Molds, Mycotoxins and Public Health

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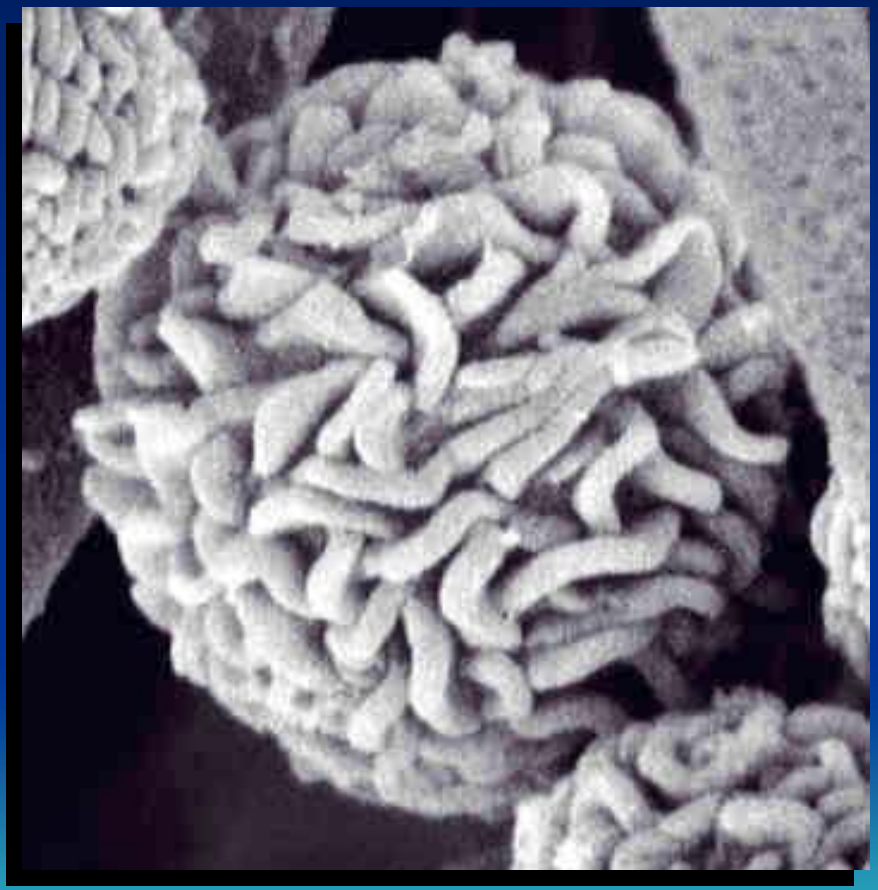


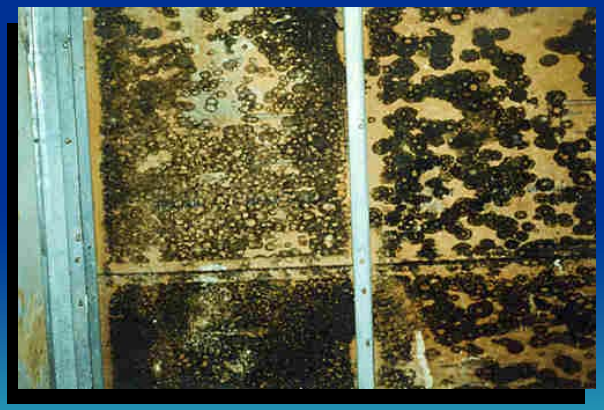
Case Study: Tucson Bank, 1994

- Bank Manager
  - 49 y.o. Married Female
  - Symptoms
    - 18 month hx arthritis (wheelchair bound)
    - General malaise
    - Excessive fatigue
    - Cognitive dysfunction w/ memory loss
    - Difficulty concentrating
    - Multiple other symptoms
- 9–10 Other Employees
  - Similar symptoms
    - Shortness of breath
    - Cognitive problems
    - Periorbital edema
    - Skin rashes limited to exposed skin.
    - Workplace related
    - Worsened on Mondays
    - Improvement on weekends & vacations

Case Study: Tucson Bank, 1994

- Clinical Findings
  - Urticarial & granulomatous skin changes
  - Small airway obstruction & reactivity
  - Immunologic hyper activation & simultaneous suppression
  - Multiple inflammatory symptoms
  - Elevated EBV IgG antibodies
  - Cognitive deficits
- Environmental findings
  - Presence of multiple filamentous molds
  - Pipes leaking in common wall to air handler & bathroom
  - Elevated *Stachybotrys* spore counts detected in:
    - Air and surface
    - Highest on the manager's desktop
    - All employees passed this desk to go to break room

Hidden Fungi



Historical Perspective

- Biblical Warning
  - *If your house be contaminated with plagues, molds, and Leprosy, put the contents in the middle and set it aflame*

    --Leviticus
- *Robigalia- April 25th*
  - *7th to 8th Century BC*
  - *To protect trees & grains from rusts or mildew*
- *Occupational Disease*
  - *Brown Lung Disease*
  - *Farmer's Lung*
  - *Pigeon Breeder's Disease*
  - *Yellow Rice Disease*

Toxic Effects of Mycotoxins in Humans

- Trichothecenes
  - "This family of mycotoxins causes multiorgan effects including emesis and diarrhea, weight loss, nervous disorders, cardiovascular alterations, immunodepression, hemostatic derangements, skin toxicity, decreased reproductive capacity, and bone marrow damage"
    - *Medical Aspects of Chemical and Biological Warfare, Chapter 34: Trichothecene Mycotoxins, 1997*

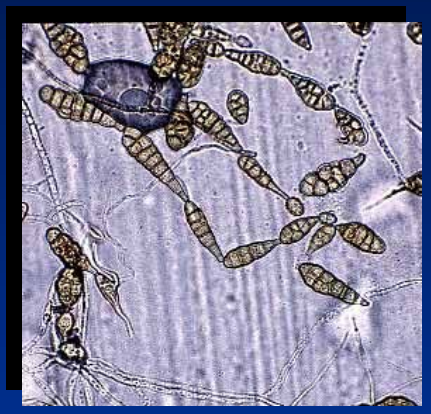
Fungi Producing Trichothecene Toxins

- Fusarium
- Trichothecium
- Myrothecium
- Cephalosporium
- Stachybotrys
- Verticimonosporium
- Cylindrocarpon

Trichothecenes

- Major category of mycotoxins
- 1st case of mycotoxicosis
  - 1932
  - USSR
  - Alimentary toxic aleukia
    - 60% mortality
- Major chemical warfare agent
  - Yellow Rain

