

## Respiratory Toxicology: Irritants and Allergens



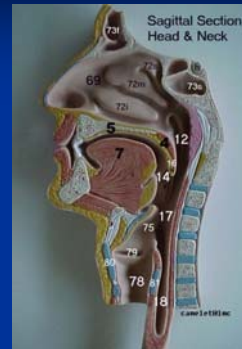
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## Topics covered

- *Anatomy & function* in the respiratory tract
- *Dosimetry* in the respiratory tract
- Distinction between allergy and irritation
- Irritant effects
  - ✓ *Spectrum of irritant effects*
  - ✓ *Inhalation fevers*
- Allergic effects
  - ✓ *Upper airway (rhinitis)*
  - ✓ *Lower airway (asthma)*

## Anatomy & Function

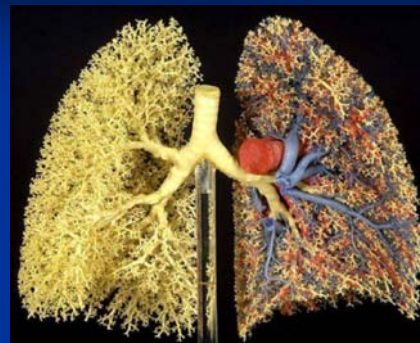
### Anatomy of the upper respiratory tract



### Functions of the upper respiratory tract

- Sensation
- Filtration
- Air conditioning
- Communication

### Anatomy of the lower respiratory tract



## Functions of the lower respiratory tract

- Primary
  - Gas exchange
- Secondary
  - Acid-base balance
  - Fluid balance
  - Metabolism of drugs & toxicants
  - Excretion of metabolic products

## Vulnerability of respiratory system

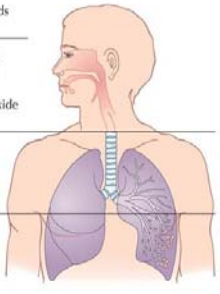
- ✓ Large *volume* of air inspired
  - 20+ m<sup>3</sup> / day in adult
- ✓ High *surface area* of tracheobronchial tree + alveoli
  - Approx. 70 m<sup>2</sup>
- ✓ Limited *defenses*
  - Gases and vapors: "Scrubbing"
  - Particulate matter: Mucociliary clearance

## Physical forms of exposure

- ✓ Gaseous phase
  - Gases
  - Vapors
- ✓ Particulate phase
  - Dusts
  - Mists
  - Fumes
- ✓ Mixed phase
  - Smokes

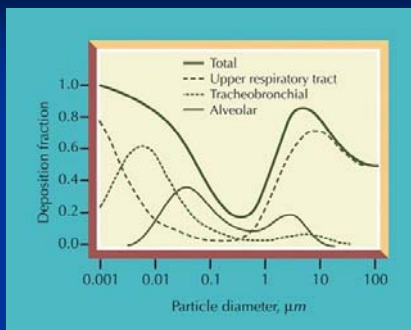
## Water solubility & initial level of impact

Water solubility	Initial level of impact	Compounds
High	Eyes Nose Pharynx Larynx	Aldehydes Ammonia Chlorine Sulfur dioxide
Medium	Trachea Bronchi	Ozone
Low	Bronchioles Alveoli	Nitrogen dioxide Phosgene



Source: Shusterman *Current Allergy Asthma Rep* 2003;3:258.

## Deposition of particulate matter



Shusterman D. *Current Allergy Asthma Rep* 2003;3:258.

## Distinction between allergy & irritation

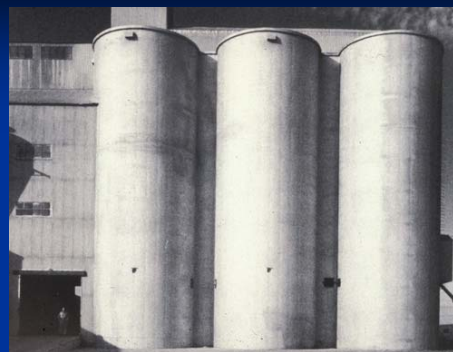
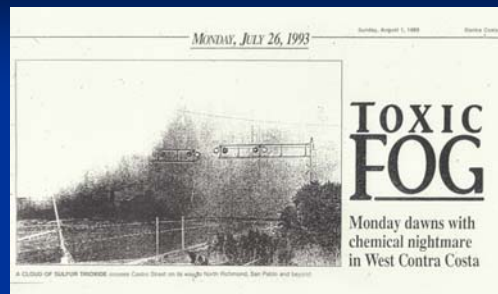
- | <u>Allergy</u>                                   | <u>Irritation</u>                              |
|--|--|
| ➤ Requires prior exposure (sensitization period) | ➤ No prior exposure required                   |
| ➤ Specific                                       | ➤ Nonspecific                                  |
| ➤ Minority of workers affected                   | ➤ Majority of workers may be affected          |
| ➤ Low-level exposures produce symptoms           | ➤ High-level exposures usually involved        |
| ➤ Often requires long-term reassignment          | ➤ Occasionally requires long-term reassignment |

