Objectives for Environmental Effects on the Upper Airway

To learn:

1. Pertinent anatomy and functions of the upper airway
2. Which environmental agents cause benign disorders and which cause malignancies
3. The evidence for environmental agents causing disease
4. Morphologic changes caused by environmental agents
1. Note that there is very little separating UA system from the brain. So infections or neoplasias in the area can easily get to the brain and cause problems.

2. Vestibule has long, coarse hairs. More prominent in older males.

3. And we have the turbinates which will be important later.

Relationships between nose, sinuses, and brain
Once again, note that the UA is close to the brain and the orbit. The whole area is translucent. Infection can spread into the orbit, and you can get redness or proptosis (protuding eyeball).

Relationships between orbit, brain, nasal cavity, and ethmoid sinuses
Caldwell-Luc approach to the maxillary sinus

Prof goes off on a story about a 17th Century woman sticking things into her maxillary sinus. Her doctor had the space named after him: Antrum of Highmore.

Note that if you have inflammation in your maxillary sinus, your tooth could hurt. If you have a neoplasia in the maxillary sinus then you can get proptosis or your teeth can begin to fall out.
Types of mucosa: A-hair-bearing non-keratinizing squamous; B-E: decreasing squamous and increasing respiratory. Squamous usually stops at D. Shaded area is olfactory epithelium.

1. Vestibule with the hairs. Skin-like. So anything that can affect skin can affect this portion of the nose.

2. The hairs are there to prevent large objects from entering into the nasal pasageway.

3. The rest of the nasal passageway is covered with Schneiderian mucosa. Schneider was the first guy to figure out that snot came from your nose not your brain by discovering seromucal glands in the nose.

4. This Schneiderian mucosa has pseudostratified columnar cells with mucus glands. Some mucous-secreting cells can be transient (come and go within an hour).

5. Snot traps bad things and doesn’t let things go farther down the airway. What if it traps good things?
Normal Nasal Mucosa

A mucus cell that has formed. It will come and go.

In the anterior portion of the nose, the cilia beat forward to push things out of the nose. At the turbinates, they beat the other way.
CI, OV, RC are parts of the olfactory cells. The gland is Bowman’s gland which secretes material to help molecules adhere to receptor cells. The fat columnar cells are supporting cells. On = olfactory nerve.
Environmental and Genetic Influences on Facial Form
Queen Nefertiti. A legendary model of beauty and ideal facial proportions
Head of an old man by Da Vinci. Note the Nose
Reckless Youth vs. Wise Old Man

Nice divisions into thirds.

Divisions are not as nice. Drooping nose.
Bones and cartilage of the nose separate with age.

The nose has bone and cartilage. The things that connect the septal cartilage to the bone start to stretch because of gravity and so the tip of the nose starts to sag.
Normal nostrils seen from below
Allergic Rhinitis. Note swollen mucosa
Nasal mucosa in allergic rhinitis. Note the stromal edema.
The ample blood supply helps to warm the air before it travels any farther.

Vascularity of the Nasal Septum and Turbinates
Allergic rhinosinusitis

- Immediate (Type I) hypersensitivity response
- Involves interaction of allergen with dendritic cells and T-cells, inducing a population of IgE producing plasma cells.
- IgE interacts with mast cells and basophils to produce the hypersensitivity response, e.g., histamine release
- Eosinophils characteristic of Type 1 reaction, but what stimulates their production is unclear
- Eosinophils produce cytotoxins as well as a variety of cytokines, including some which increase vascular permeability which leads to edema

1. You have various cells that interact with the allergen like pollen (Welcome to NC!) causing plasma cells to produce IgE.