Fungi Common in Sick Building Syndrome



Alternaria

Acremonium

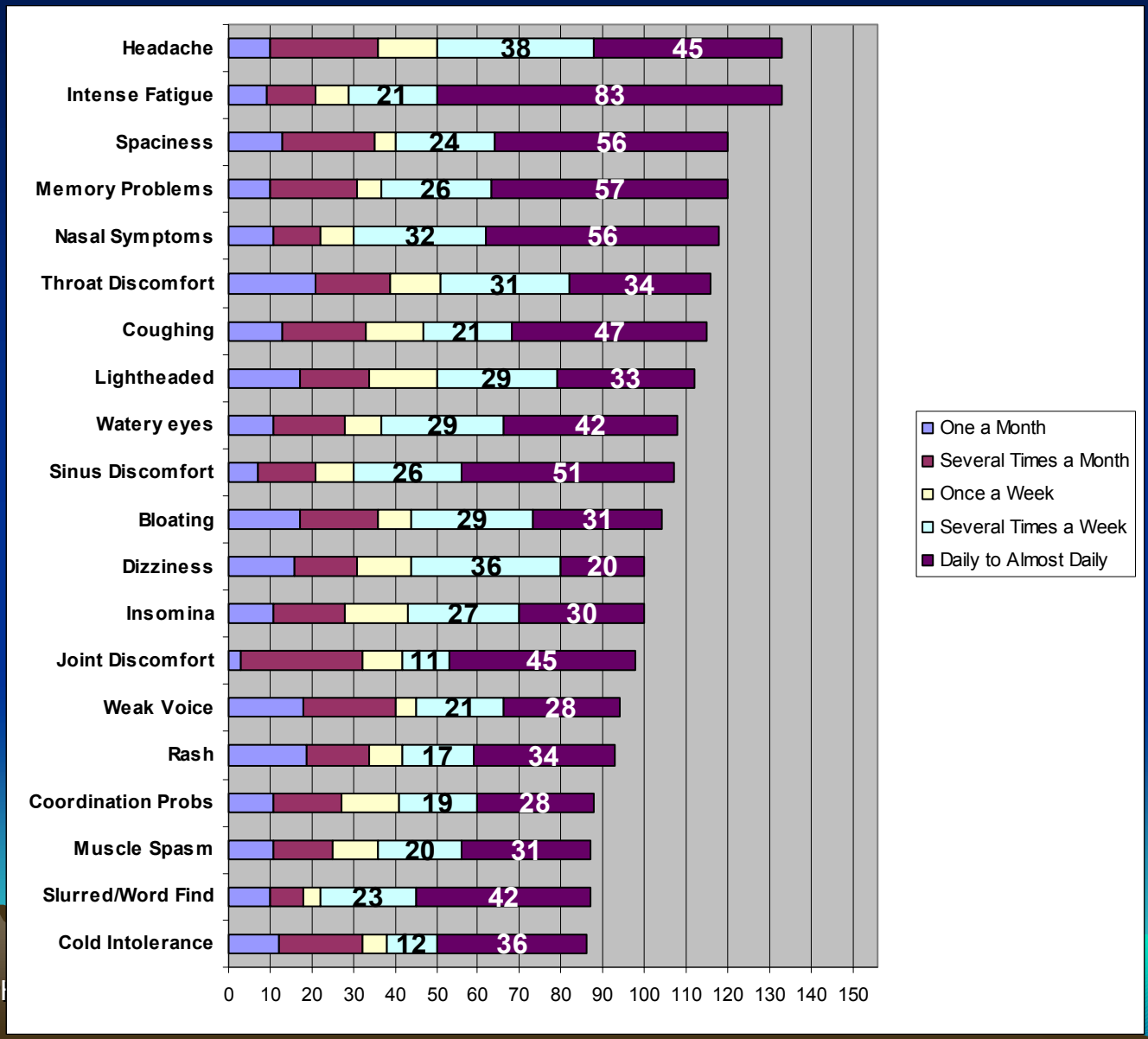
Epicoccum

Trichoderma

Stachybotrys

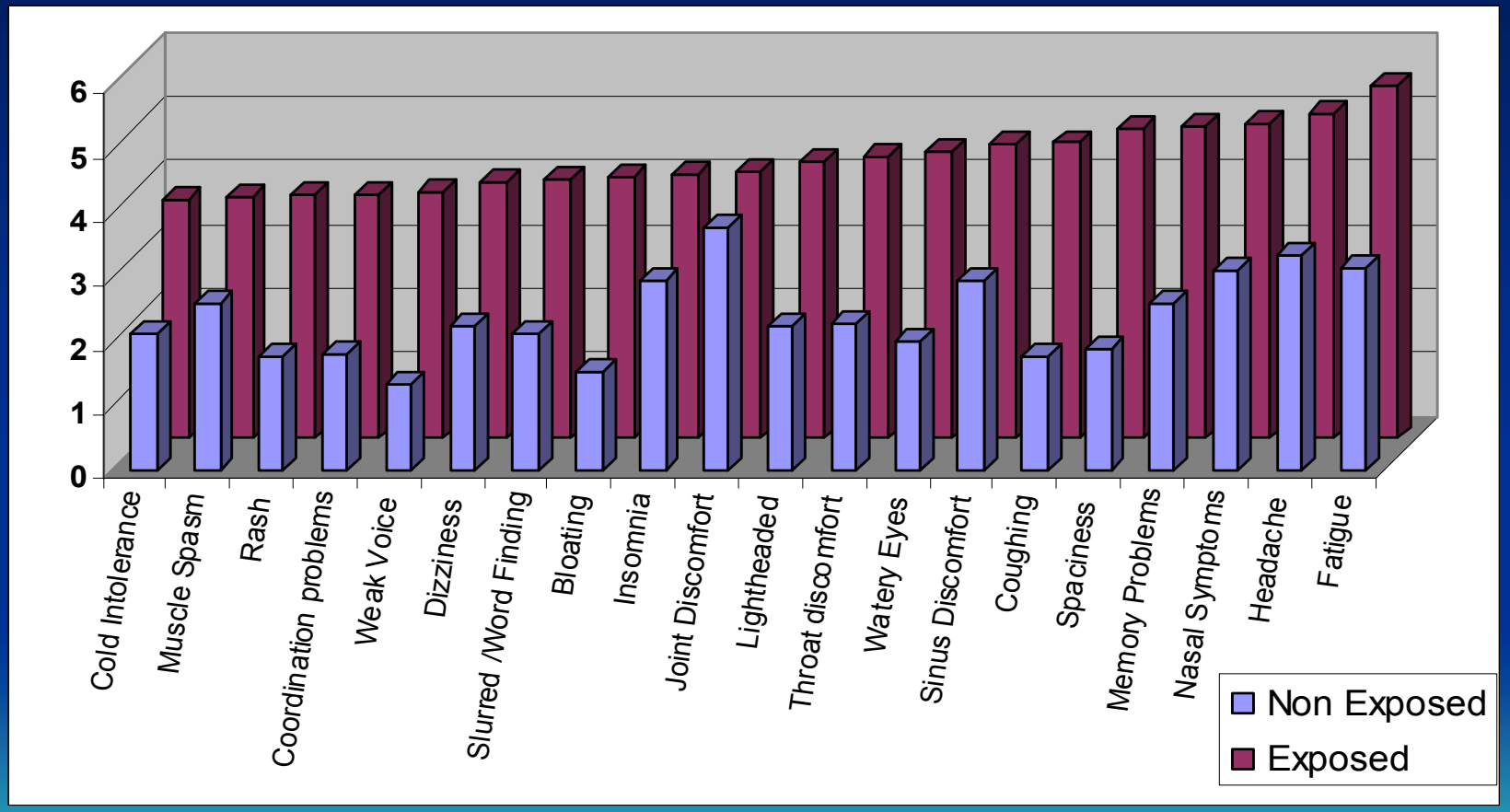
Penicillium

Top Twenty Symptoms (N=195)



Compared Symptom Profiles

156 Exposed Patient's Compared to 28 Referent Patient's Means



Historical Perspective

- Spring 1998
  - CDC MMWR 9 cases hemorrhagic pneumonitis in Infants
    - *Stachybotrys chartarum* found in lungs
  - *Stachybotrys chartarum (atra) present in homes*
  - *In National Survey Ruth Etzel, MD, Ph.D. finds 115 cases of hemosiderosis associated with mold exposure (mortality approx. 15%)*

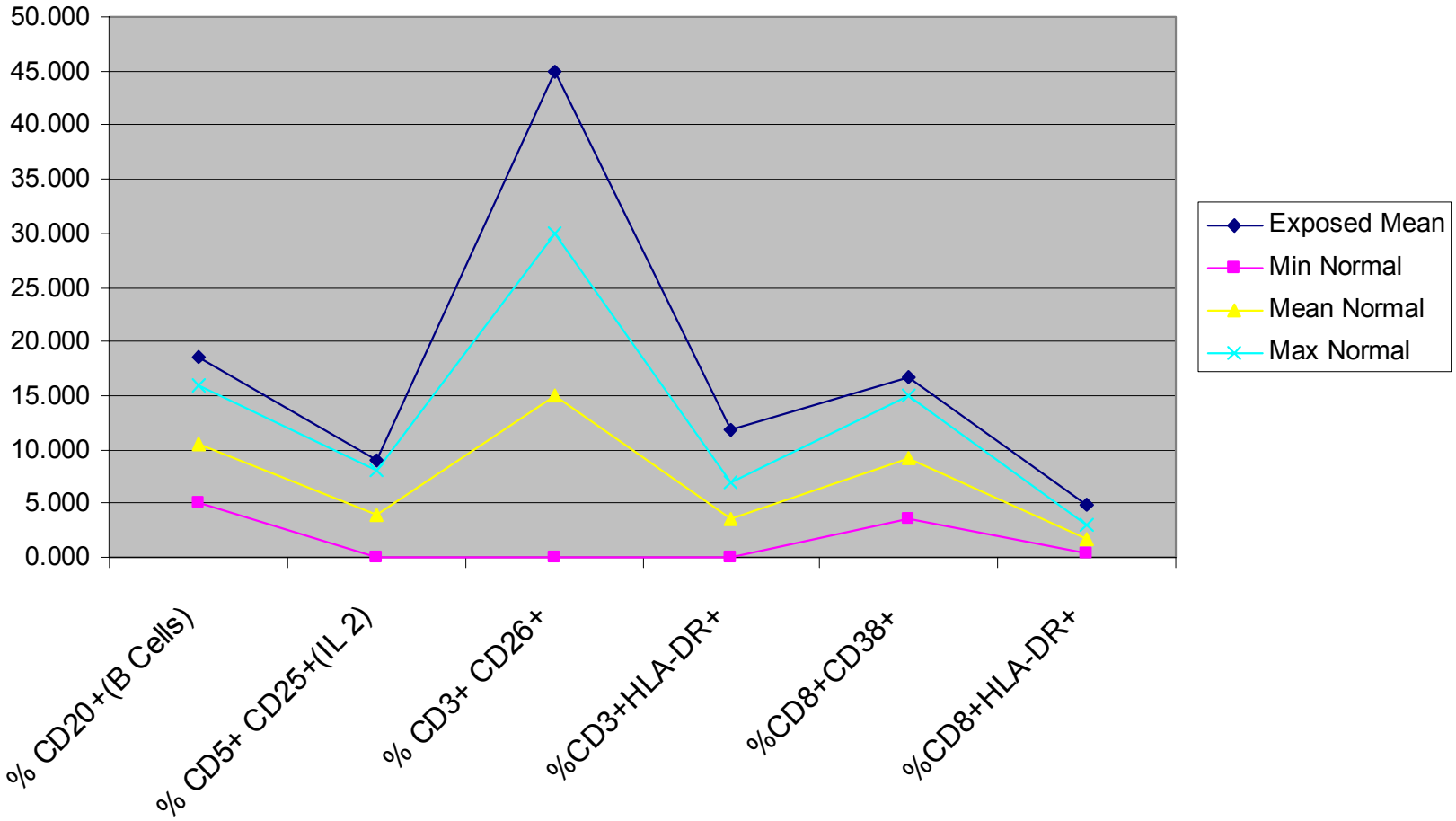
Stachybotrys chartarum

- Isolated from lung of a child with pulmonary hemosiderosis
  - Strain JS5106
  - Stachyrase A
    - New Chymotrypsin-like Serine proteinase
    - Cleaves major protease inhibitors,
    - Several active peptides, and
    - Collagen
    - All above found in the lung
      - *Infection and Immunity, Jan 2002, p 419-423*

Immune Effects

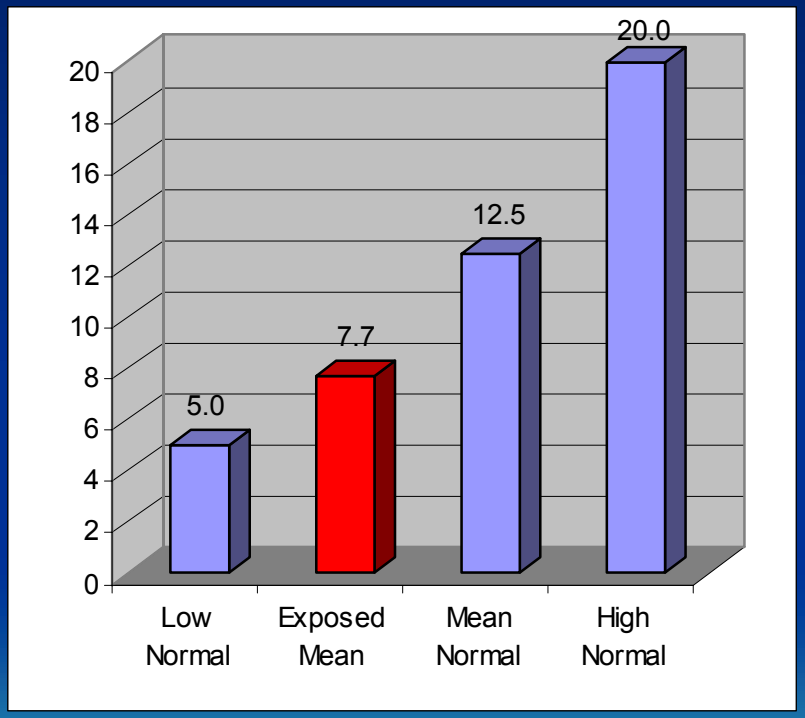
- Increased B-cells
- Excessive T-cell activation
  - CD3+CD26+(TA1) excess
  - CD3+HLA-DR+ excess
- Suppressor cell activation
  - CD8+CD38+ excess
  - CD8+HLA-DR+ excess
  - Increased Interleuken 2 Receptors on T-cells

