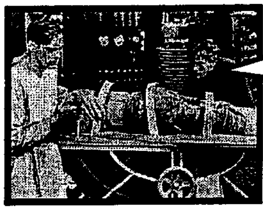
BRAVE NEW WORLD



FACT
or
FICTION?

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"Doctors are men who prescribe medicine of which they know little, to cure diseases of which they know less, in human beings of which they know nothing."

-Voltaire-
(1694 - 1778)

Fungi – Friend or Foe?

- The air we breathe is essential for life, yet it has been implicated as a source of disease-causing microorganisms.
- In fact, over 50% of the indoor air-quality cases investigated by NIOSH concern microbial contamination.
- Despite a paucity of data, fungi like *Stachybotrys chartarum* have been implicated as the cause of lung bleeding, developmental delay, neurotoxicity and a host of vague, nonspecific symptoms.

There Are Fungus Among Us

- The fungi that can affect indoor air quality are small, multi-cellular organisms that form branched hyphae.
- Interwoven hyphae form mycelium – and the myceloid fungi most commonly found indoors are called "molds".
- An open window or door, our clothing and skin are all that is needed for molds to enter our homes and work places.

"The fact that a mold is growing in a home is not good evidence for exposure of any *kind, and* certainly not evidence of danger".

H.A.Bruge, PhD
Harvard School of Public Health
(Ann Allergy Asthma Immunol 2001;87(suppl):52-56).

Fungi / Mold – Feed Me

- To grow and proliferate indoors fungi need a substrate – like wood, gypsum or other high-cellulose containing material...and water.
- Typical molds found in homes and workplaces include *Penicillium*, *Aspirgillus*, *Stachybotrys*, *Fusarium* and *Trichoderma*.
- These are also readily identified in nature, in the soil, air and in agricultural as well as urban areas. These are ubiquitous organisms.

Call a Doctor,...Maybe.

- Certain species of fungi can cause infectious diseases in humans, but this is very rare- and usually in immunosuppressed hosts.
- Some allergic symptoms, like rhinitis or asthma have been thought to be exacerbated by molds, but there is little evidence of much more than that and none linking it to causing even new-onset asthma!
- Very rarely, susceptible hosts can develop "hypersensitivity pneumonitis" after HEAVY and REPEATED exposure to some fungi... but even this is an unusual diagnosis to make.

The Fungi "Fear Factor"?

- Some fungi produce mycotoxins – which are natural organic compounds that can irritate the skin and mucosa with inhalation.
- Molds can also produce volatile organic compounds – such as alcohols and ketones – during their growth cycle.
- All fungi likely produce allergic substances – but only a few of the hundreds of thousands of these have been tested for allergenicity. We simply do not know much about the majority of molds out there!

Common Things Happen Commonly

- Allergies to common fungi are common.
- As many as 10% of the entire population and at least 40% of known asthmatics are thought to be fungal-sensitive.
- However, systemic health effects – such as headaches, fevers, fatigue, cognitive and neuropsychological effects, GI sx's and joint pains have NOT been well documented and their relationship to mold exposure is not clearly established. The alleged long-term effects of molds are also NOT well established.

But It Must Be Why I'm Sick!

- There are NO specific lab tests, physical findings or pathognomonic results that can clearly associate acute exposure to a given fungus with medical symptoms or an illness.
- In fact, in a recent study in Finland of children residing in a school identified as having mold and moisture problems, there was NO DIFFERENCE in mold-specific IgG or IgE antibodies, or skin prick tests between those children with asthma, wheezing and cough symptoms in the "moisture problem school" compared with those children at a "healthy" school.

(T.M. Taskinen et al Allergy 2002;57:9-16)

Mycotoxins or Yours?

- Many fungi produce mycotoxins – which are the bi-products of food metabolism.
- They are "secondary metabolites" since they do not provide nourishment or any apparent physiologic function for the fungus.
- At this time NO HUMAN STUDY has been able to unequivocally document a connection between inhalation of mycotoxins and disease, NONE.
- In fact, the overwhelming majority of info re the health effects of these toxins are from either animal or rare human ingestions.

"People have become concerned about the health effects of mycotoxins out of proportion to currently estimated risk".

H.A.Bruge, PhD
Harvard School of Public Health
(Ann Allergy Asthma Immunol 2001;87(suppl):52-56).

Logical Thinking...Prevails?

