidance may require a move to different quarters.

High-efficiency particulate air filters (HEPA) are useful in removing spores from the air. They remove a great majority of the particles greater than 0.3 microns in size, which includes all mold and bacterial spores. However, a heavily mold-infested indoor space may overwhelm the ability of a HEPA room air purifier to significantly reduce ambient spore levels. In some cases, ozone generators have proven useful. They must be used at full power inside sealed, vacant rooms for a full day to significantly reduce fungal growth. It is important to stress that occupants should not be exposed to ozone, which is toxic. The ozone is unlikely to kill spores or deeply situated mycelial elements. Therefore, the process generally has to be repeated at least bimonthly. The ozone levels achieved in the room may not be safe at any times for individuals with asthma, chronic obstructive pulmonary disease (COPD), or other forms of respiratory distress; however, handling the ozoning process (i.e., initiating and terminating the treatment) is only slightly disagreeable to the normal individual. Mold cells are similar to human cells in their makeup, which means that ozone levels likely to kill mold cells are also likely to irritate the human respiratory mucosa.

B. FOOD MOLDS

Fungi are prolific enzyme and toxin generators, which is the basis for much of their use in modern food technology. Bread will rise more quickly and require less baking time and lower baking temperatures if amylase is added to the dough. The amylase digests the cross-linkages

of the cellulose in the dough, making it less tough. This results in considerable economic gain for the baking industry. Its downside is that it has produced substantial illness in bakers, and it loads the bread with mold products that add to the burden of a mold-sensitive individual. These additives are listed on the ingredient labels of breads as dough conditioners or malted grains (for malt, read *mold*). Fruit juice manufacturers discovered that if hemicellulases (of fungal origin) are added to the crushed fruit prior to squeezing out the juice, the yield can increase as much as 25%. The enzymes digest the cellulosic structure of the fruit and allow more juice to be obtained from the cells. This is a wonderful economic gain for juice makers but adds fungal elements to the juice.

Citric acid is perhaps the greatest misnomer in the ingredients listing of any food. It is added to most processed foods including soft drinks, jams and jellies, frozen meals, etc., as a preservative. It conjures up visions of lemons, oranges, and limes. It is none of these; it is a direct product of *Aspergillus* fermentation in commercial quantities. It is a highly impure ''citric acid'' contaminated by many other *Aspergillus* products including toxins, antibiotics, etc. One wonders if pure citric acid would confer the same excellent preservative properties as commercial ''citric acid'' on foods? Again, this is an excellent product for the food industry in extending the shelf life of foods, but it adds fungal elements to the food.

Some foods are obligate products of fermentation such as aged cheese (usually *Penicillium*), soy sauce (usually *Aspergillus*), chocolate (mixed molds), and black tea (*Aspergillus*). While wonderful on the educated palate, they must be eliminated in a mold-free diet. The patient trying to avoid mold in his food must be instructed in how to maintain a fresh food diet. This means shopping more frequently than weekly. Farmer's markets are often excellent sources of fresh fruits and vegetables. This may be especially difficult in small towns where the supermarket is the only source of food.

C. COLONIZATION

Colonization of the human mucosa is a common phenomenon that seems to be poorly understood. The human body is colonized by bacteria in the nasopharynx, mouth, gastrointestinal tract, skin, etc. No one questions this, and the concept of a balanced ecology in the gut is considered essential for proper gastrointestinal (GI) function and a stable supply of nutrients such as vitamins. Fungal colonization is also a widely accepted phenomenon—as for example toenail fungus,

athlete's foot, vaginal candidiasis, chronic fungal sinusitis, and seborrheic dermatitis. But the concept that fungi can become part of the normal mucosal flora, and that once established, fungal colonization can place a heavy burden on the body's defenses is not always appreciated. Some fungi produce toxins, and all fungi produce and secrete enzymes into their environment. The body has to protect itself against all foreign proteins, especially those that carry enzymatic activity. The immune response is that protection. Foreign enzymes are known to be among the most powerful stimulants of an immune response (Larson *et al.*, 1996).

Patients who have become ill from living or working in a moldy space are often improved when they move, but their health does not always return to normal. This means either that the fungal exposure resulted in permanent damage, which is quite possible with tissue-deposited immune complexes or certain mycotoxins, or there is continued exposure to the fungus because of colonization. Colonization is more likely to occur first where there has been previous tissue damage. The nasopharynx is the first filter for airborne fungi and would expect to be first to be colonized along with adjacent communicating structures like the sinuses or middle ear. Colonization is more likely to occur where there are residual scars from past disease or surgery. This is where the body's first line of defense—mucous flow, ciliary action, and IgA secretory antibody function—is likely to be missing. The lungs are easy targets for colonization when there has been previous damage as in a past pneumonia. Children with cystic fibrosis are virtually 100% colonized in the lungs (Etzel *et al.*, 1998), and patients with chronic asthma are said to be about 30% colonized. The esophagus is a common site for colonization because of its vulnerability to damage from hot foods, spicy foods, and acid reflux.

D. ANTIFUNGALS

When possible, colonization is best treated topically. The oral cavity and esophagus can be treated with liquid fluconazole (40 mg/ml) or Itraconazole (10 mg/ml), 40 or 50 mg four times daily. Neither of these is well absorbed in a non-acid medium, and they can be quite effective topically until they reach the stomach, where they may be absorbed. Nystatin is a non-absorbed antifungal with an excellent safety record. It can be given as a powdered suspension in water at 500,000 units four times daily. It will continue to provide antifungal activity throughout the GI tract as it courses its way from mouth to anus.

