Environment and the Upper Airway

APPROVED

Edward H. Bossen M.D.

March 23, 2010

He flies through a lot of the lecture. I would just worry about the main points. The histo slides did not seem overly important.
Note from Dr. H
I agree with this student's assessment. Important topics for Step 1 are Sinonasal Ca and Laryngeal Ca

UA = Upper Airway

:22

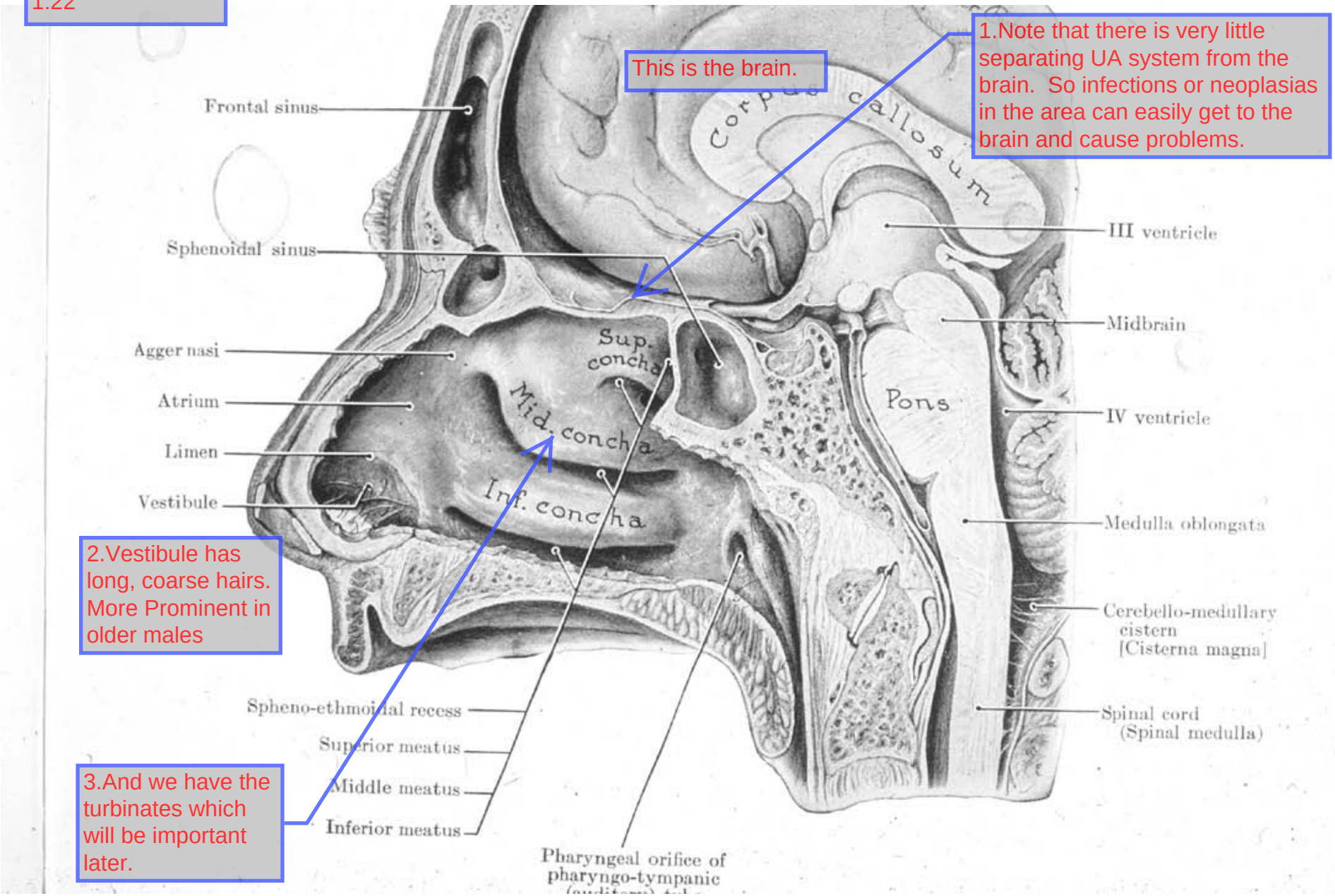
Objectives for Environmental Effects on the Upper Airway

We are going to review (i.e. learn) a little anatomy of 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

See objectives at end

1:22

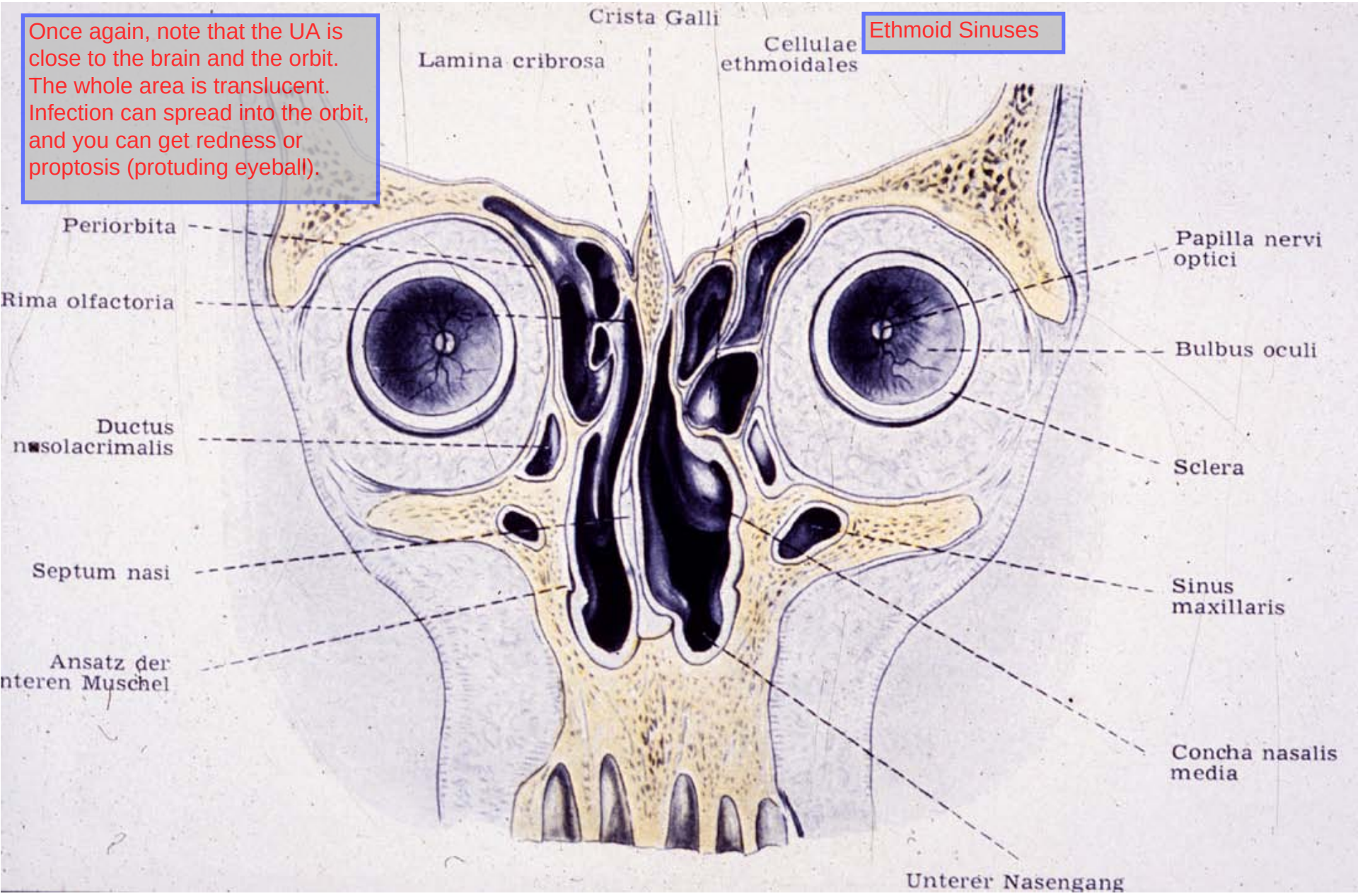


Relationships between nose, sinuses, and brain

2:41

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).