- Symptoms caused by exposure to mold should disappear once exposure ceases.
- This association needs to be established to help assess if exposure to molds is more likely linked to health problems.
- Unfortunately, it is unclear if there are thresholds for exposure above which ill health effects can be seen.
- There are simply NO STANDARDS to define levels of mold exposure that are "safe" or "unsafe". NONE.

How Does It Get Ya?

- The association between moisture problems in buildings, mold growth and respiratory symptoms have been reported in several epidemiological studies.
- However, the mechanisms by which this occurs remains unclear.
- Exposure is one of the "missing links" between the presence of fungi and human disease.
- How a common organism that lives all around us enters our bodies and causes a specific symptom or disease is unknown.

How Much is Too Much?

- To cause disease, fungi must produce toxins, transfer and release them as well as distribute them within the body in amounts sufficient to cause medical symptoms.
- Unfortunately, there are NO good guidelines as to the amount of fungal growth that is likely to cause an unsafe exposure,...NONE.
- Additionally, the amounts of toxins produced by a fungus vary according to the species, genetic makeup, time growing, food and water availability, temperature et al.
- In fact, there are an enormous number of variables, including host effects that cannot be readily and reliably duplicated in lab animals or culture plates, making much of this work irrelevant.

Stachybotrys Among Us

- *S. chartarum* is one of the many common fungi that live with us daily.
- It is a potentially important contaminant of agricultural produce – found in soil, hay, straw, cereal grains, rice fields and combine dust byproducts.
- *S. chartarum* spores have been found on a variety of indoor building materials – especially organic substrates rich in cellulose, such as foam insulation, fiberboard, gypsum board, carpets and wall coverings. It requires ongoing moisture to thrive and exist.
- Overwhelmingly, *Stachybotrys* is accompanied by many other genera of fungi, and it is usually not the dominant one.

You're Going Where?

- Although some fungi like *Penicillium* and *Aspirgillus* form spores that are readily airborne – *Stachybotrys* spores require mechanical disturbance and are rarely found in the outdoor or indoor air. They are relatively large *in size and* "sticky".
- With *S. chartarum*, very few spores are typically found – even in heavily effected spaces.
- In the Cleveland, OH homes implicated to be over-run with "Killer Black Mold" that allegedly caused dozens of cases of the rare, Idiopathic Pulmonary Hemosiderosis (IPH), spore counts were nearly undetectable (<10 spores/cubic meter of air).

IPH INTRODUCTION

- Idiopathic Pulmonary Hemosiderosis (IPH) is a poorly understood and seemingly rare disorder.
- The yearly incidence has been estimated to be as low as 9.24 cases per million children, in Sweden.
- Only <u>five cases</u> were reported in Scandinavia, for example, during a period of over twenty years.

(ACTA Paediatr Scand 1979 ; 68:913 and 1984 ; 73:584)

IPH CLINICAL PRESENTATION

- Children typically present with very nonspecific symptoms, including cough, wheeze and shortness of breath.
- There is often iron deficiency anemia.
- Children may have overt bleeding from their nose or mouth, or none at all.
- There needs to be evidence of bleeding into the lungs or blood below the vocal cords, to soil the lower airways.

CASE DEFINITION - IPH

- There is presently NO clear, concise and consistent case definition for IPH.
- This is the fundamental problem when trying to report an alleged "outbreak" or case series.
- The rare case reports fail to specify a constellation of discreet clinical histologic and laboratory findings, to better define this disease entity.

DEFINITION: IPH

- 'Idiopathic' denotes no identifiable cause or associated medical illness.
- It is a nonspecific pathologic condition referring to bleeding of any source or type into the lung.
- Blood is engulfed by macrophage and broken down into hemosiderin.
- Thus, there will be hemosiderin-laden macrophage floating freely in bronchoalveolar lavage fluid (BALF) and residing in lung tissue.

HISTOLOGICALLY: IPH

- Lung tissue will show evidence of progressive filling of the alveoli with hemosiderin-laden macrophage.
- There is often interstitial and alveolar fibrosis, with minimal evidence of inflammation.
- Arterioles may have siderin impregnation and fractured elastic laminae, but this is NOT a consistent finding.
- Most importantly – there are NO specific nor pathognomonic findings using light or electron microscopy.

THE POINT – IN IPH

- The source of blood is thought to be from the lung itself, however, the lower airways will invoke their limited repertoire of responses to blood-irrespective of its source.
- The lung doesn't know or care where the blood came from or how it got there, it just deals with it!!
- This makes it difficult to clarify the pathophysiology of IPH.