2. Hopefully IgE --> mast cells --> histamine --> leaky BV --> edema is somewhat familiar to you.

3. Eosinophils are also involved in allergic responses and can aid in the production in edema.
Eosinophils and Allergy

- Persons with allergies have eosinophils in nasal mucosa prior to the allergy season
- Eosinophils increase in number and degranulation during allergy season

Other Types of Rhinitis

- Perennial allergic rhinitis
  - Associated with mites, dust, dander
  - Morphology similar to seasonal rhinitis, but more goblet cells in the mucosa
- Perennial non-allergic rhinitis
  - Allergen not identified

1. People that have problems with dirty carpets, rugs, curtains.
2. If we don’t know why they are having issues, we give them this name.
Rhinitis

- Drug and Food Allergies
  - Highly variable and individual, e.g., person allergic to something emitted by laser printers

- Non-specific irritants
  - Formaldehyde
  - Patients with allergic rhinitis have increased sensitivity
Rhinitis

- Vasomotor rhinitis (not environmental)
  - Differs from allergic rhinitis
    - Obstructive symptoms without rhinorrhea, sneezing or itching
    - Morphologically, there are mucosal goblet cells and thickened vessels, but no eosinophils
  - Thought to be due to hormones

Sometimes it is due to menstrual cycle hormones or pregnancy

This is due to hormonal influences on the nasal mucosa. Which leads to leakiness --> edema --> obstruction. But no sneezing.

Honeymoon rhinitis? Yes, the guy getting married in 4 days was curious to research this one. Shout out to Mitch and his bride:
Metaplasia in Chronic Rhinitis

- Bacteria produce substances which cause metaplastic changes in respiratory epithelium resulting in increased mucous cells and decreased cilia.

  Remember metaplasia? cell type changes under a stressor (like bacteria). examples to follow:

Normal nasal mucosa
Papillary hyperplasia in chronic rhinitis

Kind of confused about this example but Wiki says papillary hyperplasia is proliferation of squamous cells. So I guess that the metaplasia is columnar to squamous and then you get hyperplasia of the squamous. This can occur with the epithelium in chronic rhinitis.
Mucous metaplasia in chronic rhinitis

Look at all the mucous cells!

So the metaplasia is the ciliated cells to mucous cell transition.
Metaplastic (transitional) nasal mucosa in chronic rhinitis

Note that you have metaplasia to transitional epithelium (normally associated with bladder)
Chronically swollen nasal mucosa can lead to mouth breathing which can result in facial deformity in children. Surgical intervention in the past included removing the turbinates to improve breathing. Good idea? Nature provides us with an answer.
Atrophic Rhinitis Active phase

Note the 'green, stinky mess' in their nasal passage obstructing the airway. Associated with bad odor.
Atrophic rhinitis Chronic phase

When this clears up finally, you can see that the airway is abnormally large. (atrophic turbinates)
Atrophic Rhinitis

Why do patients complain of difficulty breathing their nose?
Laminar Airflow Through Nose

Normally you have laminar airflow through the nose. The air goes over the turbinates and streams down to the nasopharynx. If the turbinates are atrophic like the pic showed, then the stream is not as efficient and you get eddy currents bc of the altered air flow and you cannot breathe as well.

Can be cured by sewing up a nostril for a year and letting the turbinates return to normal and then unstitching the nostril.
Sarcoidosis

- Cause unknown. Usually grouped with granuloma-producing bacterial and fungal diseases, but no agent found.
  - 1 of the 2 initial cases had nasal involvement
- Environmental factors:
  - Increased risk in agricultural workers, physicians, middle and secondary school teachers, automobile manufacturing, bird workers
  - Patients had more exposure to insecticides, air conditioning, mold
  - No increased risk with smoking, wood dust, metals.

Sarcoidosis (sarc = flesh, -oid = like, -osis = a process), also called sarcoid or Besnier-Boeck disease, is a multisystem granulomatous inflammatory disease characterized by non-caseating granulomas (small inflammatory nodules).
Granuloma associated with the destruction of the bones of the nose.
Environmental Factors in Upper Airway Neoplasia
Sinonasal Carcinoma

- Affects 1/100,000 in Europe and 3/100,000 in Japan and Taiwan
- Distribution in the West is 60% nasal and 40% sinal; in Japan it is only 4% nasal
- 45-60% are squamous cell carcinoma
- 15% adenocarcinoma
- 3% Salivary-type carcinoma
Sinonasal Carcinoma

- Environmental Exposures
  - Wood dust
  - Leather workers
  - Heavy metals such as nickel and chromium
  - Formaldehyde
  - Smoking

Workers that do this for ~20 years, at least half will develop a dysplasia in their nasal passageways.