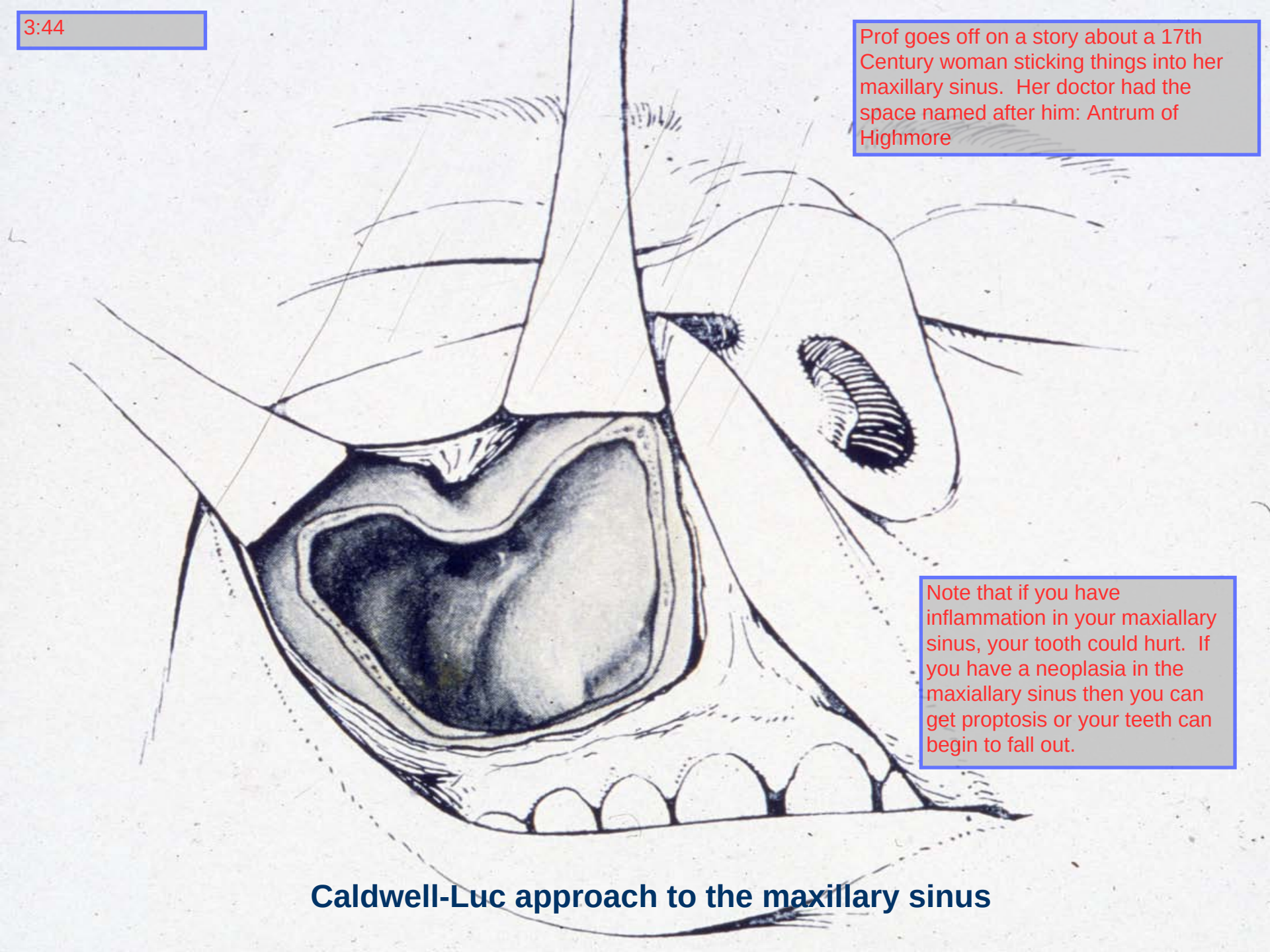
Ethmoid Sinuses



Relationships between orbit, brain, nasal cavity, and ethmoid sinuses

3:44

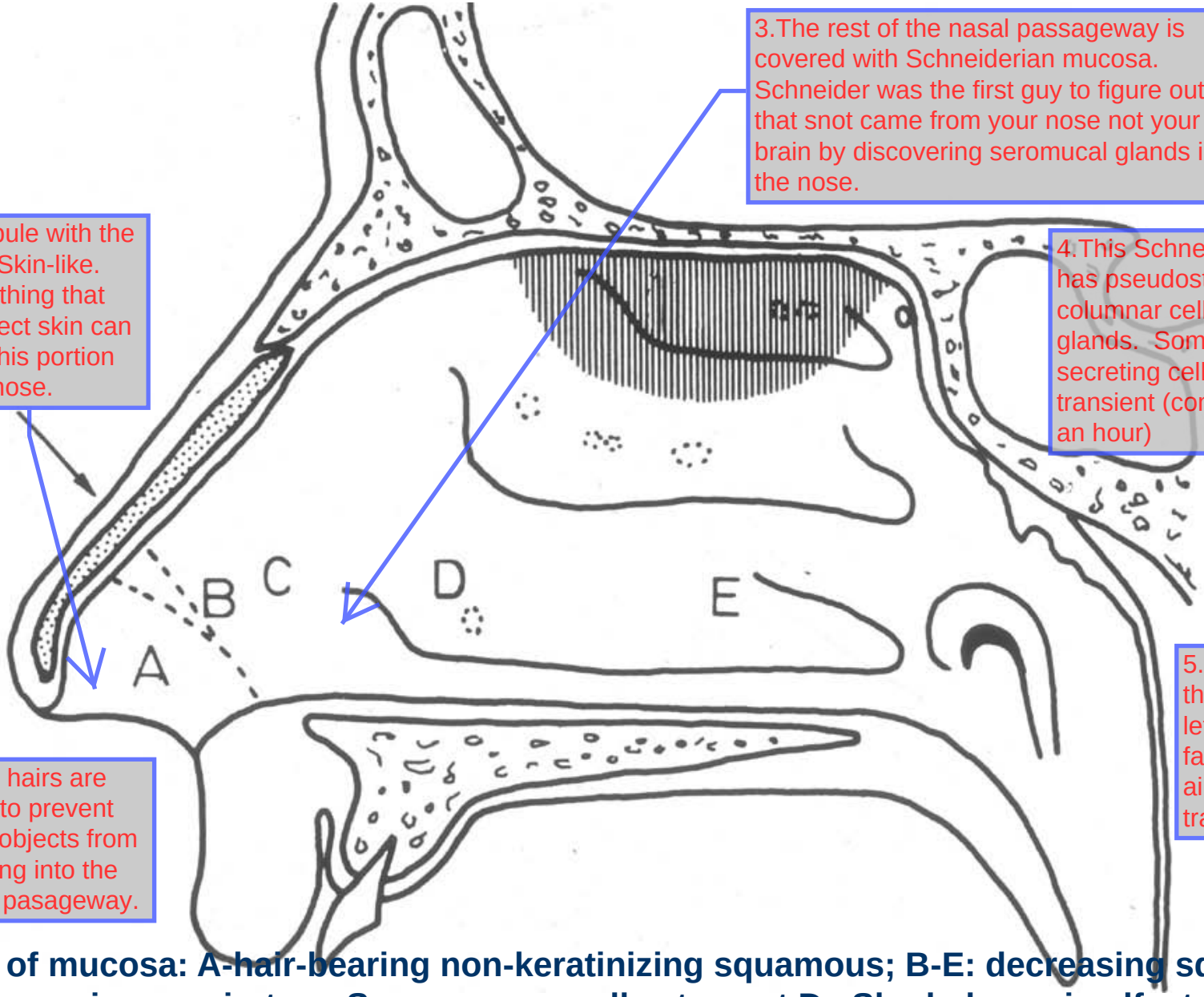
Prof goes off on a story about a 17th Century woman sticking things into her maxillary sinus. Her doctor had the space named after him: Antrum of Highmore



Note that if you have inflammation in your maxiallary sinus, your tooth could hurt. If you have a neoplasia in the maxiallary sinus then you can get proptosis or your teeth can begin to fall out.

Caldwell-Luc approach to the maxillary sinus

6:16



1Vestibule 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 Schnederian 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 doesnt let things go farther down the airway. What if it traps good things?

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

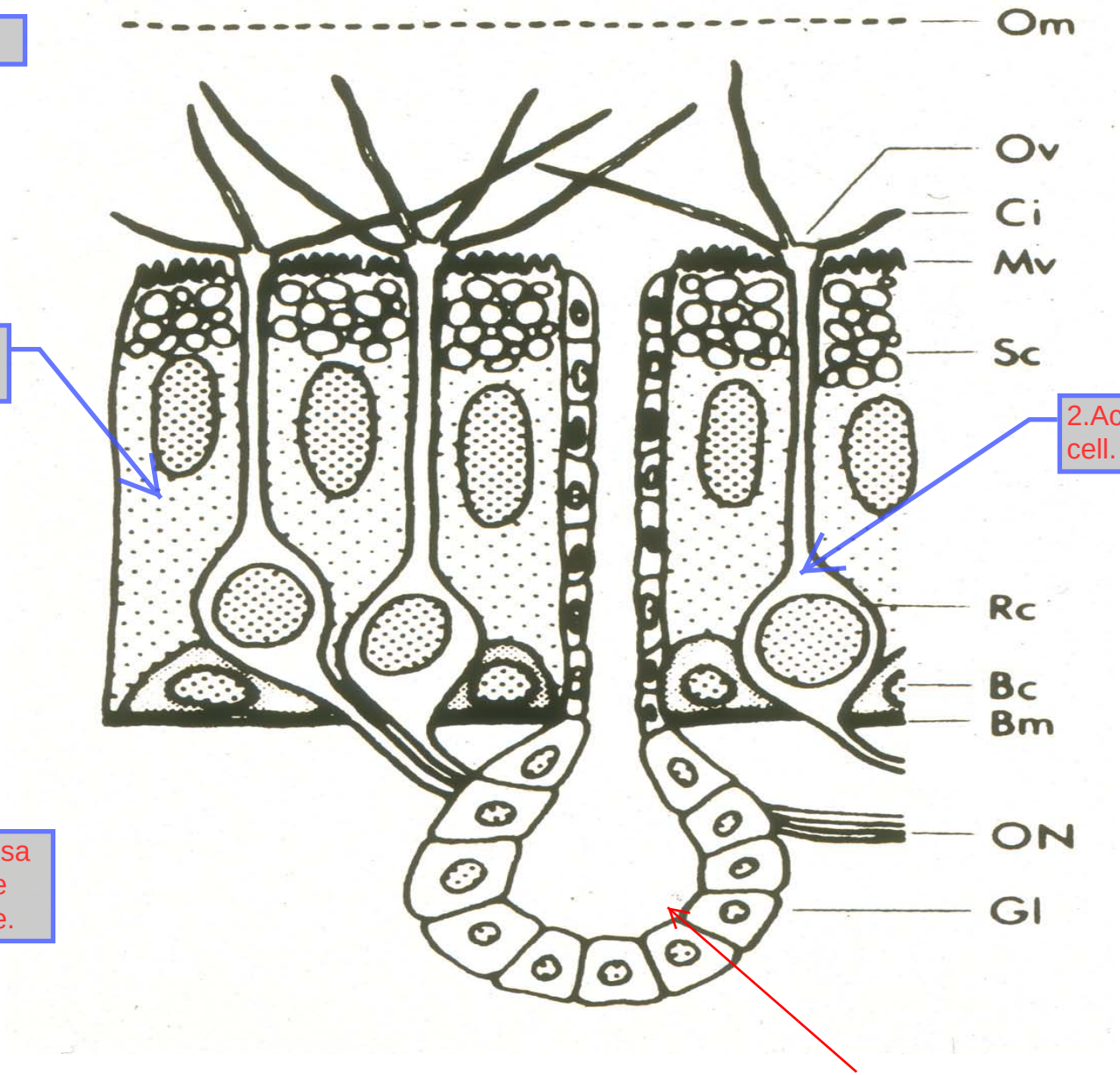
7:07

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.

9:51



Sustenacular or supporting cells

2.Actual olfactory cell.