Immune Activation Effects

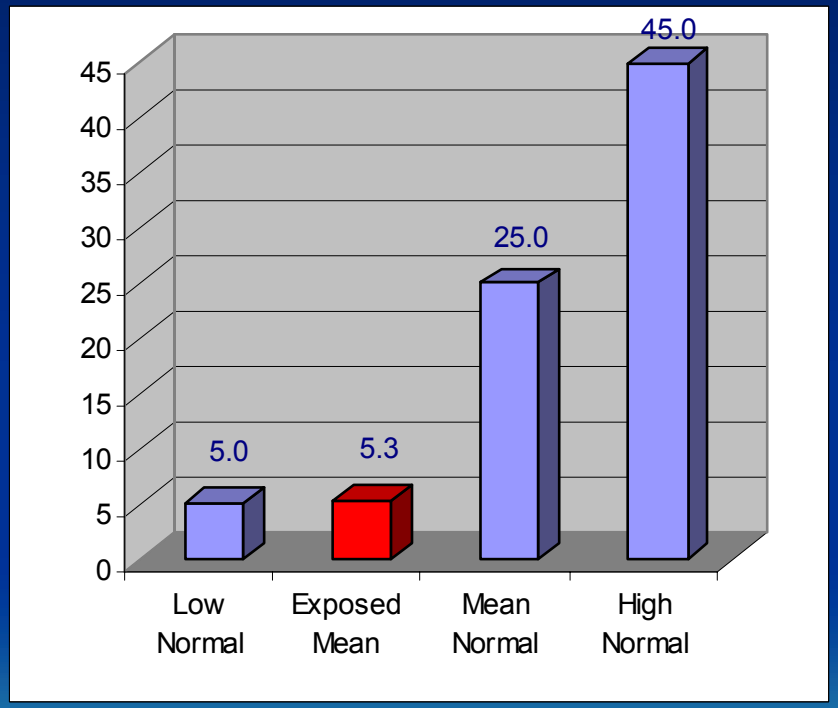


Immune Depression Effects

%CD3-CD16+CD56+ Natural Killer Cells as % Tot Lymph

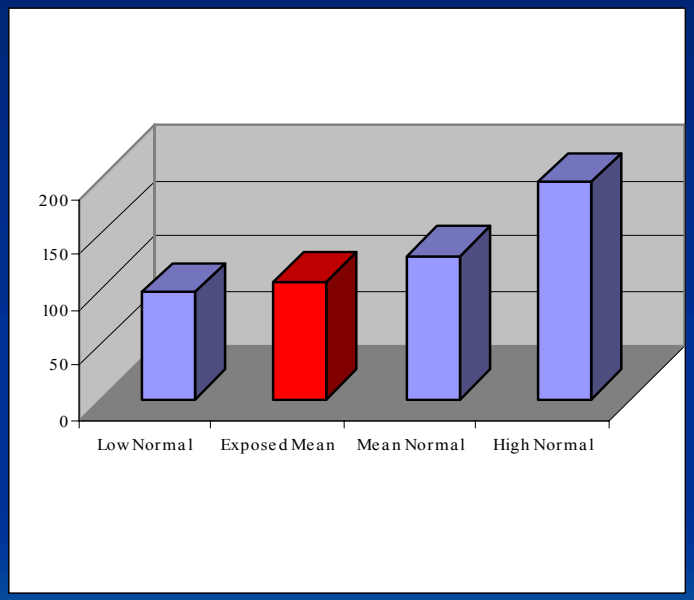


%CD8+CD11b+ Human Leuko Compliment Receptors

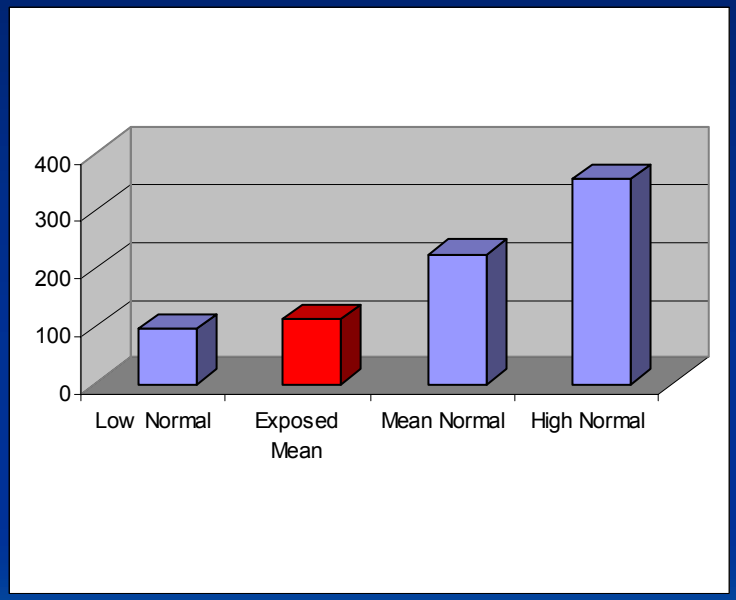


Immune Suppression

Lymph Stimulation by Phytohemagglutinin (PHA)



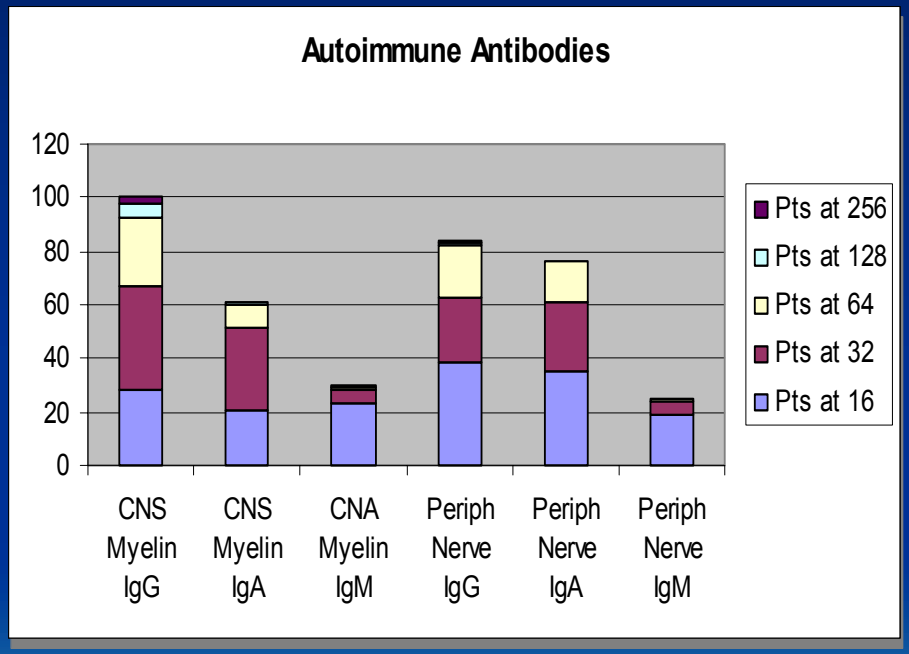
Concanavillin Stimulation

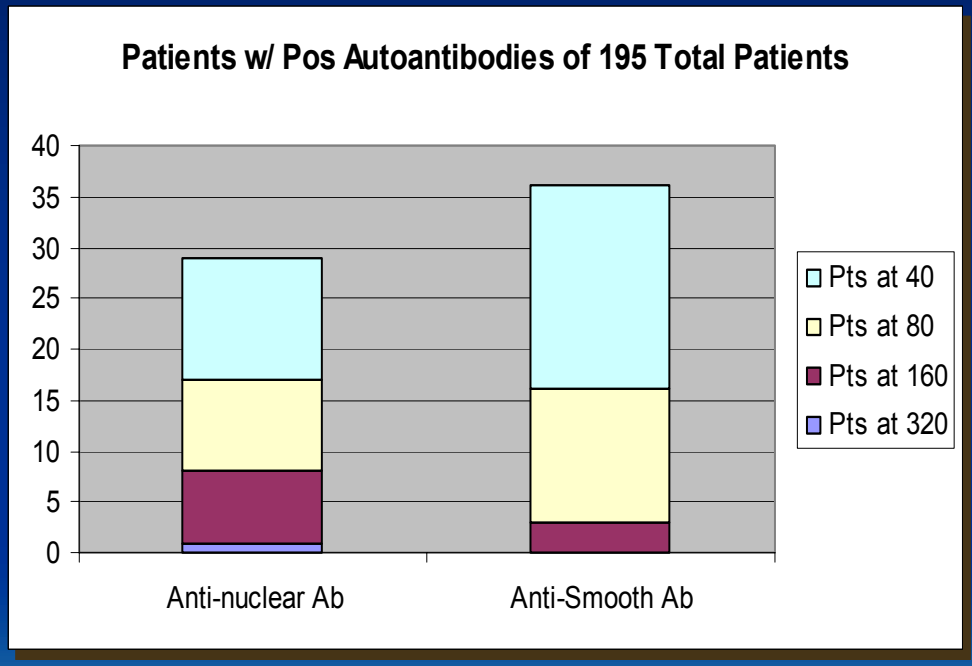


Immune Effects

- Increased markers of autoimmunity
  - Anti CNS myelin antibodies
  - Anti PNS myelin antibodies
  - Anti smooth muscle antibodies
  - Anti nuclear antibodies