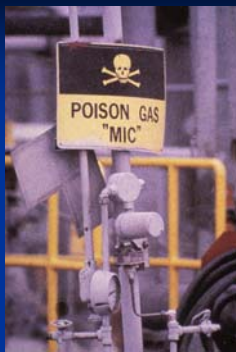
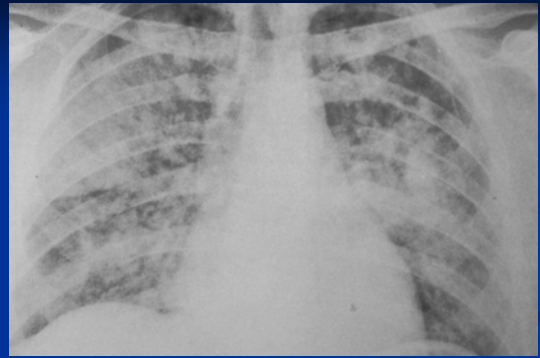
## Irritants



## Spectrum of inhalation injury

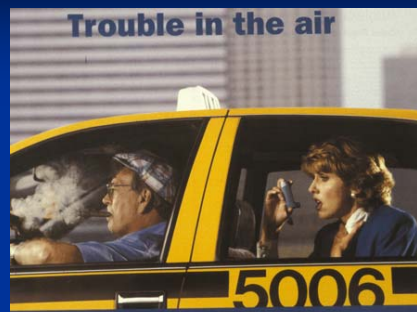
- ✓ Rhinitis / pharyngitis / conjunctivitis
- ✓ Laryngitis / VCD
- ✓ Tracheobronchitis
- ✓ Irritant-induced asthma
- ✓ Bronchiolitis obliterans
- ✓ Chemical pneumonitis





## Respiratory irritants: 1° Prevention

### Trouble in the air



When asthma triggers can't be avoided, VENTOLIN provides fast, effective relief of acute bronchospasm.

## Inhalation fevers:



## Inhalation fevers:

- ✓ Metal fume fever
- ✓ Polymer fume fever
- ✓ Organic dust toxic syndrome

## Metal fume fever

- ✓ Self-limited, flu-like, illnesses post-inhalation of *selected* dusts and fumes
- ✓ Typical latency = 4-6 hours
- ✓ Typical duration = 18-36 hours
- ✓ Pathophysiology = phagocytosis of ZnO particles by PAMs w/ cytokine release
- ✓ Minimal inflammation on BAL



## Polymer fume fever

- ✓ Exposure scenarios
  - Welding near teflon (PTFE) parts
  - Use of teflon tape on manifolds
  - Initial use of electrical pad heaters
  - Smoking PTFE-contaminated cigarettes
    - Electronics / textiles / ski wax
- ✓ Potential pulmonary infiltrates on CXR (temp-dependent spectrum of toxicants)

## Parrot Squawks A Fire Alarm, Dies of Fumes

Associated Press

Boulder, Colo.

An African gray parrot alerted its owner by calling out his name when a Teflon-coated pan caught fire, but it died from the fumes after the fire was extinguished.

## Organic dust toxic syndrome

- ✓ Agricultural handling of...
  - Moldy grain
  - Moldy wood chips
  - “Cured” silage (“silo unloader’s syndrome”)
- ✓ Recreational exposure to moldy hay...
  - Hay rides
  - Hay parties

## Occupational Respiratory Allergy

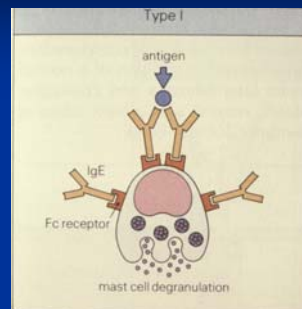
## Allergy concepts

- What is an “allergic reaction”?
- How does one test for allergy?
- How does the respiratory tract react to allergens?
- How do respiratory allergy & irritation interact?

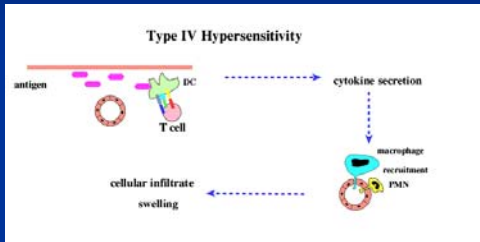
## What is an “allergic reaction”?