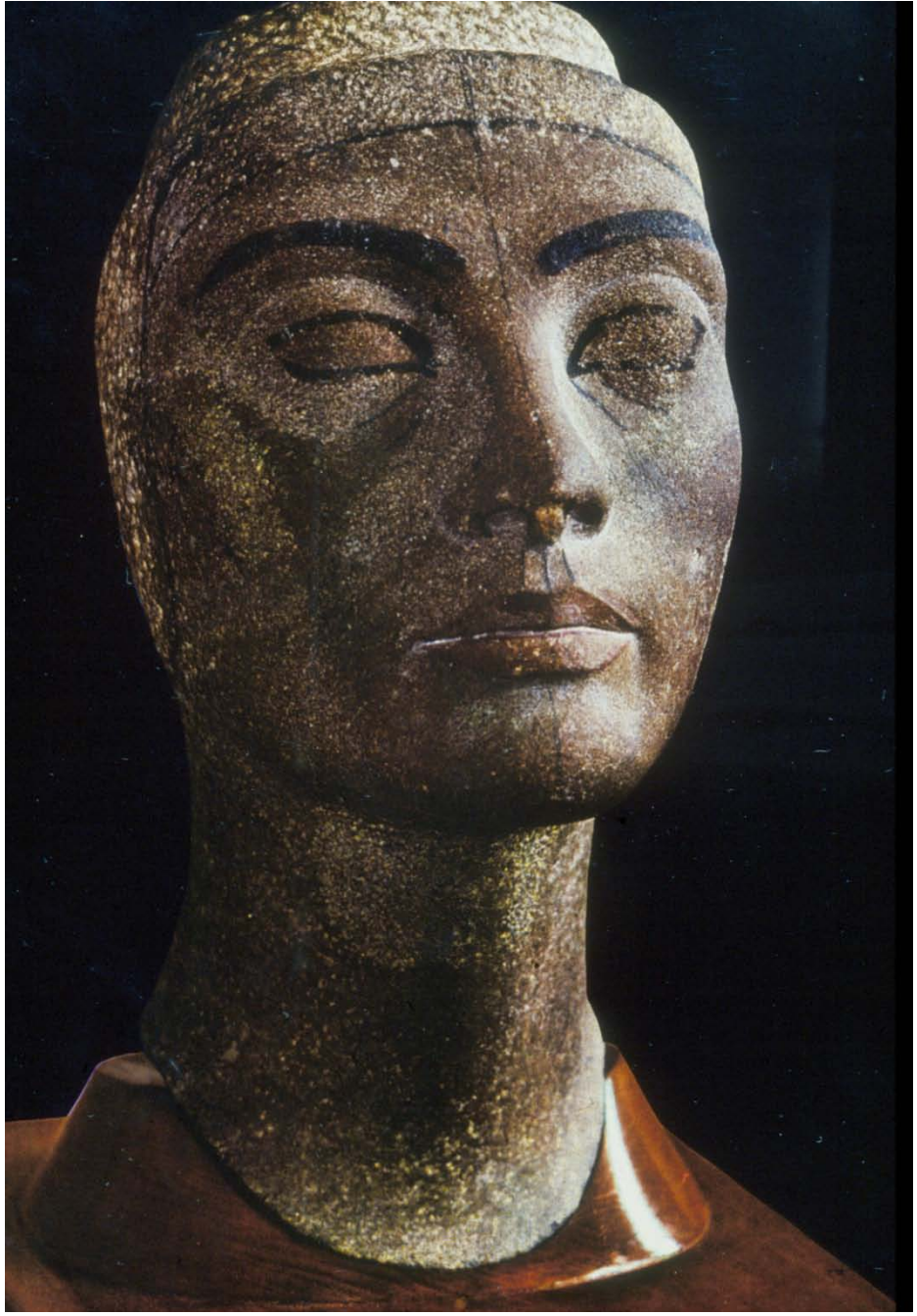
Olfactory mucosa is located in the roof of the nose.

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

10:43

Beautiful because of symmetry in her face and nice third divisions. More on this later.



Queen Nefertiti. A legendary model of beauty and ideal facial proportions

11:09

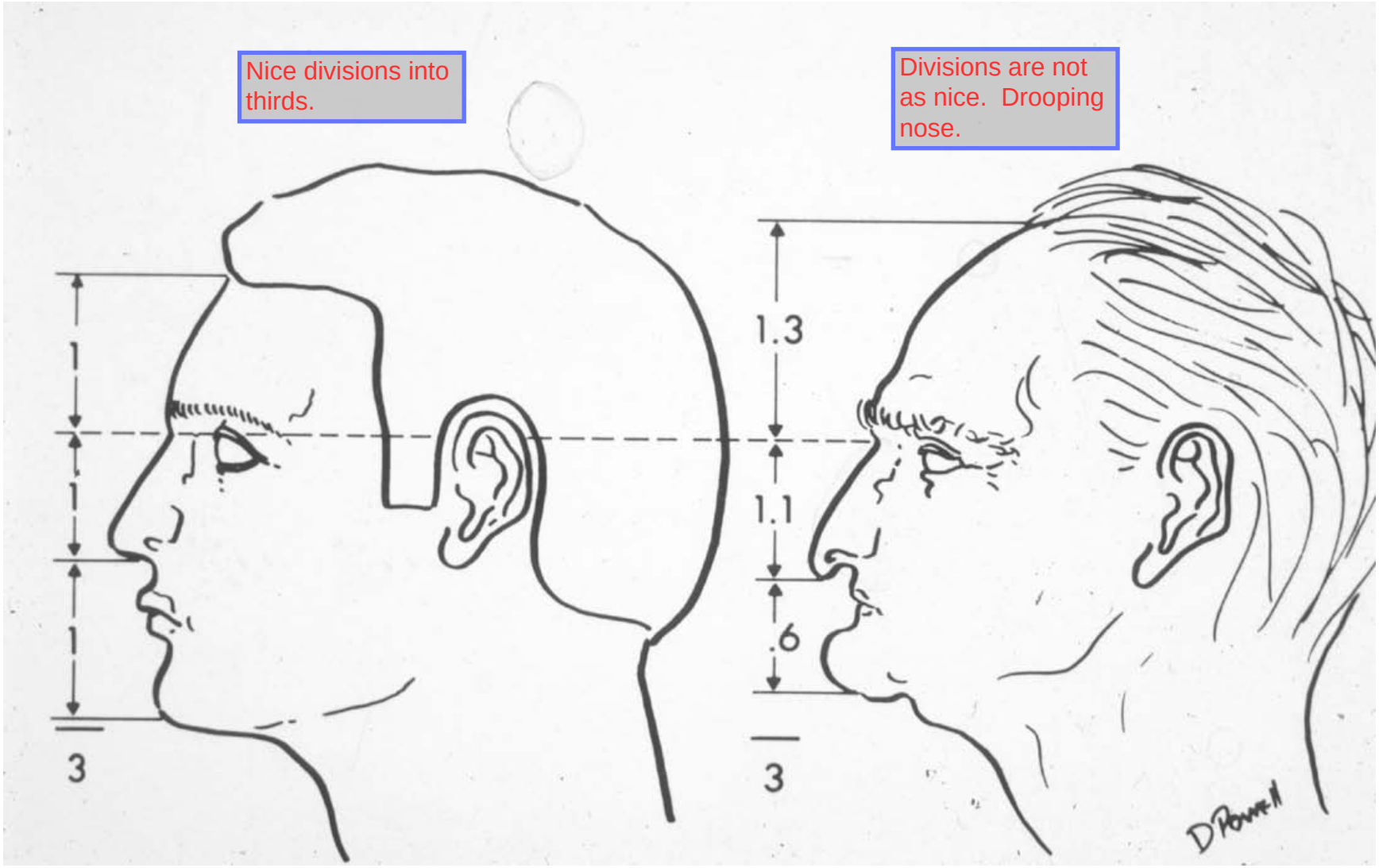
72. HEAD OF AN OLD MAN. C. 1511–12.
Black chalk, 11 3/8 × 6 1/8″.
Royal Library, Windsor Castle. Reproduced by Gracious Permission of Her Majesty Queen Elizabeth II

Not as beautiful.

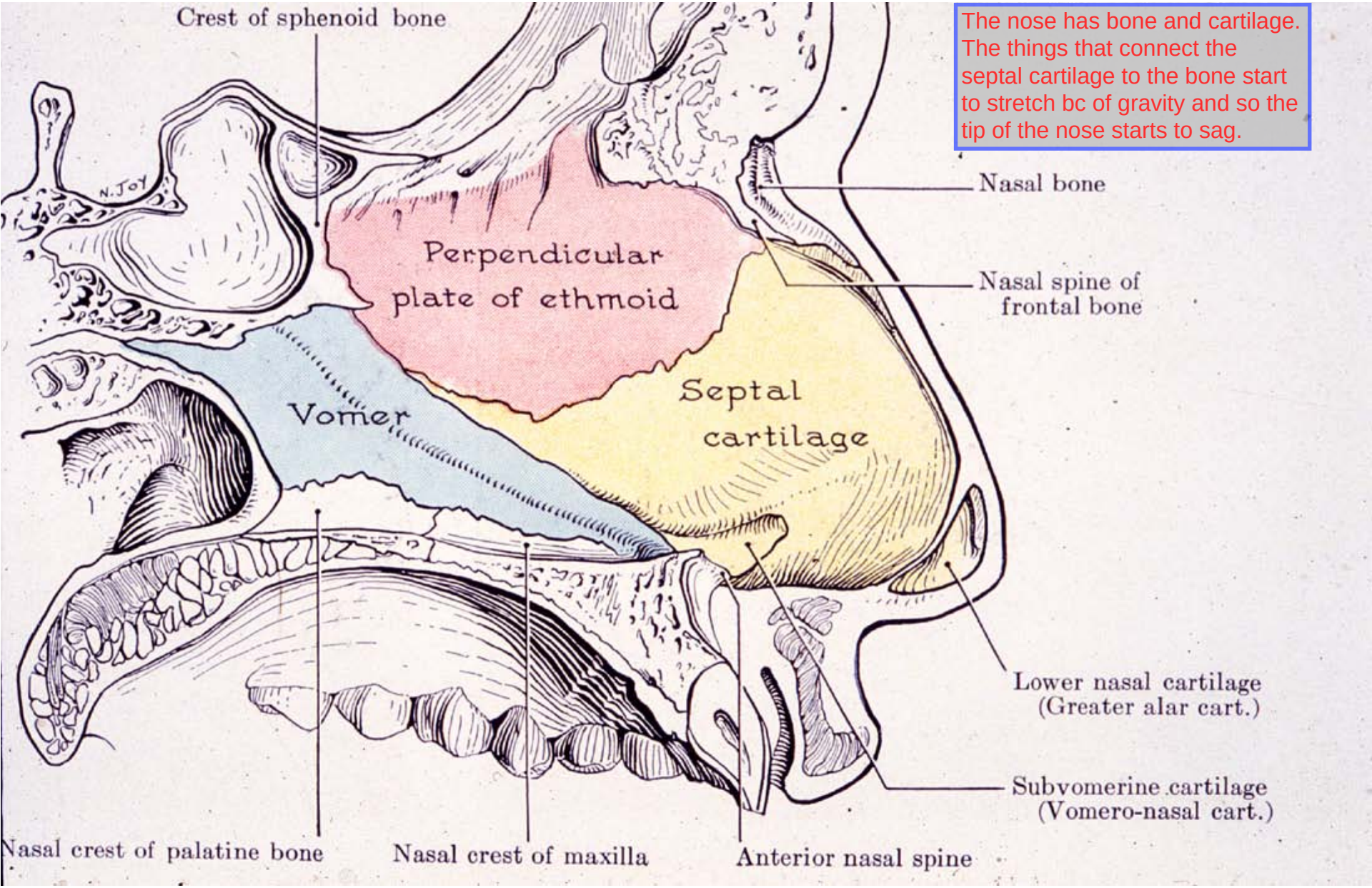
Head of an old man by Da Vinci. Note the Nose