We will mostly focus on 1, 4, & 5.

Long-term exposure is necessary!
Wood dust

Slight increase in squamous cell carcinoma in workers dealing with soft woods such as pine

- Up to 500 x risk of adenocarcinoma in finishers of hard woods such as beech, oak. Related to working conditions

- Colonic-type adenocarcinoma of the ethmoid sinuses in hard wood workers
Why Does Wood Dust Increase Risk of Carcinoma?

Raw wood contains a variety of organic and inorganic chemicals. Some are:

- Waxes, alcohols, terpenes, sterols, tannins, flavonoids, quinones, and lignans.

Chemicals are added to wood as preservatives and hardening agents. These include:

- Formaldehyde, arsenic, creosotes, phenols, and pentachlorophenol (PCP)
- Higher concentration of toxins in hardwoods
Formaldehyde

- Well-known as a tissue fixative
- Also used in building materials (FEMA trailers) and in trouser creases
- Normal metabolite
- Rats exposed to 14 ppm: 50% get carcinoma; at 5 ppm only 1%
- Humans rarely exposed to over 1 ppm
Formaldehyde

- Increased risk of sinonasal adenocarcinoma, particularly in women
- Most cases also associated with wood dust exposure, but this is minor in women.
- In US and Europe embalmers and pathologists do not have increased risk, but this may be a statistical problem because of few numbers of cases.

Luce et al, Cancer causes and Control 13:147, 2002
Formaldehyde

- Estimated increased risk of sinonasal carcinoma is 3-4 X after adjusting for exposure to wood dust.

- Wood dust and formaldehyde exposure additive

  Olsen et al. Int J Cancer 34;639, 1984
Other Environmental Exposures Contributing to Adenocarcinoma

- Exposure to leather dust increases risk of sinonasal adenocarcinoma in men and women.
  
  When we process leather, we add junk like glutaraldehyde to it.

- Smoking increased risk for squamous cell carcinoma.

Benign Papilloma

you can see the irregular growth associated with the carcinoma.

Carcinoma

Squamous cell carcinoma arising in inverted papilloma
We can see this squamous pearl and so we know that it is squamous cell carcinoma.
Sinonasal colonic type adenocarcinoma

generally occur in the ethmoid sinuses. Why colonic up in the UA? Unknown.
Cells with bright red cytoplasm are Paneth cells, which are normal in the small intestine and parts of the colon.
Environmental Factors in Laryngeal Disease
Polyps, Nodules, Ulcers

- Abuse of voice is the major cause
  - Environmental factor?
  - Duke-UNC basketball game in Cameron Indoor Stadium.
Fig. 95. Gross asymmetry in mature vocal cord nodules.
Vocal cord polyp

edema

blood

Hemorrhage
Vocal cord polyp with edema and hyalinization

You can get fibrin deposition bc of traumatic injury and that can lead to a hardened nodule.
Contact Granuloma

Another type of growth that can occur.
Can be treated with rest and/or resection
Laryngeal Carcinoma

- 99% squamous cell carcinoma
- Most are males over 60
- Alcohol and smoking are factors
Squamous cell carcinoma of the larynx

Far-advanced carcinoma that has basically destroyed the true and false cords.
Carcinoma infiltrating in between cartilaginous roots of epiglottis

This allows the spread of the squamous cell carcinoma up to the base of the tongue.

Root of epiglottis

Carcinoma

Seromucous glands

Carcinoma infiltrating in between cartilaginous roots of epiglottis
Axial Section of Larynx

- Cricoid Cartilage
- Thyroid Cartilage

or it can invade the cartilage. (This cartilage naturally ossifies with age)

it can spread through this notch
Cancers normally don't invade cartilage, normally bone. Remember the ossification of the thyroid cartilage. You have BVs that grow into the cartilage and you get a potential space around the BVs and is utilized by the carcinoma to get into the bone.
Laryngeal Carcinoma Survival

- Superficial-vocal cord: 90%
- Fixation of cords: 50-70%
- Lymph node involvement: 20%
- Thyroid involvement: 14%

If you catch it early, that is good. If you get the carcinoma on the true cord, you would present earlier because of hoarseness and there are no true lymphatics so it doesn't spread easily.