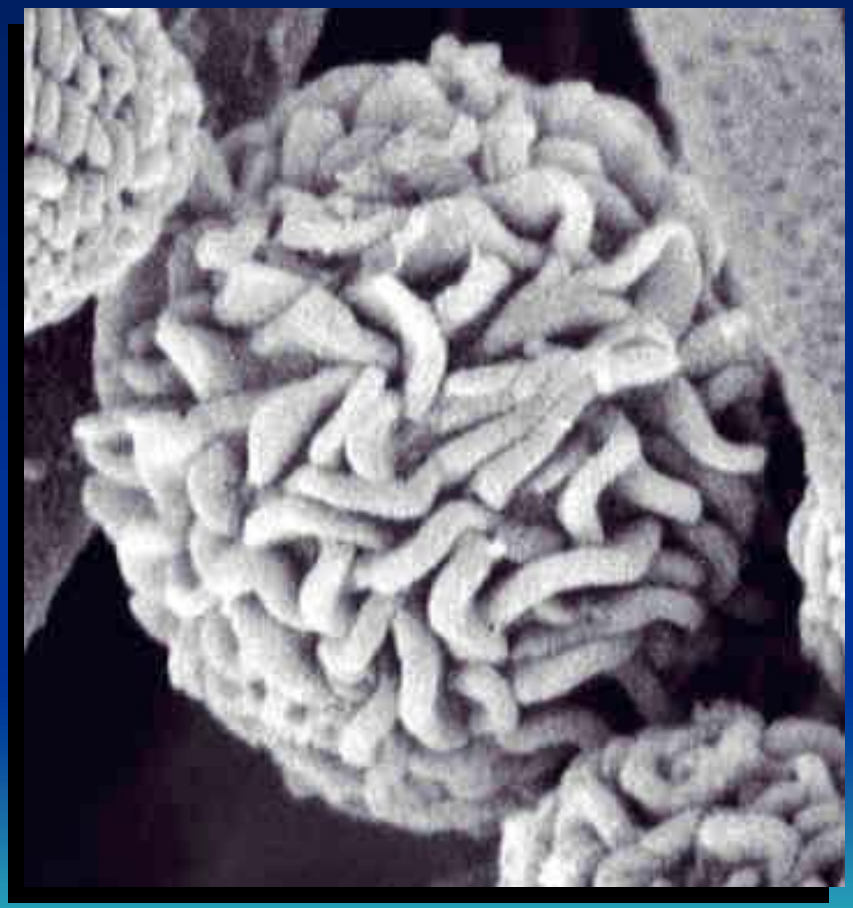
Immune Effects (n=195)



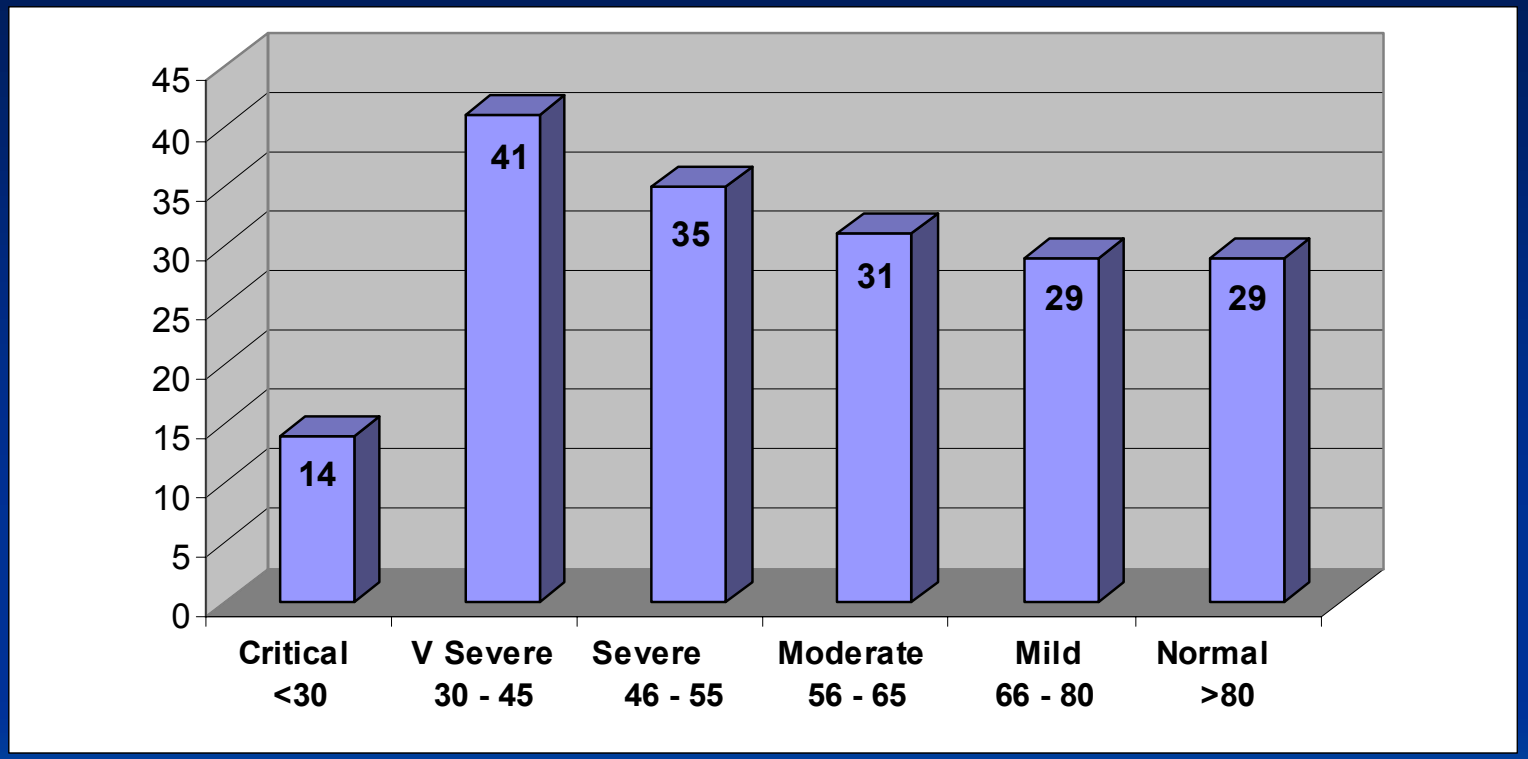


Factors affecting respirability

- Particulate size
  - Greater than 5 microns
    - Non-respirable
    - Except if aspect ratio > 1:3
  - 5 microns to 0.005 micron
    - Considered respirable
    - Reaches alveoli
    - Passive filtration is useless