12:31

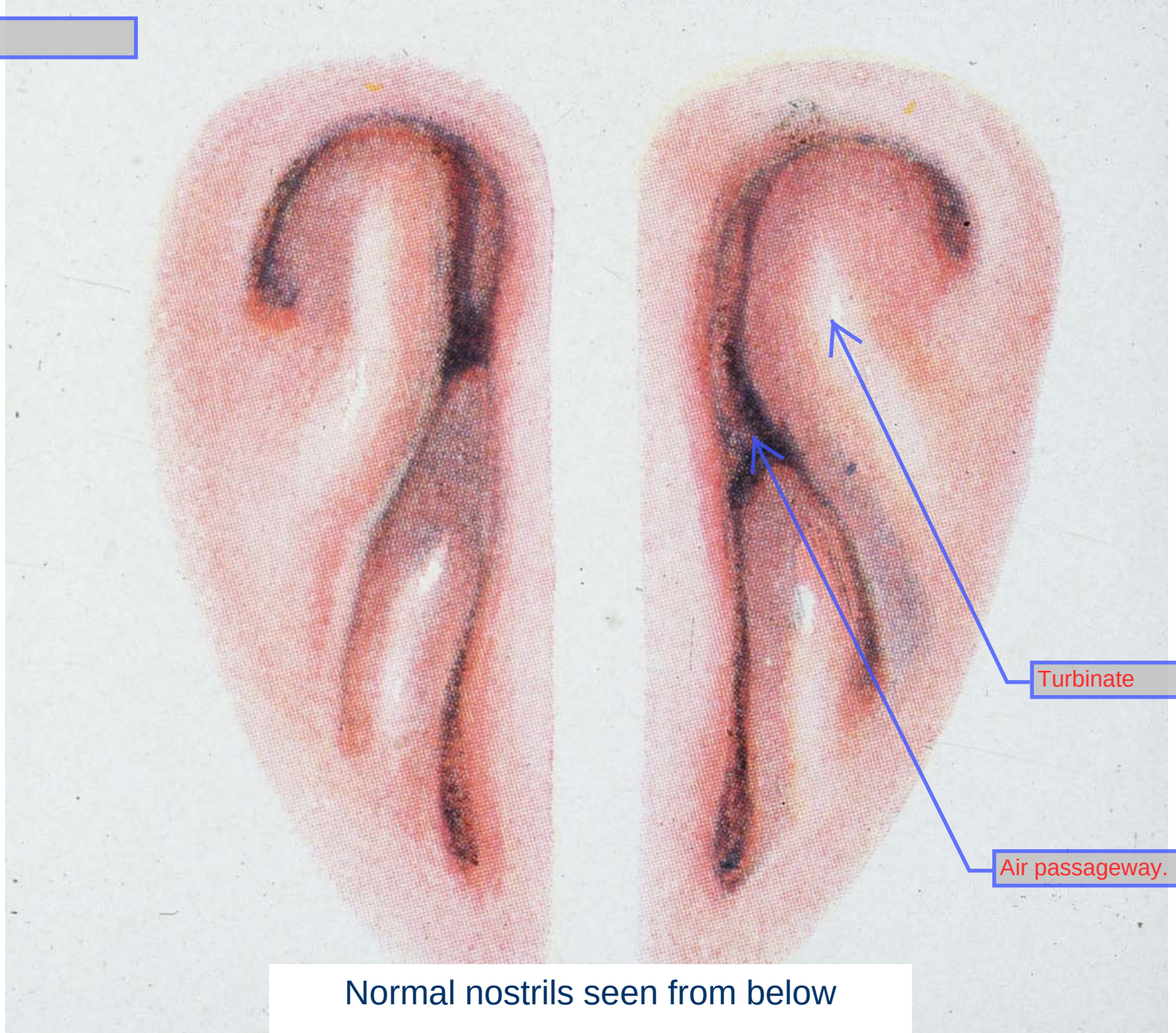
Reckless Youth vs. Wise Old Man



13:20



Bones and cartilage of the nose separate with age

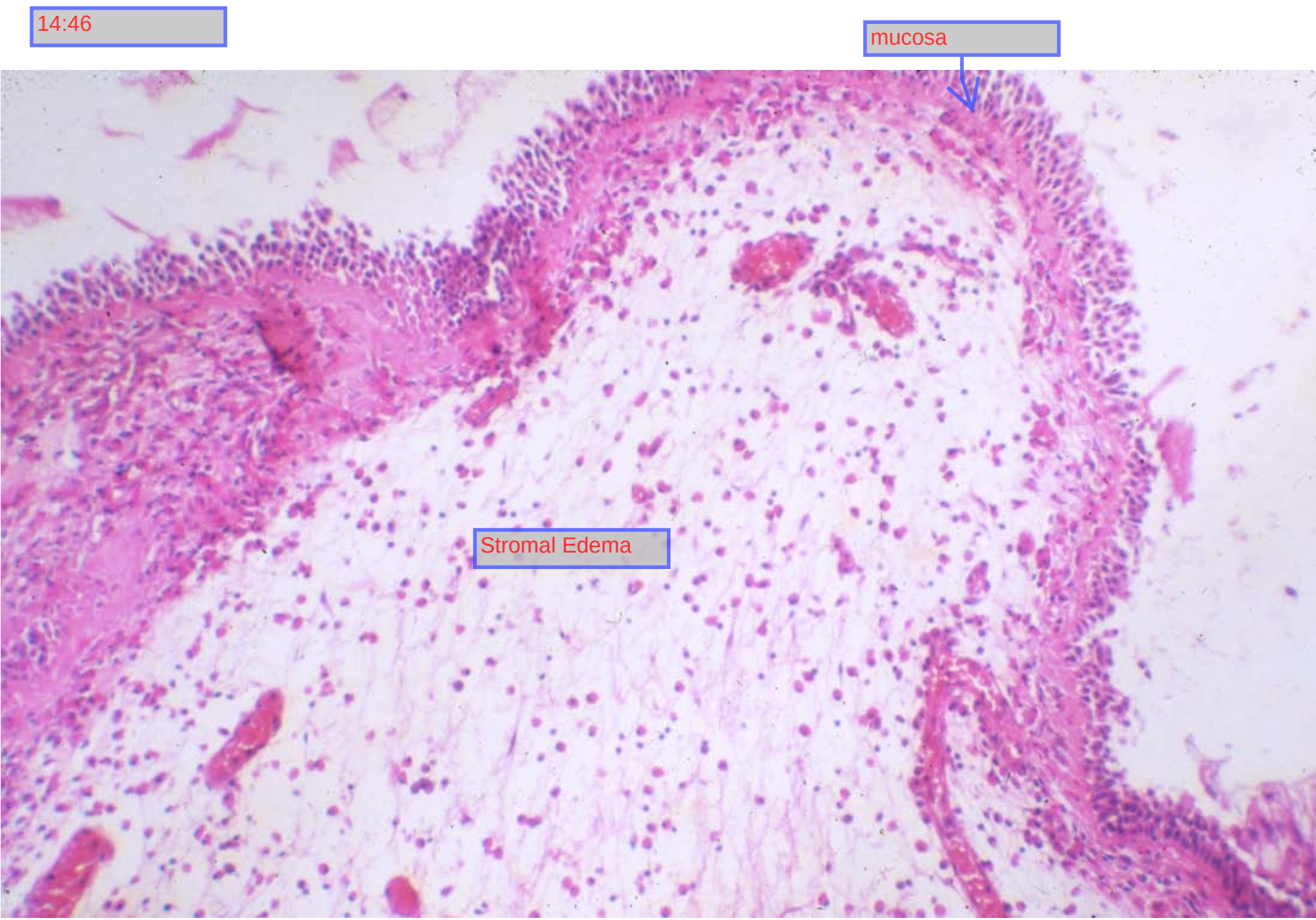


Normal nostrils seen from below

14:23

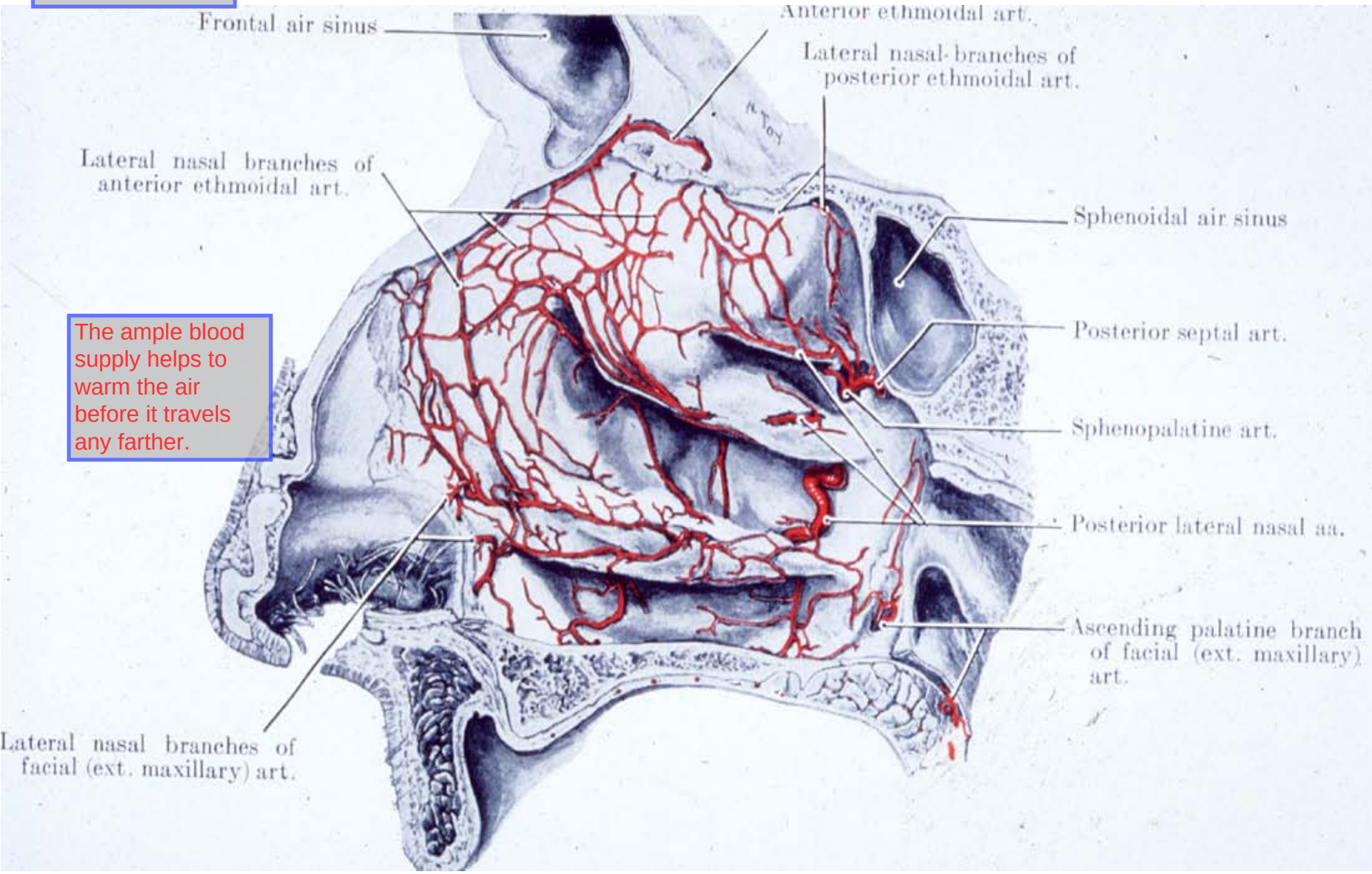
Air passageway is practically obsolete bc of swollen turbinates.

Allergic Rhinitis. Note swollen mucosa



Nasal mucosa in allergic rhinitis. Note the stromal edema

15:04



The ample blood supply helps to warm the air before it travels any farther.

Vascularity of the Nasal Septum and Turbinates

15:38

Allergic rhinosinusitis

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

- 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

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.

17:19