CLINICAL PRESENTATION - IPH

- Most often infants and young children present with:
  - onset of cough, shortness of breath and wheezing.
  - Pallor, cyanosis and diminished breath sounds or crackles over the areas of bleeding, to auscultation.
  - Transient infiltrates are often seen on chest X-ray.
  - Iron deficiency anemia has been reported in IPH.
  - NO consistent pattern of hematologic, serologic or immunologic findings have been noted.

CLINICAL COURSE - IPH

- Highly variable clinical course and outcomes
- There can be only one bleeding event, or multiple episodes over months to years.
- Years can pass with seemingly no overt symptoms or decompensations, making the efficacy of therapies hard to interpret and quantify. There are no controlled studies.
- The prognosis varies from complete resolution to sudden death from hemoptysis or end-stage lung disease.
- Pulmonary fibrosis with disabling lung disease is not uncommon following repeated bouts of bleeding.

CASE DEFINITION – THE POINT

- Without a clear case definition of IPH it is foolhardy to think that any consensus can emerge for the etiology, or proposed combination of host & environmental conditions necessary for emergence of this disease state.

PULMONARY HEMORRHAGE / HEMOSIDEROSIS AMONG INFANTS – CLEVELAND, OH 1993-1996

- Geographic cluster of 10 cases of pulmonary hemorrhage/hemosiderosis.
- The diagnosis was purportedly made by "demonstrating alveolar hemosiderin-laden macrophage in biopsy specimens or in BAL 3 to 6 weeks after the initial hemorrhage."
- Unfortunately, it was never reported if each of these infants actually underwent this type of evaluation or not!! And what criteria were used to make this decision.

IPH – CLEVELAND, OH 1993-1996

- It was never clarified:
  - How many of these infants underwent bronchoscopy or biopsy at the time of "evaluation" to make this dx!!
  - What preceding procedures the premature infants in this case series underwent (i.e. intubation, mechanical ventilation, NGT) which could account for previous and unrelated lung injury and bleeding, complicating the diagnosis.
  - In fact, these investigators never attempted to define what criteria were met by each of these infants to be diagnosed with IPH at all.
  - There were NO clear diagnostic criteria to meet, which was a fatal flaw.

(Arch Pediatr Adolesc Med 1998 ; 152:757, Pediatrics 1997 ; 99:1)

IPH - CLEVELAND, OH 1993-1996

- The terms "acute pulmonary hemorrhage", "pulmonary hemorrhage of infancy", and "idiopathic pulmonary hemorrhage and hemosiderosis" are used interchangeably despite the author's contention that, "pulmonary hemosiderosis is the result of chronic recurrent pulmonary hemorrhage". Yet, HALF of these 10 cases had only 1 overt bleed!!
- Of 21 episodes of acute pulmonary bleeding reported in the 10 cases, half (5/10) only had one documented episode of bleeding, thus only half of these infants meet their rudimentary definition.

(Arch Pediatr Adolesc Med 1998 ; 152:757, Pediatrics 1997 ; 99:1)

IPH - CLEVELAND, OH 1993-1996 "Rapidly Growing Lungs"

- The investigators proposed that infants are more vulnerable to lung injury by toxogenic fungi because they have "rapidly growing lungs", but there is NO medical basis for this in humans.
- In fact, older adults with larger airways and greater surface area generally have more rigid lungs that heal less effectively and sustain less reversible injury than their infant counterparts.
- Why then do we not see pulmonary hemorrhage and similar symptoms in cohabitating adults?

IPH - CLEVELAND, OH 1993-1996

- The timing of the evaluations of these 10 children and their homes is critical in the meaningfulness of the data collected. There appears to have been little or NO consistency in data collection.
- The depth and extent of these medical and environmental evaluations also remains obscure. This is a rare disorder with limited diagnostic criteria and a diagnosis of exclusion, yet virtually all of the other probable causative factors in these infants were ignored or went unreported.
- What testing was done was not reported in the manuscripts nor at the CDC at the time of review. This was another error.

IPH – CLEVELAND, OH 1993 - 1996
Unexplained Hemolysis

- Blood smears were suggestive of a "micro-angiopathic hemolytic process", which is unusual and unique, yet NO attempt was made to incorporate this into the case definition or use it to explain how it might explain the role of toxins or other exposures?
- Is this indicative of another, unique causative factor such as a pesticide or narcotic exposure ?
- Can the hemolysis help explain the respiratory tract bleeding? No one knows.