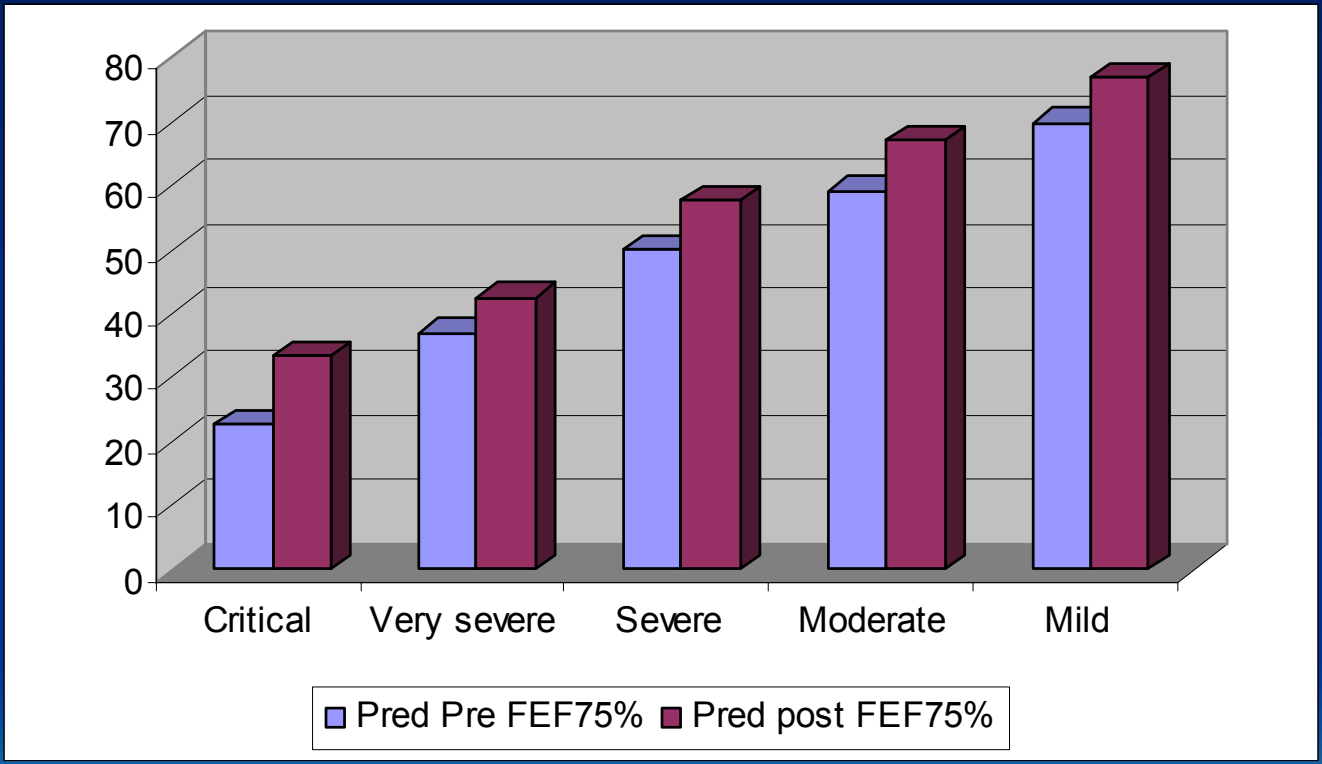


Pulmonary Effects of Spores Smokers and Nonsmokers

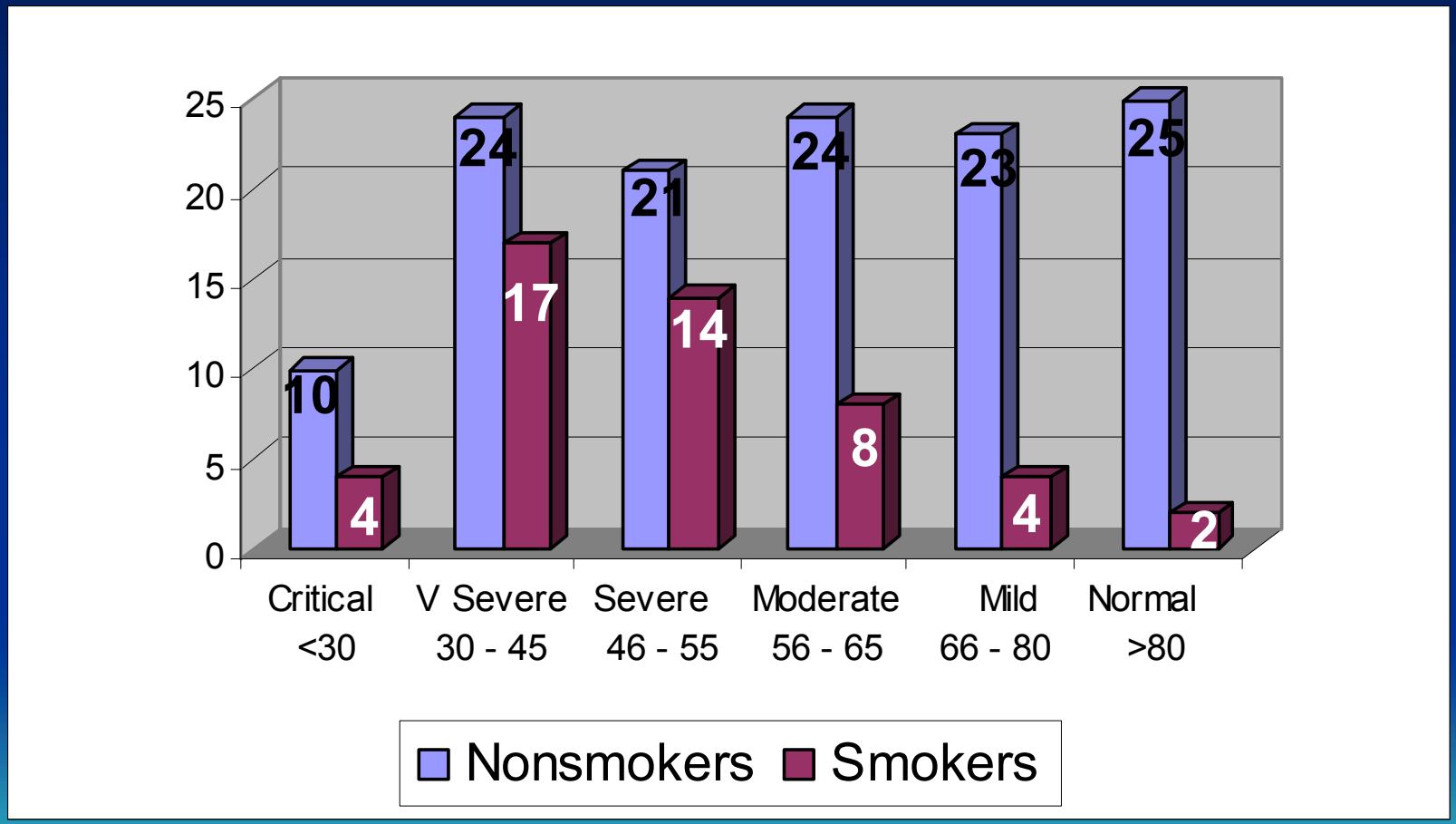


Degree of Small Airway Obstruction Percentage of Predicted FEF 75%

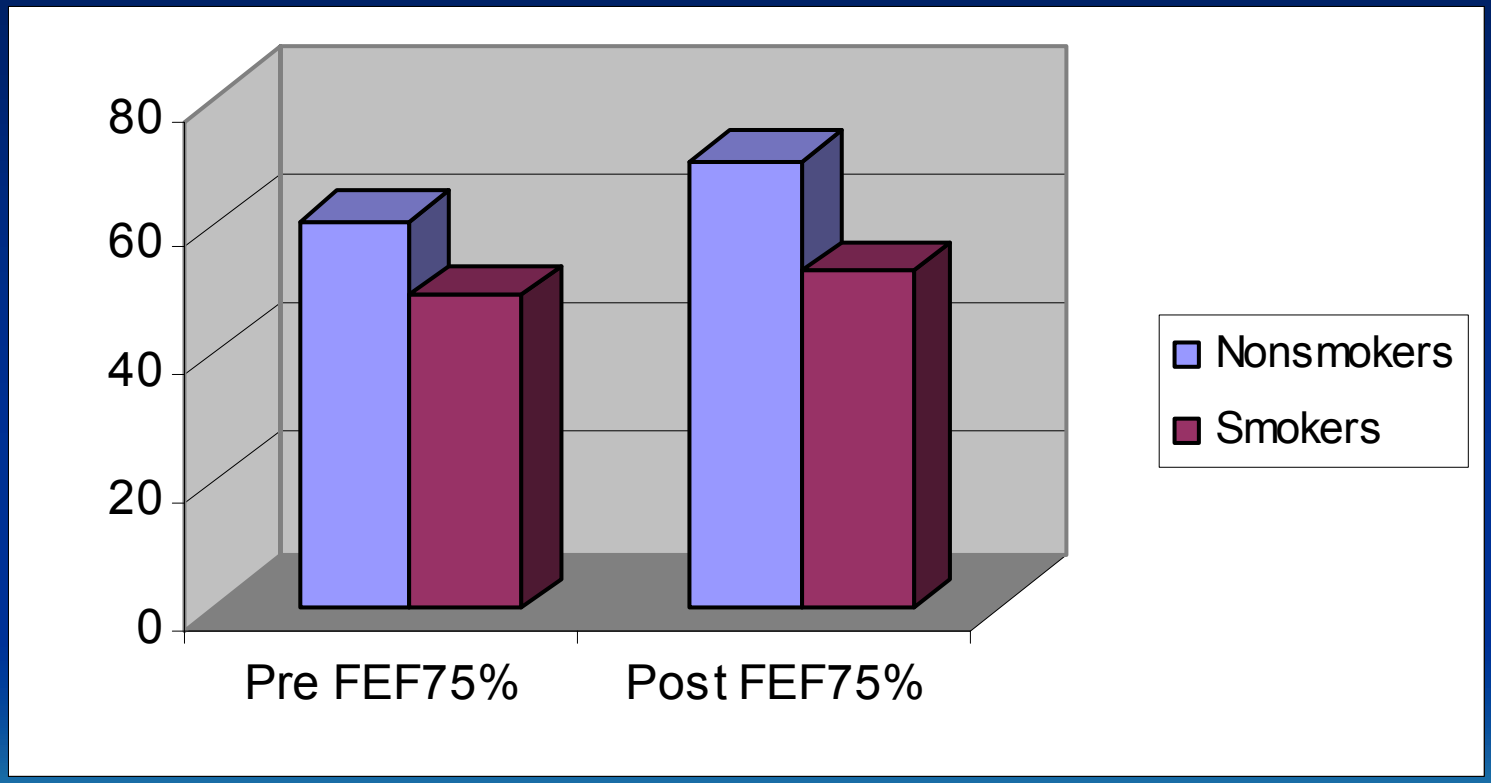
Pre and Post Bronchodilator FEF 75% Combined Smokers and Non-Smokers



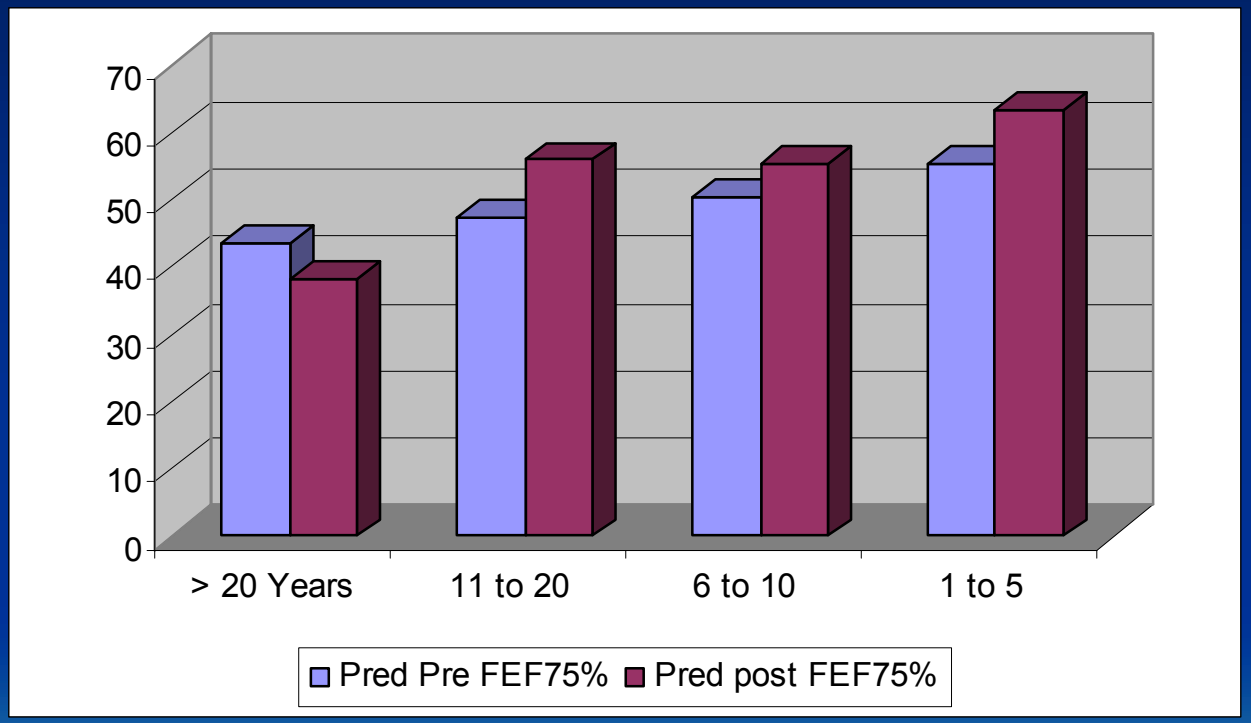
Pre Dilator Degree of Severity Smokers vs. Nonsmokers