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

There is always an individual suceptibility to rxn.

- Ahlstrom-Emanuelsson et al, Eur Respir J 24:750, 2004

17:56

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.

18:42

Rhinitis

Just read this one.

- 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

19:15

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

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

Sometimes it is due to menstrual cycle hormones or pregnancy

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

19:59

Metaplasia in Chronic Rhinitis

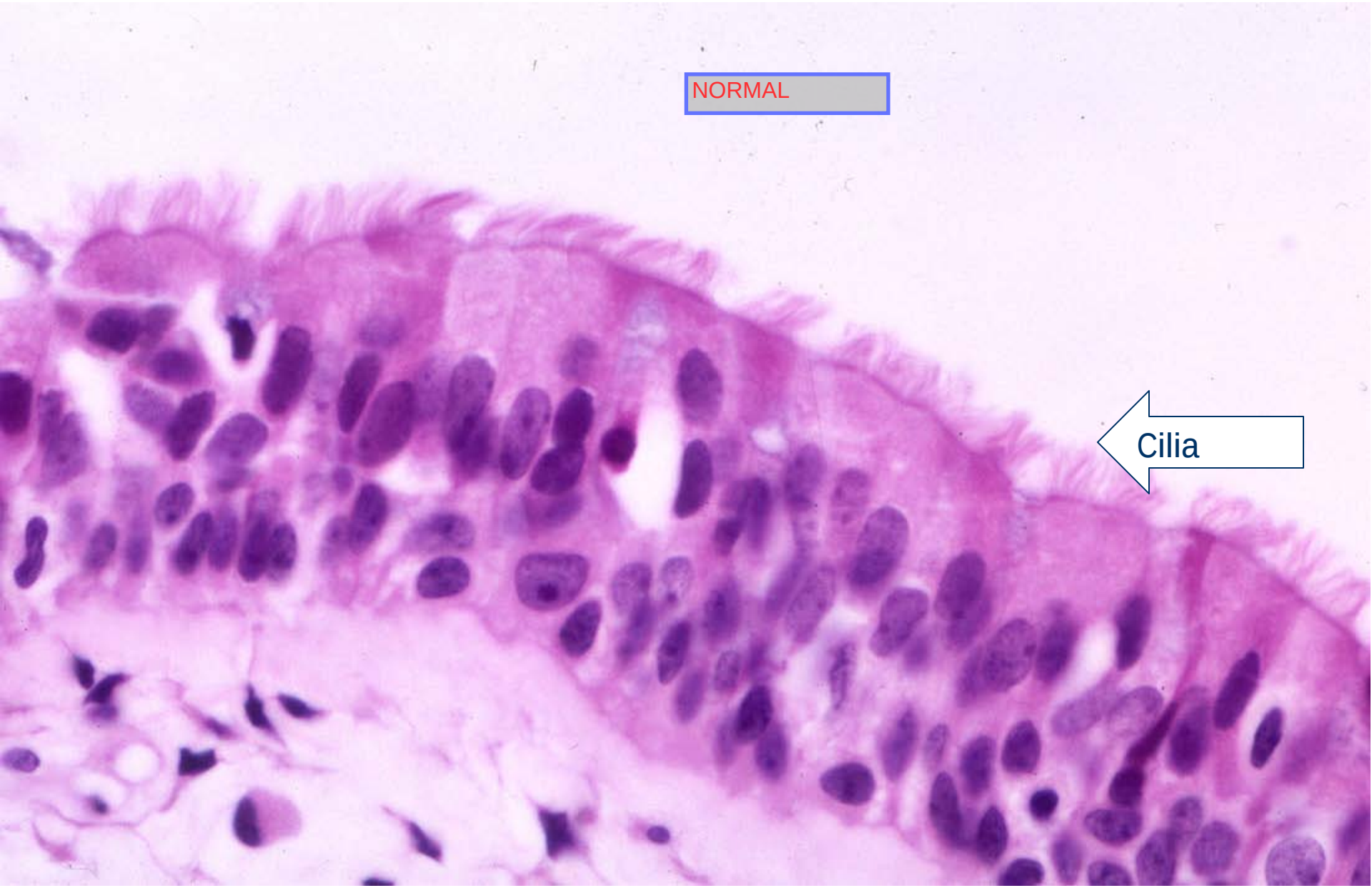
- Bacteria produce substances which cause metaplastic changes in respiratory epithelium resulting in increased mucous cells and decreased cilia.