The carcinoma has extended to the stroma and the survival goes down.
Role of Smoking in Upper Airway Carcinoma

General Considerations:

- Tobacco smoke contains 81 carcinogens
- Causes cancer at more sites than any other substance
- Induces sister chromatid exchanges, DNA strand breaks, translocations, microsatellite instability
- Genetic abnormality in newborns
- Aneuploidy in sperm
Smoking and Head and Neck Carcinoma

- Relative Risk for Various Sites
  - Oral cavity: 4.0-5.0
  - Oro-and hypopharyngeal cancer: 4.0-5.0
  - Larynx: 10.0

Reference: IARC Monogr Eval Carcinog Risks Hum 2004;83:1-1438
Smoking and Upper Airway Carcinoma

- Dose - response relationship for cigarette smoking and head and neck cancer.
- 75% of carcinomas attributed to combination of alcohol and smoking
- 24% of head and neck cancer occurs in smokers who do not drink alcohol

Role of Alcohol in Laryngeal Carcinoma

- 25-80% of carcinomas of oral cavity, pharynx, esophagus, and larynx linked to alcohol with or without smoking. Alcohol 2005;35:161-168

- Increased head and neck cancer in non-smokers limited to those consuming 3 or more drinks a day. JNCI 2007;99:77-89

Smoking + Drinking = Synergy of badness
Alcohol and Cancer

- ETOH can act as a solvent, enhancing penetration of carcinogens.
- Acetaldehyde (AA) believed to be responsible
  - First metabolite of ethanol oxidation
  - Produced in liver and GI tract
  - Binds to DNA and interferes with synthesis and repair, causes point mutations, sister chromatid exchanges and chromosomal aberrations
  - Induces inflammation in mucosa (reflux?)
  - Inhalation causes nasopharyngeal and laryngeal carcinoma

Reference: Alcohol and Alcoholism 39:155-165, 2004

ETOH is converted to AA which leads to DNA issues which leads to carcinomas
Alcohol and Cancer

- Acetaldehyde (AA) produced by alcohol dehydrogenases in liver and GI Tract. Alcohol increases a cytochrome-P-4502E1 which converts ETOH to AA
- Also produced by oral bacteria implicating poor oral hygiene in cancer and by smoking
- Persons with abnormal acetaldehyde dehydrogenase gene at increased risk

Reference: Alcohol and Alcoholism 39:155-165, 2004
Alcohol, Tobacco, and Head and Neck Carcinoma

- Alcohol and Tobacco are independent risk factors, but combined exposure enhances risk.
- Alcohol acts a solvent, enhancing effects of carcinogens in tobacco

Cancer Epidemiol Biomarkers Prev 2006;15 (2196-2202)
Tobacco and Head and Neck Cancer Genetic factors

- Glutathione S-transferases (GST) play a role in metabolism of carcinogens in tobacco
- GSTM1 absent in 50% of Caucasians
  - Have a 30% increased risk of H&N Cancer
- GSTT1 absent in 20% of Caucasians
  - Have a 50% decrease in H&N Cancer risk

Cancer Epidemiol Biomarkers Prev 2006;15 (2196-2202)
Diet and H&N Cancer

- Some evidence that fruit and vegetable consumption reduces incidence of H&N cancer, even in cases of heavy smoking and alcohol intake.

Who is he and why is his photo here? Some want Ronald Reagan to replace him.
The Ear

- Deafness
  - Aging
  - Exposure to Loud sounds

- Tinnitus ("ringing in the ears")

Remember that the ear is connected to the UA system through the eustachian tube.
The Musical Note
You can get rocks in your ears if you go diving in the surf.