Mean Pre and Post FEF 75% Nonsmokers vs. Smokers



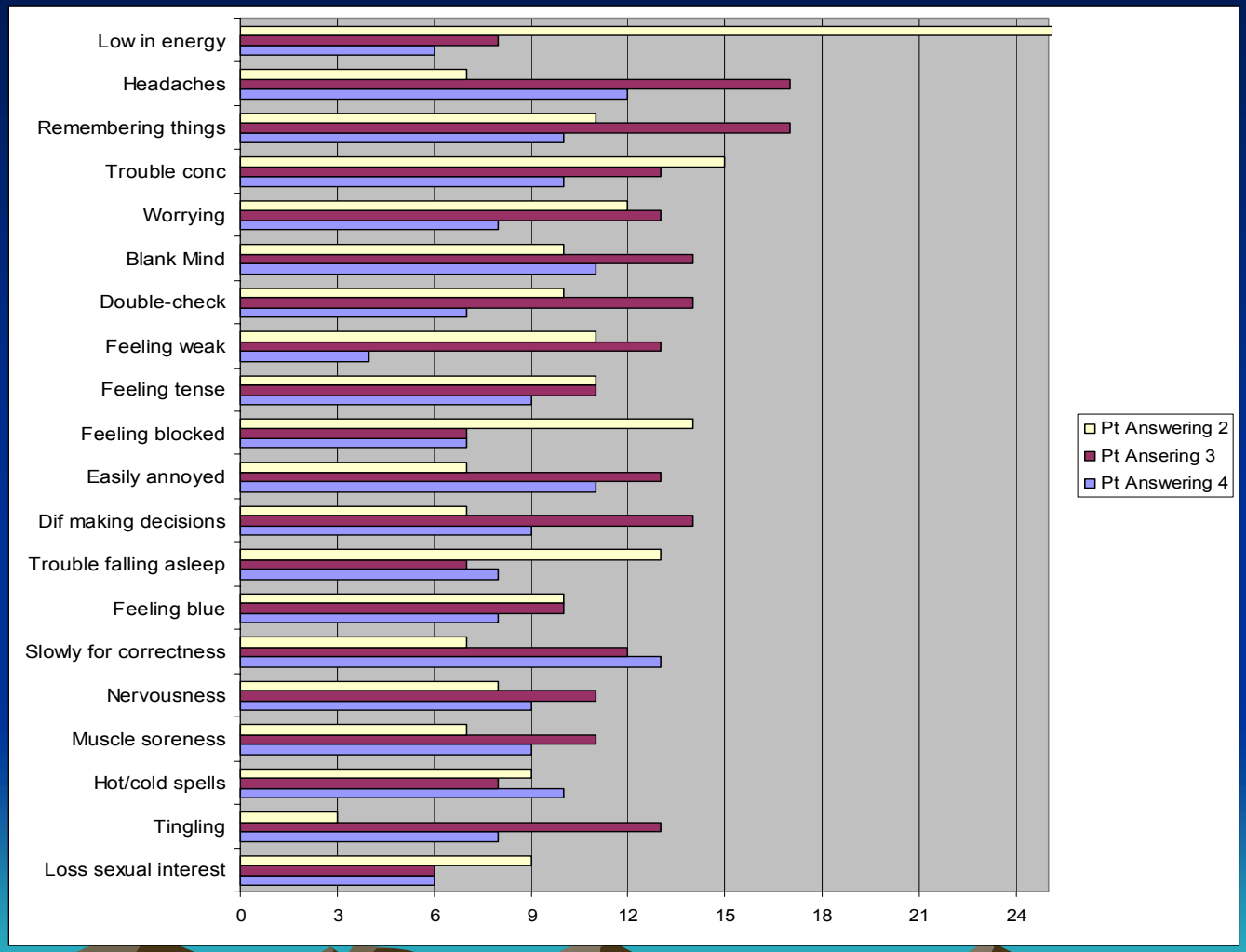
Pre and Post FEF 75% by Smoke Pack Years



Pulmonary Mycotoxicosis

- Pulmonary Nodules
  - Associated with intense chest pain
  - Aspergillus common, but not only cause
  - Presence across fissure line implies “kissing” lesions reflecting exodigestion—secretion of digestive enzymes
  - Antifungals effective, but often induce toxicity (liver, bone marrow, kidneys vulnerable)

Symptom Profiles – Dr. Crago



Kilburn Neurotox Data

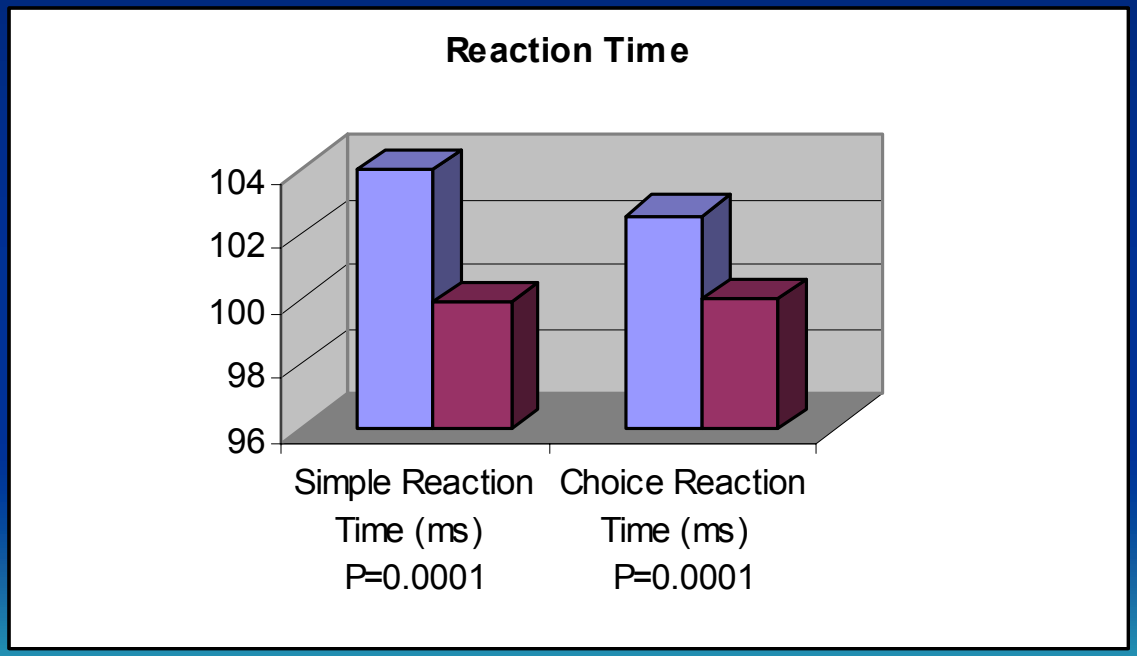
- The following data is Dr. K. Kilburn's analysis of 43 mycotoxin exposed patients and 202 non-exposed referent subjects as precent of predicted (PFTs), means, Standard Deviation (SD), and P values by analysis of variance

Demographic Data

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Age (years)	48.2 +/_ 13.9	46.6 +/- 20.6	0.624
Education (years)	15 +/- 2.6	12.9 +/- 2.3	0.0001

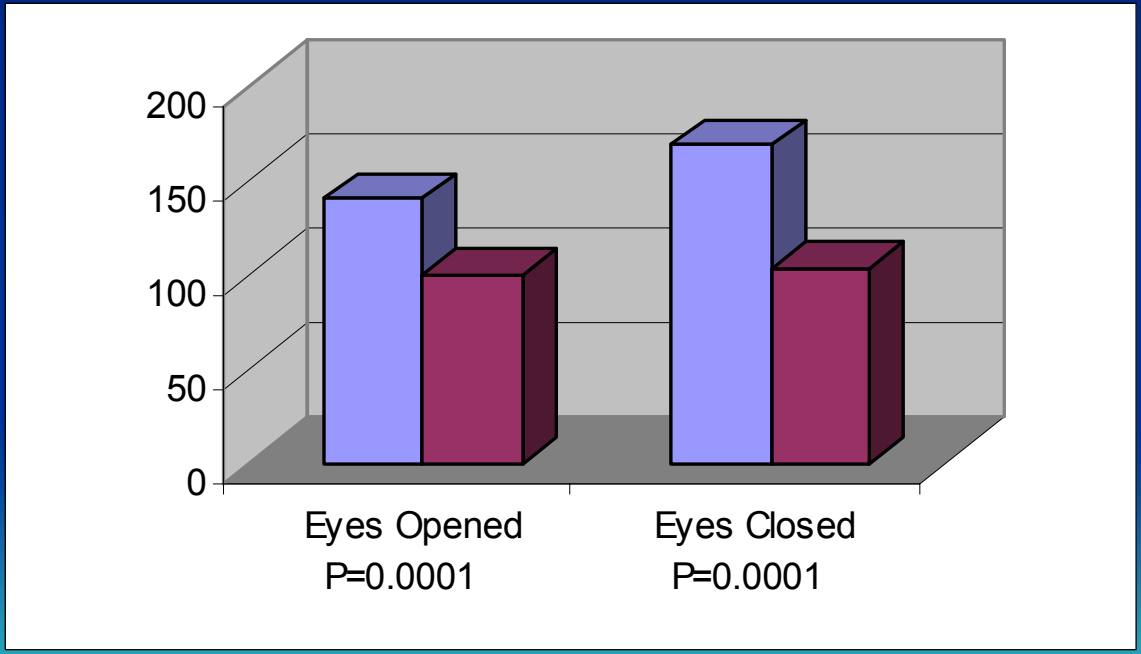
Reaction Times (ms)

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Simple	104.0 +/_ 6.6	99.9 +/- 3.7	0.0001
Choice	102.6 +/- 6.6	100.0 +/- 3.7	0.0001



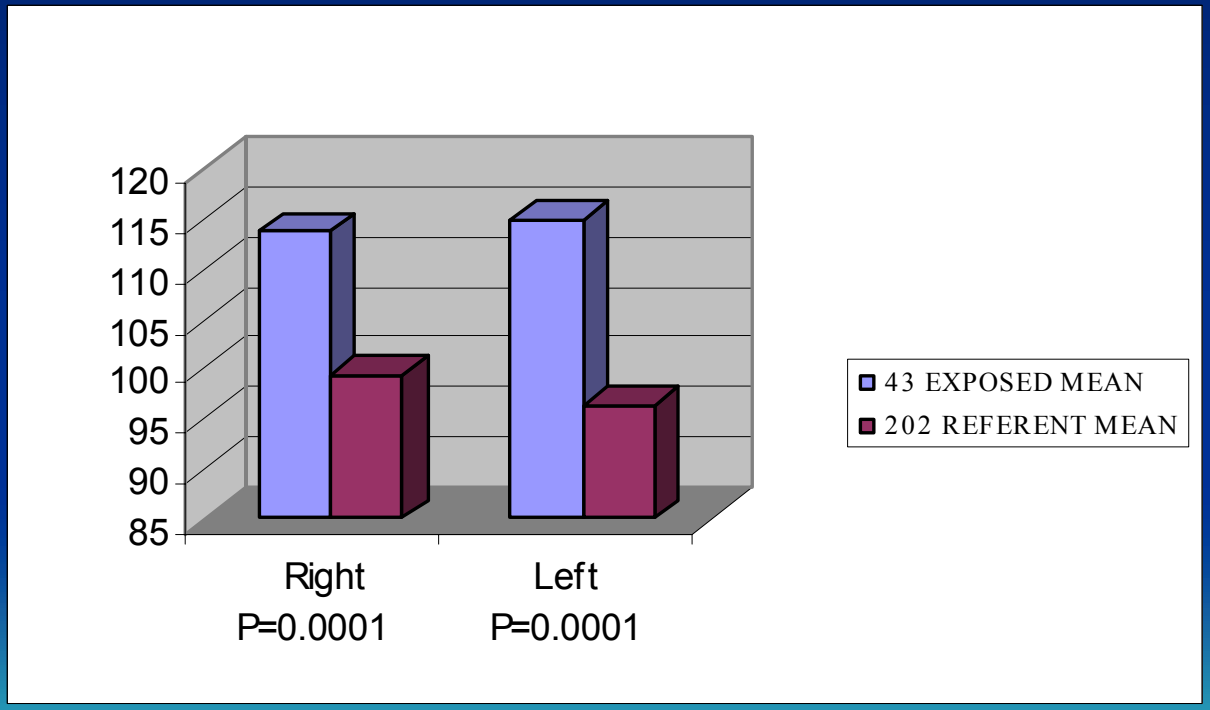
Balance Sway Speed (cm/sec)