Fungal colonization of the nasopharynx, sinuses, and middle ear is best treated with an antifungal nasal spray. A 2% ketoconazole suspension or a 0.01% amphotercin B solution applied generously four times daily to the nose is effective in many cases. It must be delivered deep into the nasal cavity and be felt passing into the pharynx. Neither will be significantly absorbed in the pH-neutral mucosa of the nose. The benefits of therapy are likely to be noted within a few weeks but a cure, where therapy can be safely stopped without recrudescence of the illness, is months and sometimes years in the future. This is likely due to the resistance of the spore to killing with available antifungal drugs, which means that therapy must be continued until all spores are eliminated or germinate and become susceptible to the action of the antifungal.

Colonization of the lungs and sometimes the sinuses requires a systemic antifungal such as Itraconazole, ketoconazole, or voriconazole. Each are given at 200 to 400 mg per day (Gallin *et al.*, 2003; Schubert, 2000). In some cases of lung disease a nebulized antifungal is helpful. Ketoconazole has been successfully used by nebulizing 50 mg per treatment, twice daily.

Many physicians show great concern when talking of systemic antifungals because of the possibility of liver damage. This concern is grossly overstated. Most antifungals used in high doses are given to immunocompromised individuals with severe fungal infections including blood-borne dissemination. Elevated liver enzymes in such catastrophic illness is not rare and must be considered in the decision to use such therapy. However, in my 10-year experience with antifungals in immunologically normal individuals colonized by fungi, I have yet to see a single episode of elevated liver enzymes, which can be attributed to the use of the antifungal. Testing for liver function at 2- to 4-month intervals is recommended by the FDA. It has been reported that in rare instances in which liver enzymes have risen, cessation of therapy results in a rapid return to normal in all but a few rare instances. The antifungals are metabolized in the liver and place some burden on the detoxification enzymes of the liver, which are also used to metabolize certain drugs. The use of antifungals may influence the serum and tissue levels of such drugs, generally causing a rise in concentration as the rate of metabolism of the drug is reduced. Such changes can be handled by careful assessment of tissue levels of drugs used simultaneously with the antifungals.

Fungal colonization of the GI tract is a relatively common phenomenon encouraged by the overuse of antibiotics in medicine and their use in the production of meat for human consumption. This usually

manifests as abdominal discomfort, heartburn, increased gastric emp-tying time, bloating, crampy abdominal pain, and increased transmu-cosal uptake of large food protein molecules (leaky gut). Treatment is best begun with a non-absorbed antifungal such as Nystatin or poorly absorbed antifungals such as miconazole or econazole. Nystatin is best given as a powdered suspension, 2 to 3 million units per day in divided doses (b.i.d. or t.i.d.). The miconazole and econazole are not generally available in pure powder form from regular pharmacies and must be formulated. This increases the cost somewhat but still leaves them far cheaper than the newer antifungals already mentioned. They are given in 250 mg capsules twice daily.

1. *Jarisch-Herxheimer Reactions*

The treatment of fungal colonization in patients hypersensitive to fungi almost always produces a Jarisch-Herxheimer (JH) reaction if given too aggressively. It is safest to begin with one quarter or less of the therapeutic target dose and advance every 3 to 4 days in doubling doses to reach the desired dose. The JH reaction can occur at the initial dose or at any time the dose is increased. It manifests as a flu-like reaction in its broadest sense (i.e., headache, rash, low-grade fever, myalgia, arthritis, night sweats, malaise, cough, diarrhea, etc.). When it appears, treatment should be stopped until the symptoms disappear (usually 1 to 2 days), and then a lower amount should be introduced and held there for 2 weeks before any attempt to increase the dose. It is best to be guided by the patient, who quickly learns if there is a limit to the dose he can tolerate, but he may subsequently have to be encour-aged to try to take more medicine if past experience has been severe enough to be alarming. The JH reaction can also occur when the patient who is seemingly stable (on full dose) suddenly experiences a larger fungal burden, such as in staying in a moldy hotel room on a trip or following a day of spreading compost in a vegetable garden.

Colonization of the skin in the form of abscesses on the skin or dry scaly rashes over the palms of the hands (dishydrotic eczema) can be treated with topical antifungal creams, sometimes coupled with systemic antifungals. The topical antifungal action on the skin can be enhanced by use of occlusive dressings. Patients are directed to apply the cream liberally at bedtime and then cover the lesion with a watertight membrane (e.g., plastic food wrap), which remains overnight.

All fungal therapy must be prolonged, often for a year or longer. This is likely due to the resistance of fungal spores to any medicine and the rapid reestablishment of colonization should therapy be ended too

soon. All the spores must have been shed or have germinated and been killed by the action of the antifungal and the body's natural defense system before the colonization is truly ended.

IX. Conclusion

The best treatment for health problems arising from exposure to high fungal levels is prevention. A key prerequisite to prevention is education. Information about the nature of fungi, their presence in foods, their rapid proliferation after water intrusion in homes, workplaces, and schools, and their potential for health effects must be made easily available to the general public. The Internet has already provided such information to millions who use computers. Insurance companies are excluding mold damage from the coverage provided in homeowner policies, and this may alert the homeowner to the danger and to his/her responsibility to move rapidly to minimize the effects of water leaks. Reports in the media of litigation by celebrities experiencing fungal illness also helps increase public awareness of the problem. Public health service organizations have to date been more concerned to quell the public's concern about mold problems by suggesting that it is not an important issue. This is a disservice. It would be far better to acknowledge the potential health effects of mold exposure along with suggestions for controlling mold levels in homes, workplaces, and schools.

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