External Ear Canal after a visit to the beach
External Ear Canal

The Buzz
Environmental influences on upper way disease include:

- Allergies → nasal airway obstruction
- Wood dust and heavy metals → sinonasal carcinoma after many years of exposure
- Alcohol and smoking → Laryngeal Carcinoma
  - Alcohol might increase absorption of carcinogens
  - Acetaldehyde, derived from ETOH, damages DNA
  - Compounds in tobacco also damage DNA
  - Genetic differences might affect cancer development
1. Pertinent anatomy and functions of the upper airway
   The vestibule is the outer part of the UA and contains long, coarse hairs that block particle passage.
   There are turbinates (or concha) that help with the air flow and allow the stream of air efficiently moved down the pathway. Disruption of this can be seen with chronic rhinitis when you see atrophic turbinates leading to decreased air flow.
   There is good blood supply in the area to heat up cold air before it goes into the lungs. (why nose bleeds are common)
   It is important to recognize that the orbit and brain are most close to the UA and so anything (infection or neoplasm) that affects the UA can also affect the eye or brain.
   Don’t forget about the sinuses: Maxillary (where the cheek is) and the ethmoid (more medial). Can be the site of infection, neoplasm, or just spreading of disease.
   Schneiderian mucosa is important to stop bad things from entering the body. Produced by mucous cells in the epithelium. The secretory cells can be transient.
   Olfactory cells in the upper part of the nasal cavity. Bowman’s glands secrete substance to trap molecules so olfactory cells can process them.

2. Which environmental agents cause benign disorders and which cause malignancies
   Benign cause rhinitis in the nose (allergies), polyps, etc in the larynx (screaming), deafness (loud noises). Malignant cause cancer (see next question).
   Allergies
   Allergic rhinosinusitis
   Type I Hypersensitivity Rxn. Allergen → Dendritic cell → T cell activation → B cell activation → IgE production → attaches to mast cell → next exposure mast cells expels histamine → leaky BVs → edema
   Eosinophils are also involved – not as clear how activated but their cytokines also lead to similar effects. Can be present even without stimulation.
   Perennial Allergic Rhinitis
   Associated with mites, dust, dander. More goblet cells than seasonal allergies
   Perennial Non-allergic rhinitis
   unknown etiology
   Rhinitis can also be due to foods, formaldehyde, etc. Hormones can also stimulate rhinitis. Polyps, nodules and ulcers in the pharynx is mostly due to straining the vocal cords. Deafness is normally due to age or loud noise exposure.

3. The evidence for environmental agents causing disease
   Association of environmental factors (such as career) and development of sarcoidosis.

   Environmental Exposures such as:
   Wood dust
Wood has natural defense mechanism and plus we had junk like formaldehyde to it

- hard wood has 500x increase risk of developing adenocarcinoma because of accumulation of dust on the anterior portion of turbentines
- Leather workers
  - exposure to leather dust increases risk of adenocarcinoma
- Heavy metals such as nickel and chromium – increase in COX2
- Formaldehyde
  - Rats exposed to 14 ppm 50% develop carcinoma, 5 ppm → 1%
  - But link exists between the substance and carcinomas
- Smoking
  - Related to sinonasal carcinoma and also pharyngeal carcinoma especially with use with alcohol.
    - Tobacco smoke contains 81 carcinogens
    - Causes cancer at more sites than any other substance
    - Induces sister chromatid exchanges, DNA strand breaks, translocations, microsatellite instability
    - Genetic abnormality in newborns
    - Aneuploidy in sperm
    - GST genetics affect how you metabolize the carcinogens in smoke (some are good and some are bad)
- Drinking
  - ETOH → Acetylaldehyde → DNA damage → CA
  - Also can act to carry carcinogens from smoke to parts of the body

4. Morphologic changes caused by environmental agents
- Allergies commonly cause edema bc of immunological response.
- Metaplasia can be observed bc of the irritation some agents cause.
- Examples include:
  - columnar → squamous
  - ciliated → mucous producing
  - columnar → transitional-like
- You can get nodules in the larynx due to fibrin deposition. You can also see hemorrhage and edema in laryngeal polyps due to straining of the vocal cords.
- Allergies can cause swelling of the turbentines that leads to poor breathing via the nose.