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Eyes Opened	140.5 +/_ 49.9	100.2 +/- 2.5	0.0001
Eyes Closed	168.7 +/- 102.7	103.1 +/- 26.7	0.0001



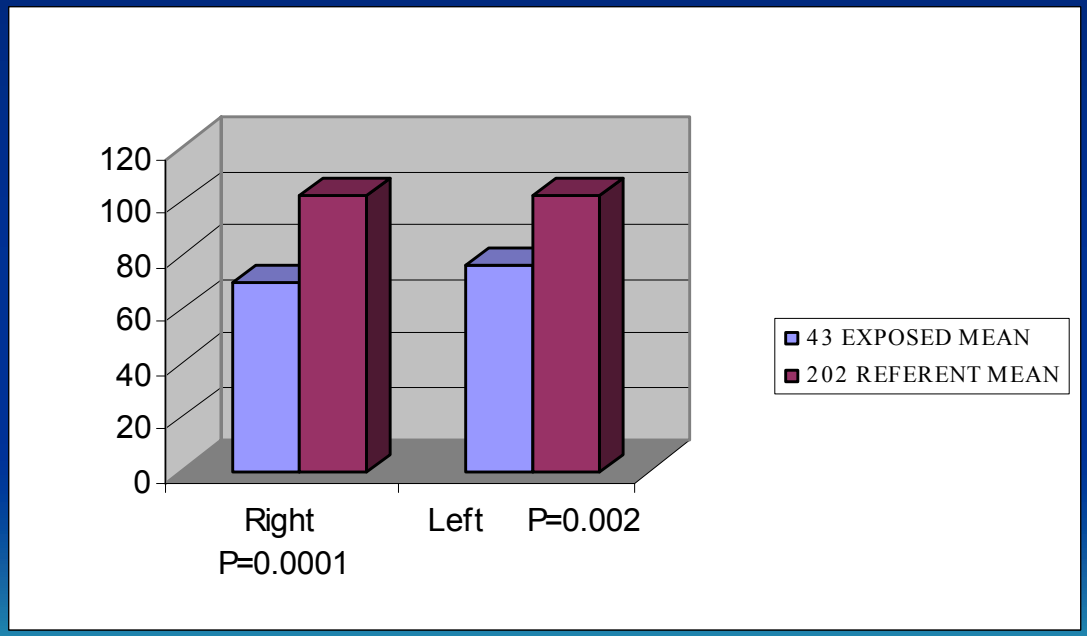
Blinking Reflex Latency R-1 (ms)

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Right	113.9 +/_ 10.8	99.4 +/- 14.6	0.0001
Left	115.1 +/- 11.4	96.4 +/- 13.2	0.0001



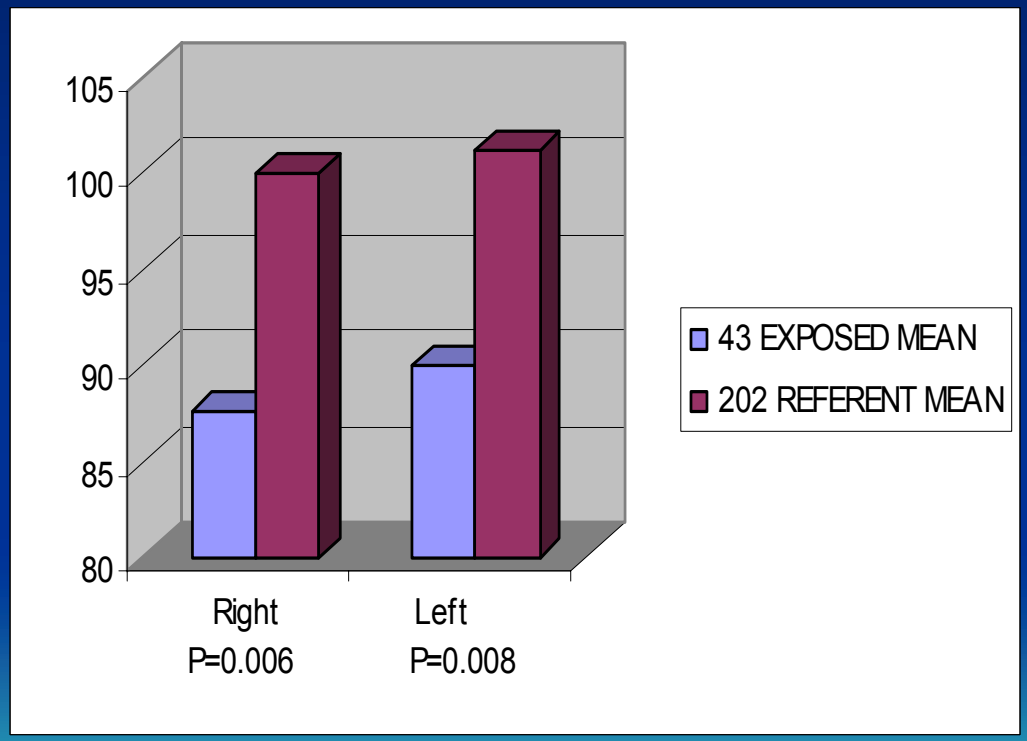
Color Perception Score

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Right	69.6 +/_ 40.8	102.6 +/- 51.1	0.0001
Left	75.8 +/- 48.8	102.6 +/- 51.1	0.002



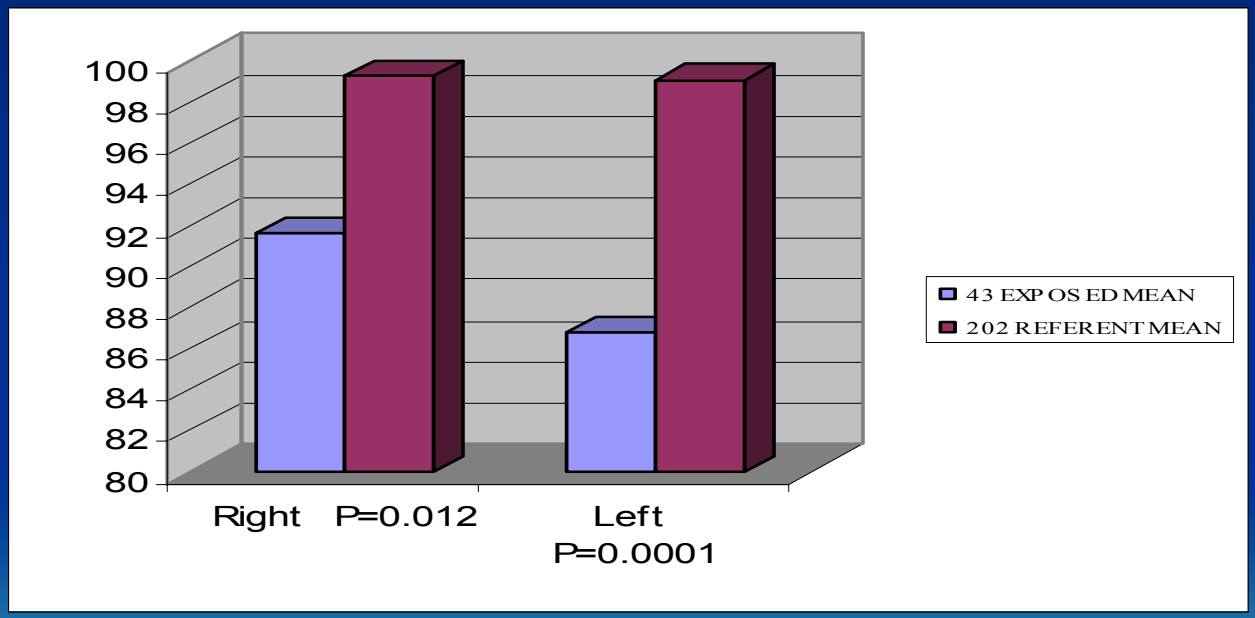
Visual Performance

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Right	87.5 +/_ 23.9	100.0 +/- 22.8	0.006
Left	90.0 +/- 20.9	101.1 +/- 21.7	0.008