- Allergy (or “hypersensitivity”) is a biological reaction to a foreign substance involving cellular *recognition of* (and *memory for*) that *specific substance*.
- *Four types of hypersensitivity* are recognized by immunologists (“Gell-Coombs Types I – IV”).
- Two of these types of hypersensitivity are known to be involved in *occupational allergy*:
  - ✓ *Immediate hypersensitivity* (“Type I”)
  - ✓ *Delayed-type hypersensitivity* (“Type IV”)

## Type I (immediate) hypersensitivity



## Type IV (delayed-type) hypersensitivity



## Allergic skin reactions

Type I  
(immediate hypersen.)



Type IV  
(delayed-type hypersen.)



## How does one test for allergy?

Type I  
(immediate hypersen.)

✓ *In Vivo* testing:  
Skin prick testing

✓ *In Vitro* testing:

- RAST
- ELISA
- ImmunoCAP

Type IV  
(delayed-type hypersen.)

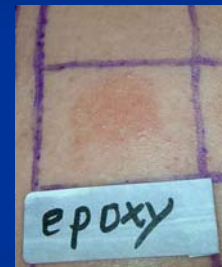
✓ *In Vivo* testing:  
[Skin] patch testing

## *In Vivo* skin testing

Skin prick testing



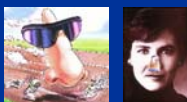
Patch testing



## How do different parts of the respiratory tract react to allergens?

Upper respiratory tract

- Sneezing
- Secretion (rhinorrhea)
- Nasal obstruction



Lower respiratory tract

- Cough
- Secretion (bronchorrhea)
- Bronchoconstriction



## How do "allergy" and "irritation" interact?

➤ *Allergy* affects *reactivity to irritants*:

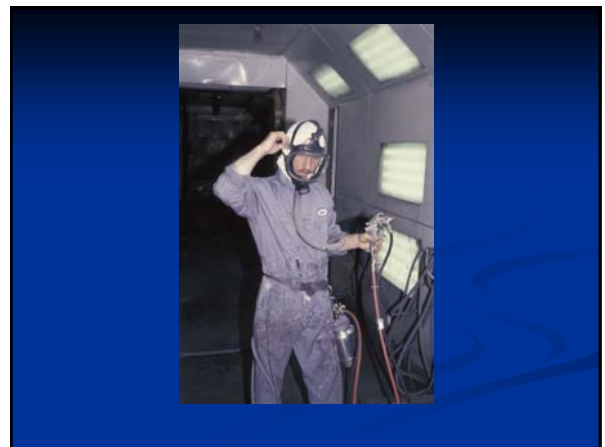
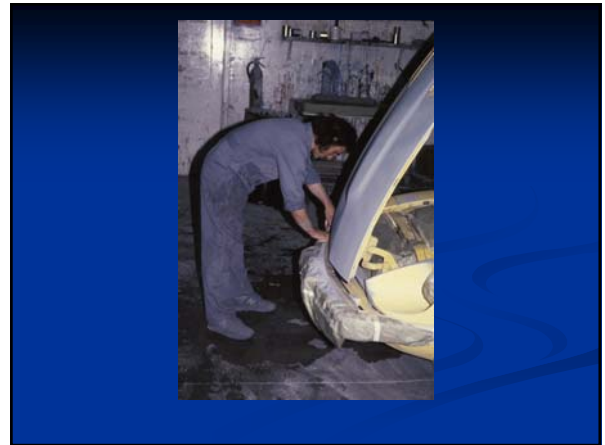
- ✓ Bronchial hyperreactivity: *Asthmatics* have a greater bronchospastic response to cold air, hyperosmolar solutions, or biochemicals (methacholine or histamine).
- ✓ Nasal hyperreactivity: *Rhinitics* have a greater nasal obstructive and / or secretory response to cold air, hyperosmolar solutions, biochemicals or chemical irritants.

## How do “allergy” and “irritation” interact?

- Some *irritants* can affect the development or expression of respiratory allergies:
  - ✓ DEP and SHS predispose to the development of nasal sensitization.
  - ✓ DEP and SHS intensify the response to allergens administered to the nose.



## Site visit to auto body shop

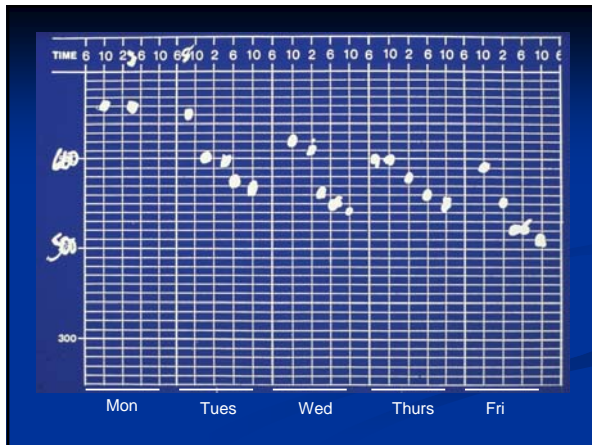






## Pulmonary Function Testing

- Lung Volumes
  - TLC 7.41 (112%)
  - RV 1.96 (105%)
- DLco 40.4 (109%)
- Mechanics
  - FEV<sub>1</sub> 4.52 (115%)
  - FVC 5.45 (118%)
  - Ratio 83%
  - FEF<sub>25-75</sub> 4.62 (108%)
- Methacholine Challenge
  - S<sub>RAW</sub> doubled @ 5.1 mg/m (Normal is > 4 mg/mL)
- Interpretation:
  - “The pulmonary function tests are normal...”
  - “Borderline methocholine challenge test.”