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

- Nell and Grote, Ann Otol Rhiinol Laryngol 112:461, 2003

20:30

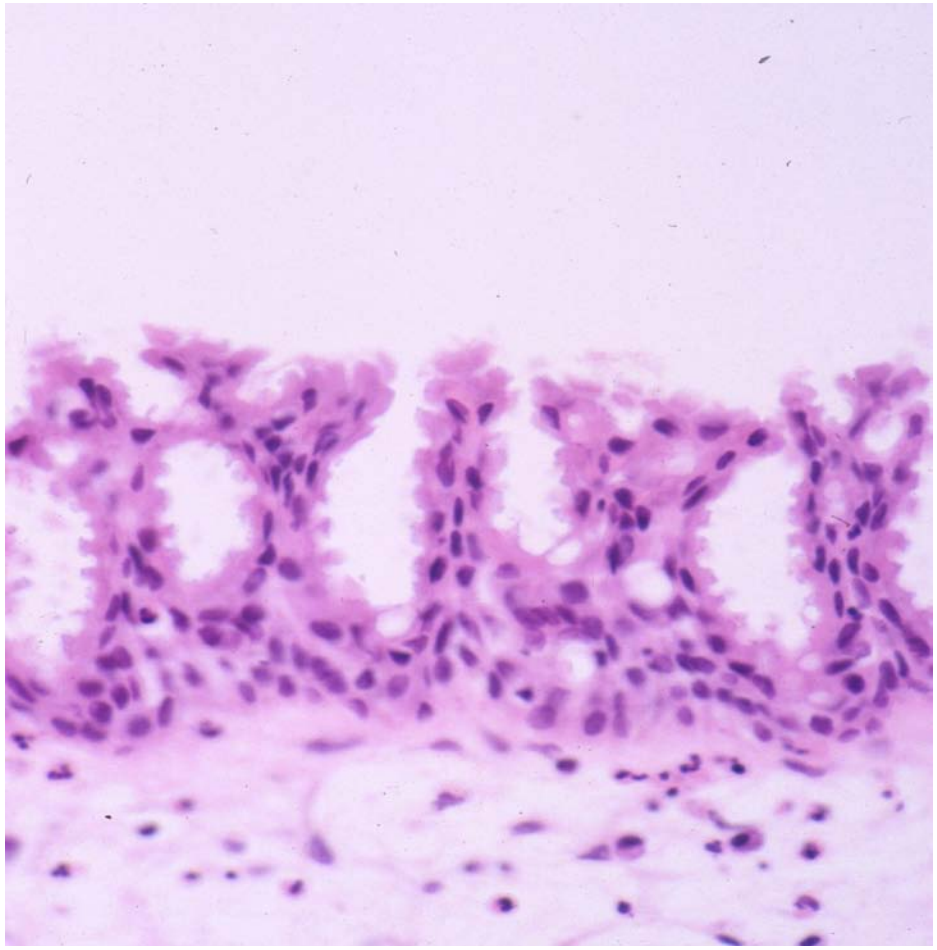
NORMAL



Normal nasal mucosa

20:38

Papillary hyperplasia in chronic rhinitis

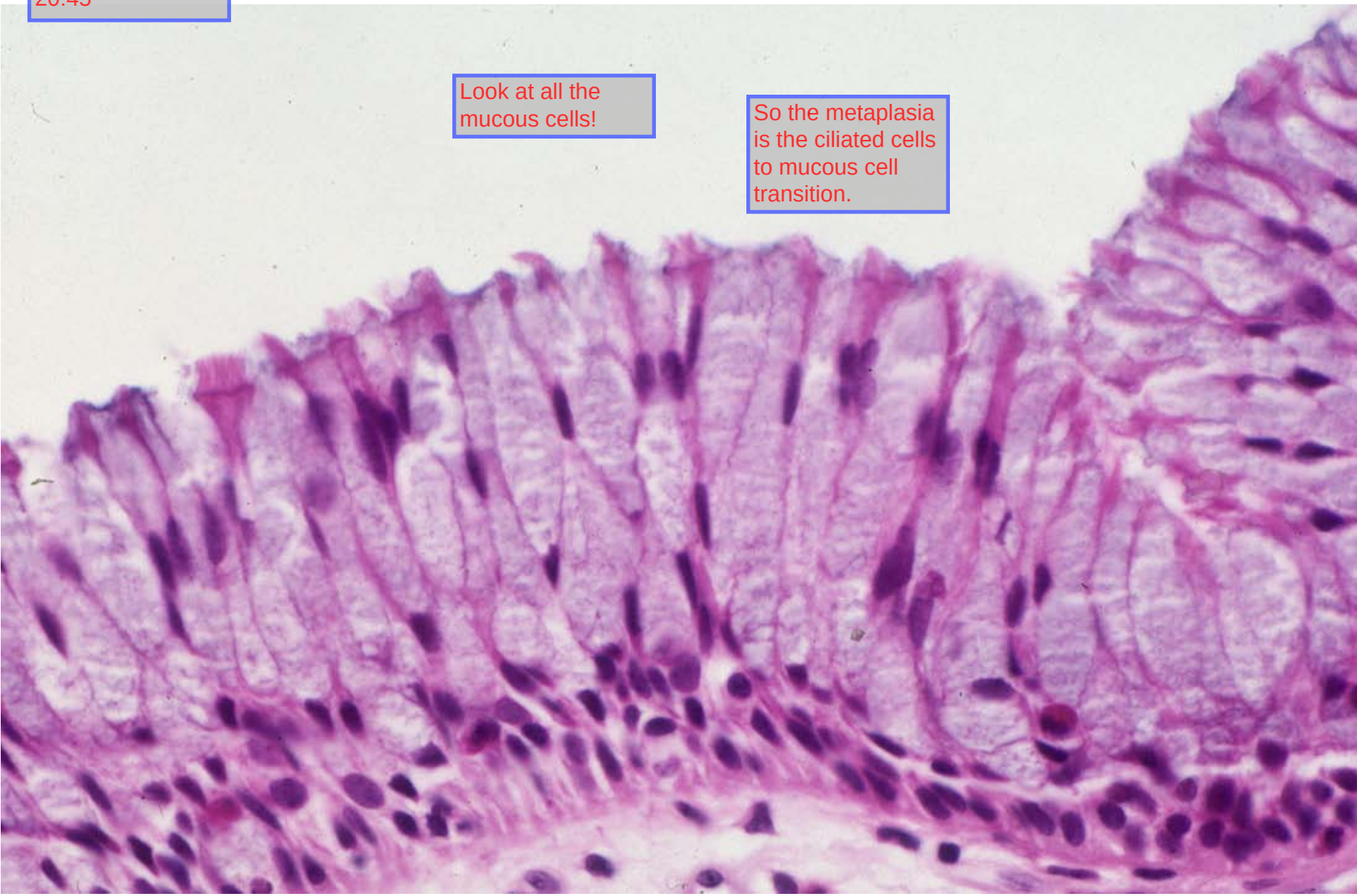


Kind of confused about this example but Wiki says papillary hyperplasia is proliferation of squamous cells. So I guess that the metaplasia is columnar to squamous and then you get hyperplasia of the squamous. This can occur with the epithelium in chronic rhinitis.

20:45

Look at all the mucous cells!

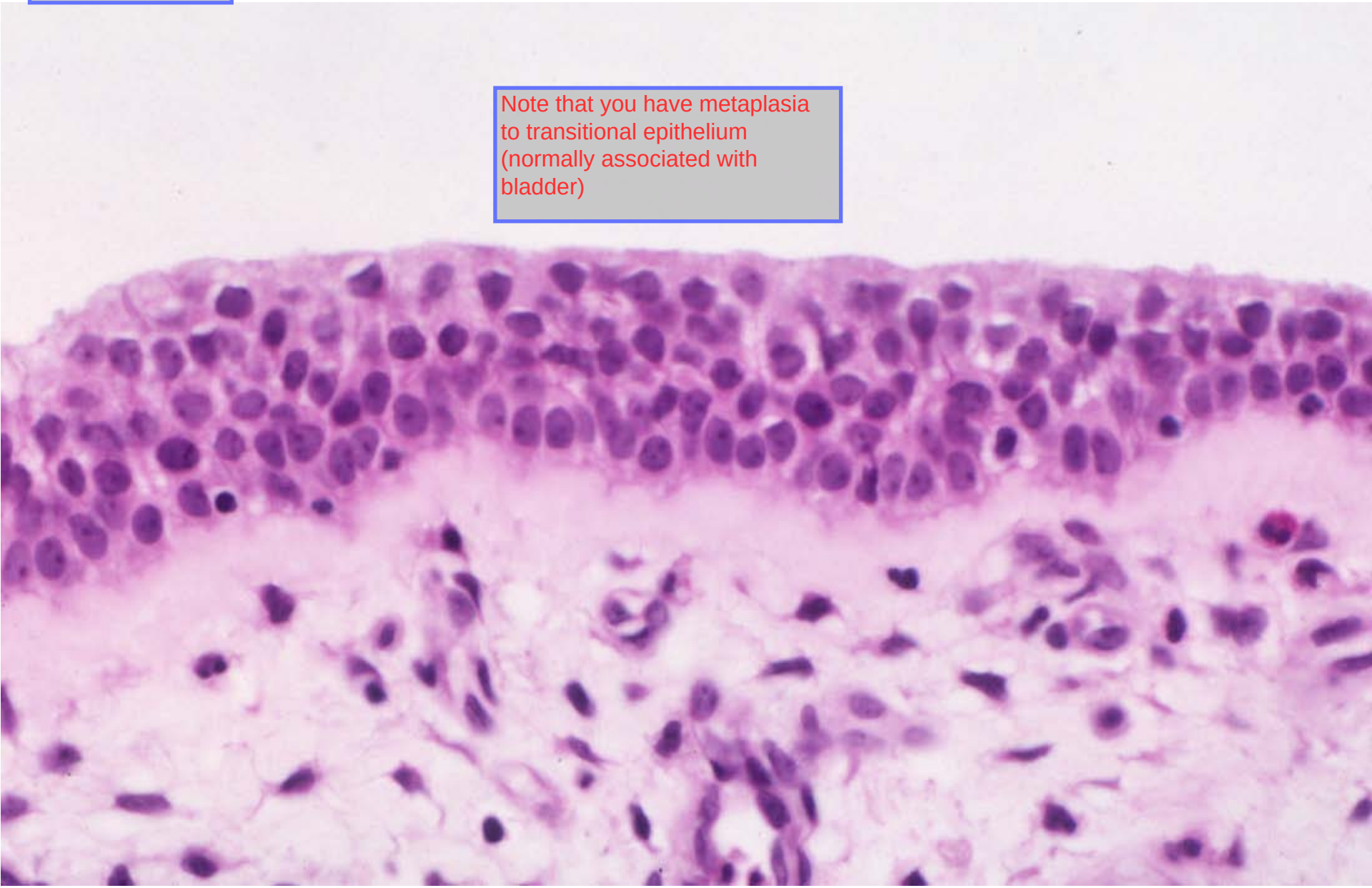
So the metaplasia is the ciliated cells to mucous cell transition.