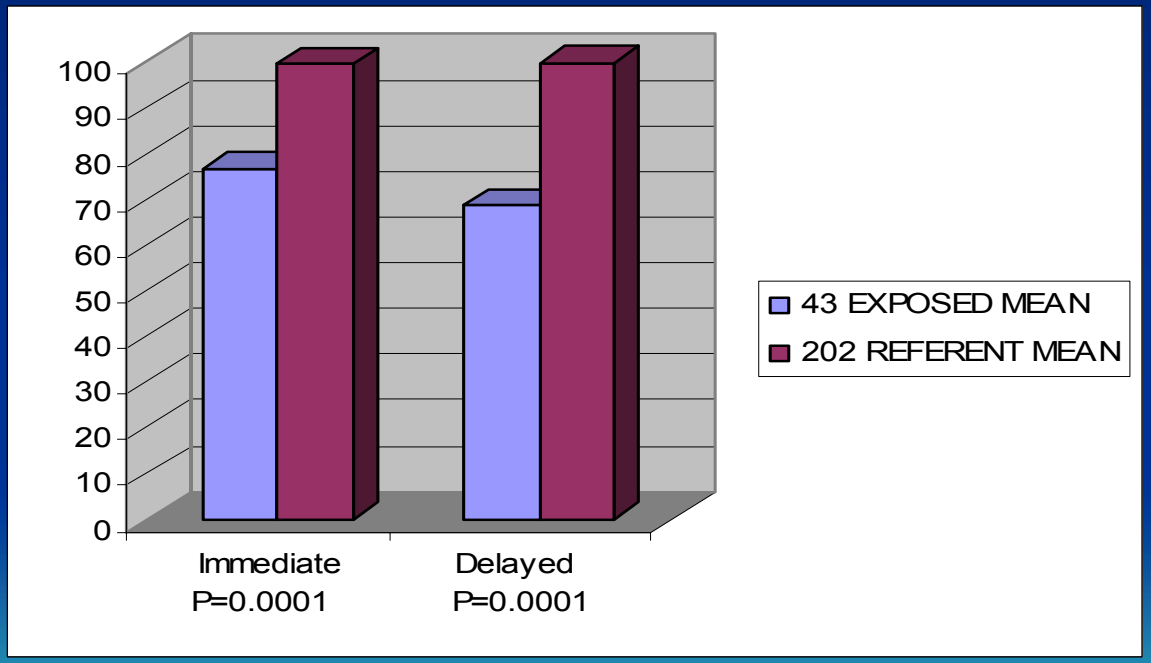
Grip Strength (lbs)

	43 exposed Mean +/-SD	202 referent Mean +/-SD	P value
Right	91.6 +/_20.0	99.3 +/- 17.5	0.012
Left	86.8 +/_ 22.5	99.1 +/- 17.5	0.0001



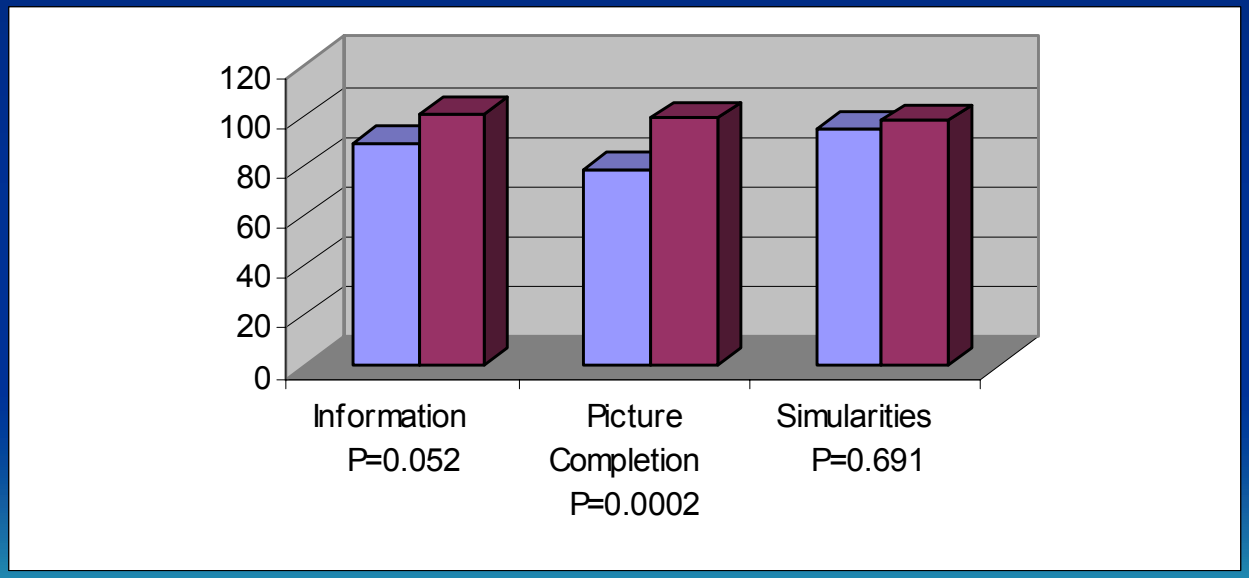
Verbal Recall

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Immediate	76.7 +/_ 23.4	99.8 +/- 31.1	0.0001
Delayed	68.7 +/- 38.2	99.9 +/- 41.3	0.0001



Information, Pictures, Similarities

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Information	88.9 +/_ 34.7	101.5 +/_ 39.4	0.052
Picture Completion	78.8 +/_ 30.7	99.3 +/_ 32.2	0.0002
Similarities	95.5 +/_ 25.8	98.1 +/_ 41.2	0.691



Profile of Mood States

	43 exposed Mean +/_ SD	202 referent Mean +/-SD	P value
Score	59.7 +/- 41.8	21.0+/- 31.6	0.0001
Tension	16.1 +/- 8.5	9.1+/- 5.8	0.0001
Depression	14.6 +/- 12.2	8.1+/- 9.3	0.0001
Anger	13.4 +/- 10.1	8.3+/- 7.9	0.0003
Fatigue	15.2 +/- 7.3	7.6+/- 6.1	0.0001
Vigor	10.3 +/- 6.7	18.3 +/- 6.3	0.0001
Confusion	12.9+/- 6.9	6.1+/- 4.5	0.0001

Mechanism for Neurotoxic Effects of Micotoxins

- Fumonisin B1 (FB1) enzyme inhibitor blocking biosynthesis of sphingolipids and accumulations of sphiganine
- Resultant brain hemorrhage (leukoencephalomalacia) *(Wilson, 1992)*
- Sterigmatocystin interferes with sphyngosine metabolism: an essential component of neuronal membranes
- Tremulo- and Vomitoxins are mycotoxins

Fungal Effects

- Neurological Component
  - Cognitive dysfunction
    - Confusion and spaciness
    - Memory loss
    - Spatial disorientation
    - Dyslexia
    - Seizures
- Attention Deficit Disorders
  - Suspect intrusion of paroxysmal increased brain wave frequency and activity

Mycotoxin Effects

- Neurological
  - Behavioral changes
  - Cognitive changes
  - Ataxia
  - Convulsions
  - Multiple sclerosis
  - Optic neuritis
- Immune suppression
- Interferes with protein synthesis
- Pulmonary
  - Small airway obstruction
  - Hypersensitivity pneumonitis
  - Hemorrhagic pneumonitis
- Cardiovascular
  - Vascular permeability

Mycotoxin Intoxication

- Acute and Chronic Mycotoxicosis can cause serious and sometimes multisystem diseases with severe and sometime fatal outcomes.
- The possibility of Mycotoxin intoxication should be considered when an acute disease occurs in several persons when there is no evidence of infection with a known etiologic agent, and no improvement in the clinical picture follows treatment.

Assays for Trichothecenes

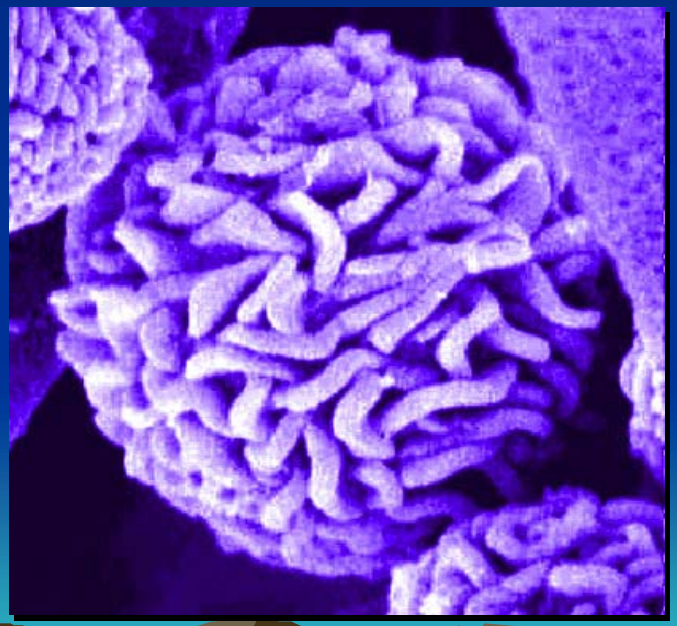
- Protein Translation assay in Airborne Particulates
  - Rapid, inexpensive assay using firefly luciferase has been developed to detect and quantify the fungus-derived toxicity of airborne particulates
  - Entire testing procedure can be accomplished in 2 hours
  - Authors demonstrated T-2 toxin, Satratoxin, and DON inhibit luciferase mRNA in a cell free rabbit reticulocyte system
  - Results are highly reproducible
    - Applied and Environmental Microbiology, Jan, 1999, p. 88-94

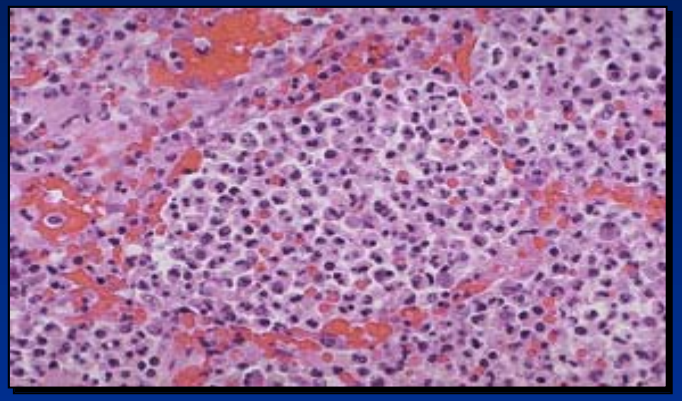
Symptoms of Sick Building Syndrome

- Head, Eyes, Nose, Throat
  - Headache
  - Dizziness
  - Dry eyes
  - Watery eyes
  - Itchy eyes
  - Epistaxis
  - Stuffy nose
  - Rhinorrhea
  - Alopecia
- Gastrointestinal
  - Nausea & Vomiting
  - Diarrhea
  - Constipation
- Respiratory
  - Cold & flu symptoms
  - Cough

Fungal Exposure & Health Effects

- Pathogenic infections
- Allergic illnesses from fungi





- Hypersensitivity pneumonitis

Conclusion

- Acute and Chronic Mycotoxicosis can cause serious and sometimes multisystem diseases with severe and sometime fatal outcomes
- The possibility of Mycotoxin intoxication should be considered when an acute disease occurs in several persons when there is no evidence of infection with a known etiologic agent, and no improvement in the clinical picture follows treatment

Afterword:

Be Not Afraid
To Look For
Zebras

--Anon

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