(Arch Pediatr Adolesc Med 1998 ; 152:757, Pediatrics 1997 ; 99:1)

IPH – CLEVELAND, OH 1993 – 1996
Other Possible Causes

- The original investigators had suspected child abuse, pesticides or other inhalation irritants as causative factors, yet:
  - Only half (5/10) of these infants had urine samples studied for organophosphates, volatile organic compounds, tobacco (cotinine) and cocaine metabolites!
  - Of note: each of these have been previously implicated as causative for diffuse alveolar injury and pulmonary hemorrhage!
  - Additionally, half of the case homes freely admitted to elicit drug use, including inhalation "crack" cocaine!
  - This was another error and missed opportunity!

(Chest 1998 ; 93(2):427, Ann Intern Med 1993 ; 119:226, JAMA 1992 ; 267(8):1044, Epidem Rev 1994 ; 16(2):315)

IPH - CLEVELAND, OH 1993-1996
The Main Problems Identified:

- NO case definition. Thus, everything and anyone can be easily fit into this case series!
- NO consistency in history nor physical exams to rule out other probable explanations.
- No consideration to other risk factors such as drug use, prematurity, chemical exposures or infanticide.
- Unblinded data collection, biased sampling and flawed statistical analysis.
- Ignoring unique and potentially important characteristics of this "case series" such as their young age, multiple environmental exposures and unusual hemolysis.

CLEVELAND, OH 1993-1996

- There is simply not enough information available to comfortably attribute cause and effect of specific mycotoxic fungi in indoor environments and pulmonary hemorrhage in children.
- The present "case series" appear to be no more than a group of patients who were found to meet loosely defined and uncircumscribed criteria, rather than meeting the diagnosis of IPH with clearly defined terms and as an exclusion of other, more common medical causes.

(Arch Pediatr Adolesc Med 1998 ; 152:757, Pediatrics 1997 ; 99:1)

Closing Thoughts on IPH

- There was no evaluation of other household members to rule out other common environmental exposures. In fact, no siblings or adults appeared effected? Why not?
- None of these cases have any evidence of colonization, infection, invasion or exposure to *Stachybotrys*.
- In fact, *Stachy* is not even in the respirable range & the mode of airway entry & lung injury remains obscure.
- Lastly why do these cases cluster in poverty ridden urban settings when water damage occurs in many places? Are there risk factors inherent to these dwellings other than mold, such as, inhalation drug use, insecticide use ("roach bombs"), second-hand smoke, nonaccidental trauma and infanticide??

"Killer Mold" on the Run

- Because of their large size, it would be anticipated that what few spores are present would deposit in the upper airway, and likely cause local symptoms...with few making it to the lower lungs. This has not been clearly described in the literature, nor well explained in the cases reported in Cleveland, OH.
- Estimates of the amount of spores and time needed to experience an ill effect have been calculated to be in the range of one billion spores per hour!!
- In fact, based on its' size, low number of spores in the air and lack of supporting evidence...*S. chartarum* is probably less of an exposure and health problem than other fungi. It just has a really bad reputation!

"Killer Mold"....Dead?

- Claims made between *S. chartarum* exposure and IPH or other medical conditions are seriously flawed...
  - There is NO logical pathway for the toxins to cause harm to humans.
  - There is NO explanation of how a sufficient dose enters the lungs to cause bleeding and injury.
  - There were also serious epidemiological flaws in population sampling and analysis done.
  - The investigators also ignored the other environmental factors – such as smoking, which was a greater risk factor with a similar P value, as well as the many other fungi found in much greater levels than *S. chartarum* in these homes!

Relax & Take A Deep Breath

- To date, no case of a human systemic or local infection caused by *Stachybotrys* has been reported and confirmed – even in immunosuppressed hosts!
  - There is NO CASE of confirmed allergy or asthma exclusively attributed to Stachy
  - There is NO CASE of hypersensitivity pneumonitis caused by *Stachy* in the peer reviewed literature.
- There is a clear discrepancy between the public perception and the current evidence concerning the health effects of *Stachy* – especially in home and work settings.
- A critical review of the current published literature DOES NOT establish a clear-cut "cause & effect" relationship to warrant the present medical claims and extreme remediation efforts.

"The current public concern for adverse health effects from inhalation of *Stachybotrys* spores in water-damaged buildings is not supported by published reports in the medical literature".

Abba I Terr, MD

(Ann Allergy Asthma Immunol 2001; 87(suppl): 57-63.)