Mucous metaplasia in chronic rhinitis

20:51

Note that you have metaplasia to transitional epithelium (normally associated with bladder)



Metaplastic (transitional) nasal mucosa in chronic rhinitis

21:09

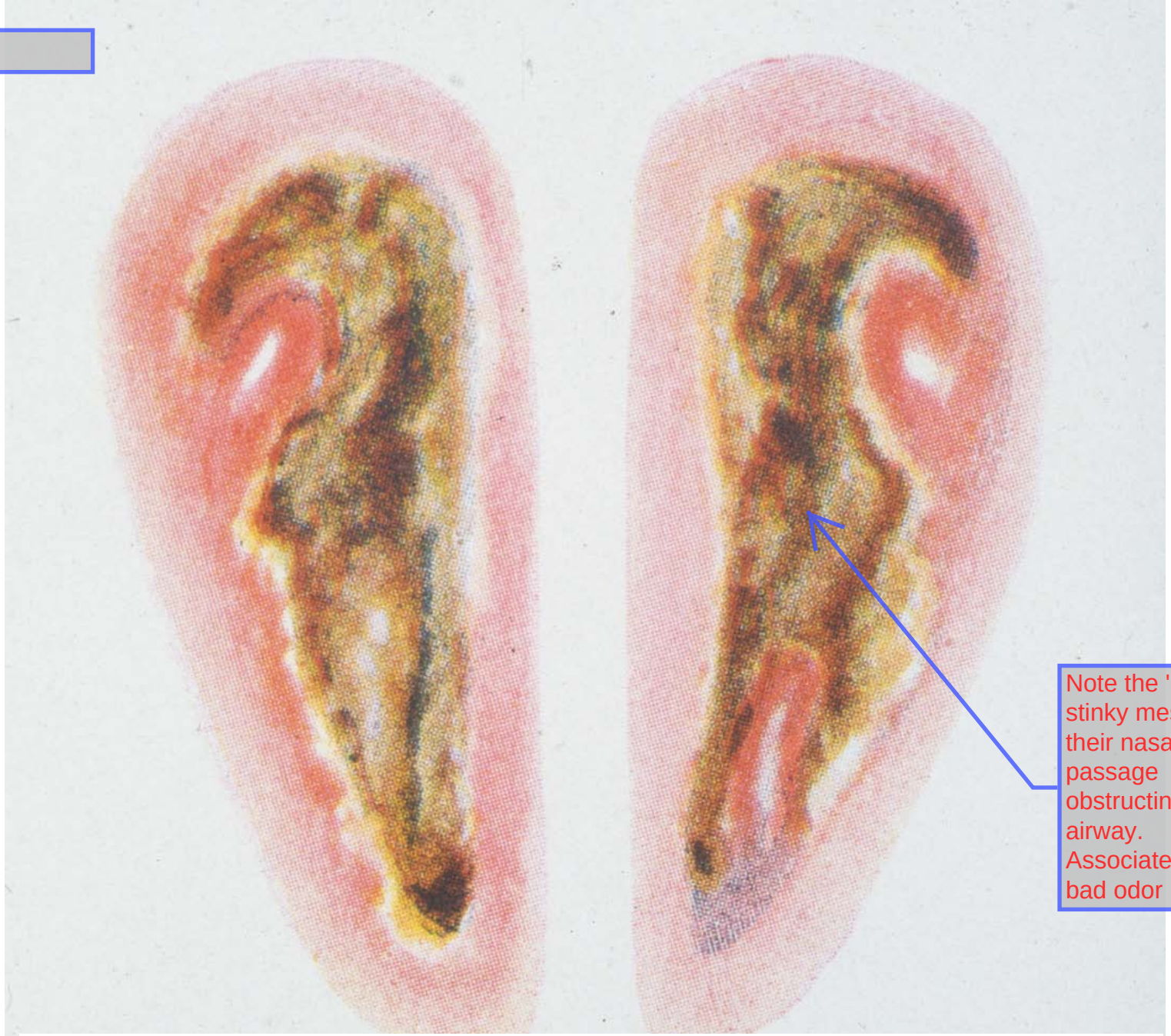
Chronically swollen nasal mucosa can lead to mouth breathing which can result in facial deformity in children.

Surgical intervention in the past included removing the turbinates to improve breathing.

Good idea? Nature provides us with an answer.

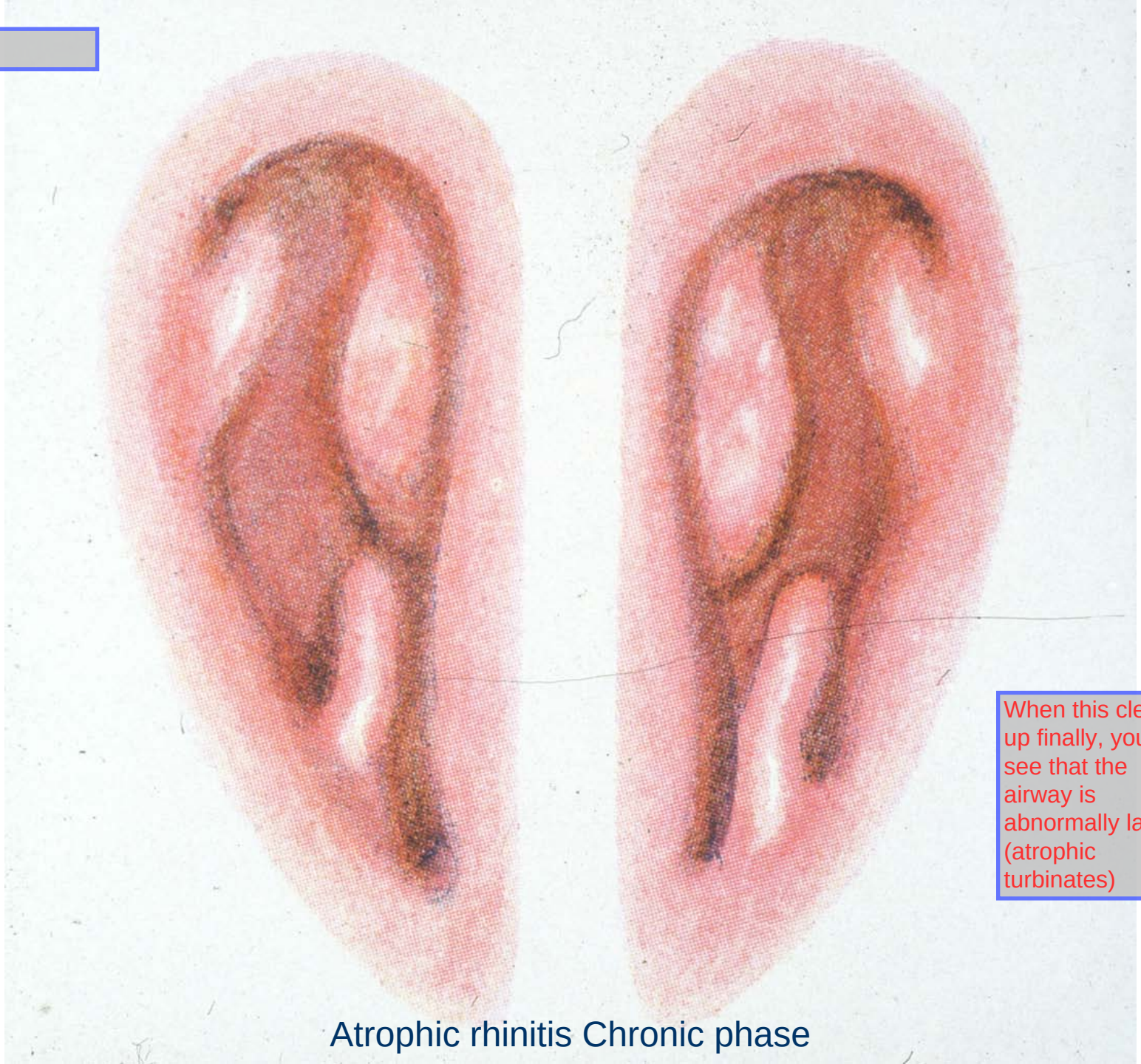
If a kid breathes through his nose too much, his face can form weird, with the jaw receeding.

22:21



Atrophic Rhinitis Active phase

22:53



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

Atrophic rhinitis Chronic phase

23:07

Atrophic Rhinitis

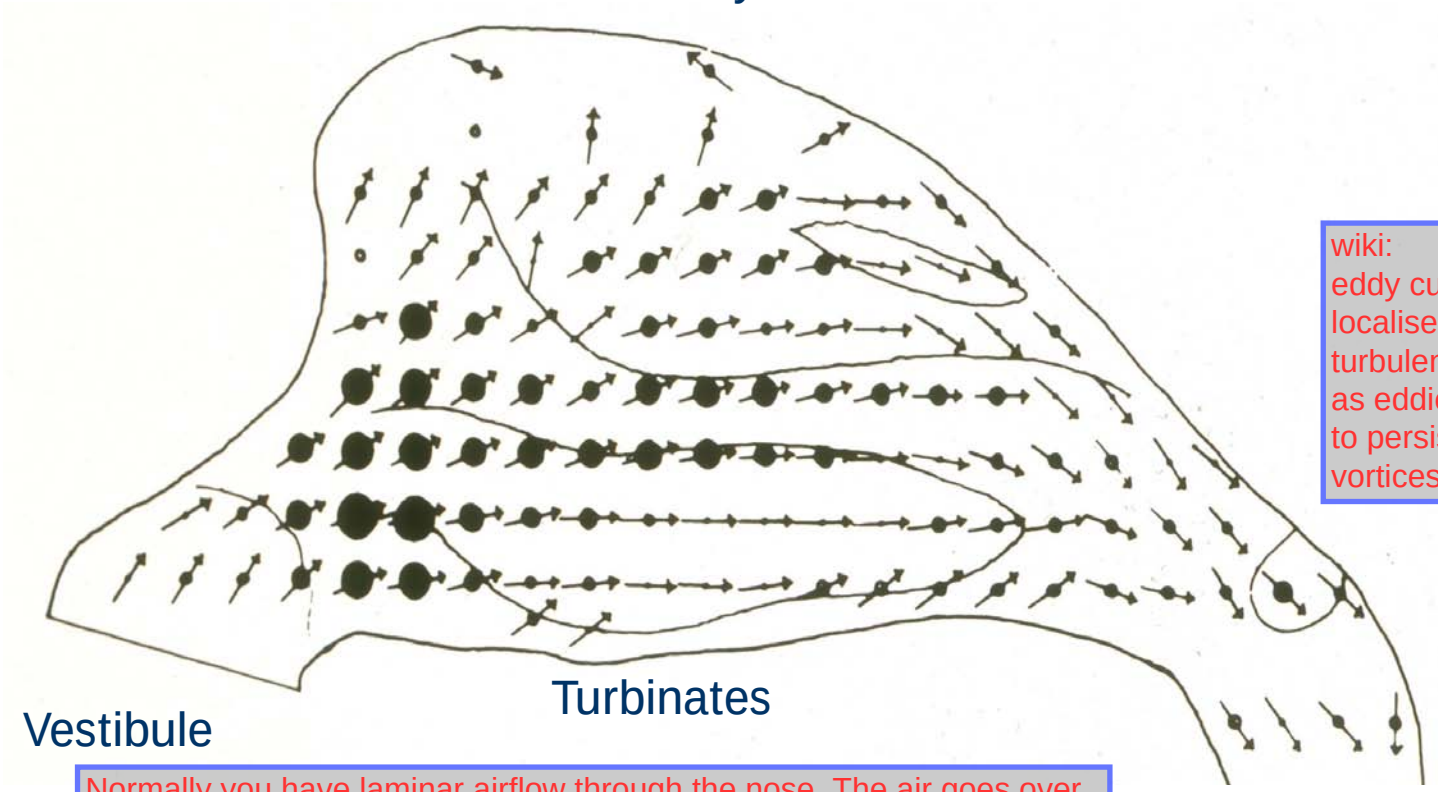
read

- Why do patients complain of difficulty breathing their nose?