## Occupational Asthma: Definition

“...variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.”

Bernstein D, et al. Definition and classification. In Bernstein IL, et al., eds: *Asthma in the Workplace*. NY: Marcel Dekker, 1993.

## Occupational Asthma: Subclasses

- Occupationally-induced asthma
  - Specific sensitization
  - Irritant-induced (“RADS”)
- Occupationally-exacerbated asthma
  - Specific sensitization
  - Irritant-exacerbated

## Occupational Asthma: Selected Sensitizing Agents

	<u>Antigen/product</u>	<u>Occupation(s)</u>
HMW	Natural rubber latex	Health care workers
	Metamucil®, Penicillin	Pharmacists, nurses
	Animal proteins	Animal handlers, Vets
	Alpha-amylase	Bakers
	Gum arabic	Printers
	Mold spores	Various
LMW	Collophony	Solderers
	Acid anhydrides	Plastics workers
	Diisocyanates	Boat builders; car painters; packing

**Occupational rhinitis / asthma:  
Natural rubber latex allergy**



**Occupational rhinitis / asthma:  
Pharmaceutical agents**



**Occupational rhinitis / asthma:  
Cleaning products**



**Occupational rhinitis / asthma:  
Animal handlers**



**Occupational rhinitis / asthma:  
Adhesives / Polymers**



**Occupational Asthma:  
Diagnostic Criteria**

- Physician dx of asthma
- Hx of work-related exacerbation of sx
- and...
  - Exposure to agent known to cause OA\*  
[OR]
  - Objective cross-shift changes in FEV<sub>1</sub> or PEF  
[OR]
  - Work-related changes in NSBR  
[OR]
  - Specific bronchial challenge response

\* NIOSH Surveillance Def.

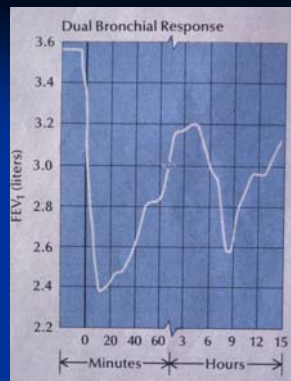
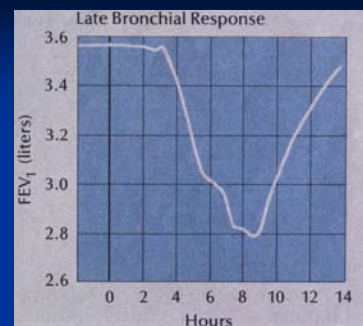
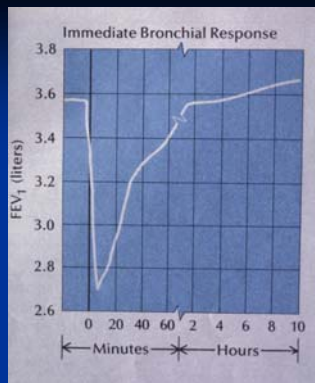
## Irritant-Induced Asthma / "RADS"

- Hx high level exposure to known respiratory irritant
- Sxs c/w asthma (wheeze, cough, dyspnea, chest tightness) start w/i 24 hrs of exposure and lasting  $\geq 3$  months
- Absence of prior chronic respiratory tract sxs
- Methacholine challenge abnormal

After: Brooks S, *Chest*, 1985

## Occupational Asthma: Assessment of Pulmonary Function

- Spirometry
  - May have no evidence of obstruction @ baseline
  - May have reversible obstruction @ baseline
  - Exaggerated diurnal variability, esp. on workdays ->
- Cross-shift peak flow measurement
- NSBR (methacholine challenge)
  - Can be compared while working and after period of removal from work
- Specific bronchial challenge



## Summary

- The respiratory tract can act as both a *portal of entry* and as a *target* of inhaled toxicants.
- The respiratory tract has limited defenses.
- Both the upper and lower respiratory tract can be affected by inhaled toxicants.
- Irritant and allergic effects can co-exist, and may influence one another.
- Syndromes with delayed onset (fume fevers, late-phase asthma) may lead to under-diagnosis.

Questions?