23:19

Laminar Airflow Through Nose

Olfactory area



Turbinates

Vestibule

Nasopharynx

wiki:
eddy currents: localised areas of turbulence known as eddies give rise to persistent vortices.

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 unstitiching the nostiril.

24:06

Sarcoidosis

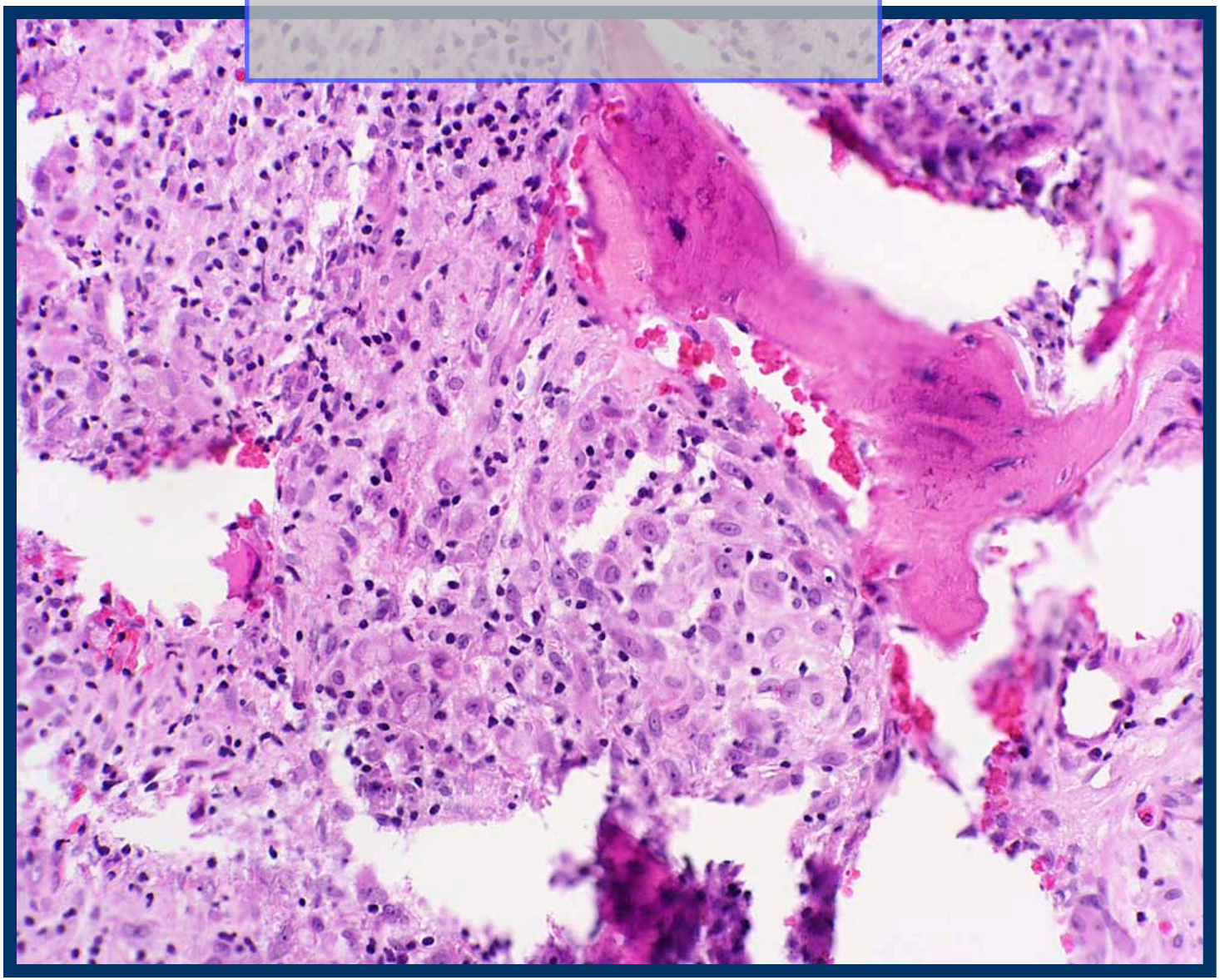
Sarcoidosis (sarc = flesh, -oid = like, -osis = a process), also called sarcoid or Besnier-Boeck disease, is a multisystem granulomatous inflammatory disease characterized by non-caseating granulomas (small inflammatory nodules)

- 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.

There are known associations with environmental factors but the exact origin of the disease is unknown.

24:45

Granuloma associated with the destruction of the bones of the nose.



Nasal sarcoidosis

24:53

Environmental Factors in Upper Airway Neoplasia

25:05

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

genetic component?

the Orient? Do people still say that?

25:25

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?

Trees naturally have defense mechanism to fend off disease and insects. These can cause neoplasia in some individuals.

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.

Plus, we add junk to our wood for various purposes.

These include:

Soft woods produce fluffy dust that our hairs can stop. Hard woods make small dust that can get past the hair and accumulate in the anterior portions of the turbinates.

- Formaldehyde, arsenic, creosotes, phenols, and pentachlorophenol (PCP)

Cabinet makers who make fine dust are more likely to get the neoplasia

- Higher concentration of toxins in hardwoods

28:45

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

parts per million

bc of laws and lab safety

31:28

Formaldehyde

Read

- 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

31:53

Formaldehyde

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

- Wood dust and formaldehyde exposure additive

Risks can be additive between substances.

- Olsen et al. Int J Cancer 34;639, 1984

32:06

Other Environmental Exposures Contributing to Adenocarcinoma

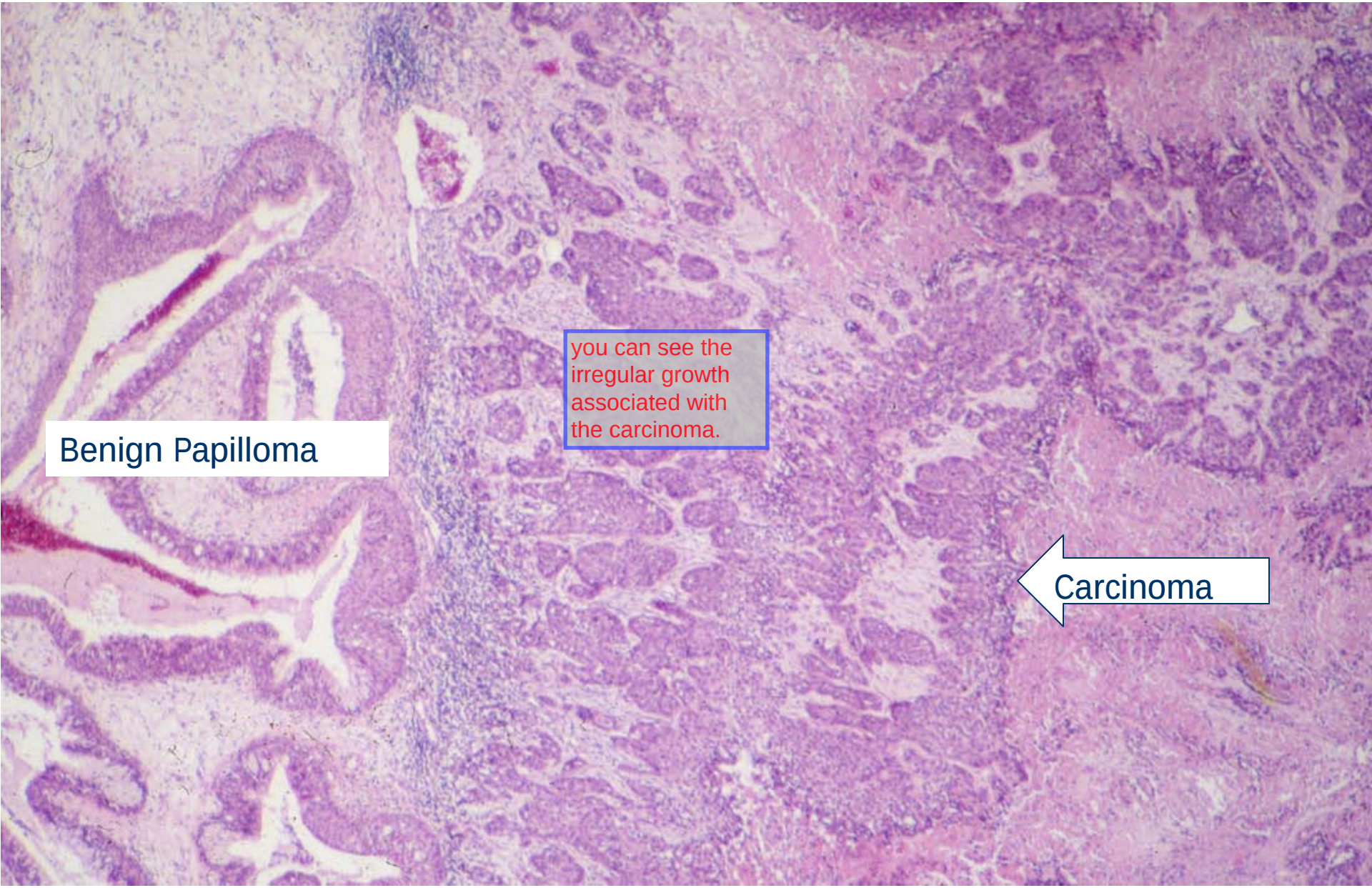
- Exposure to leather dust increases risk of sinonasal adenocarcinoma in men and women
- Smoking increased risk for squamous cell carcinoma.

When we process leather, we add junk like glutaraldehyde to it.

Smoking is always bad.

- Mannetje et al Am J Indust Med 36:101, 1999

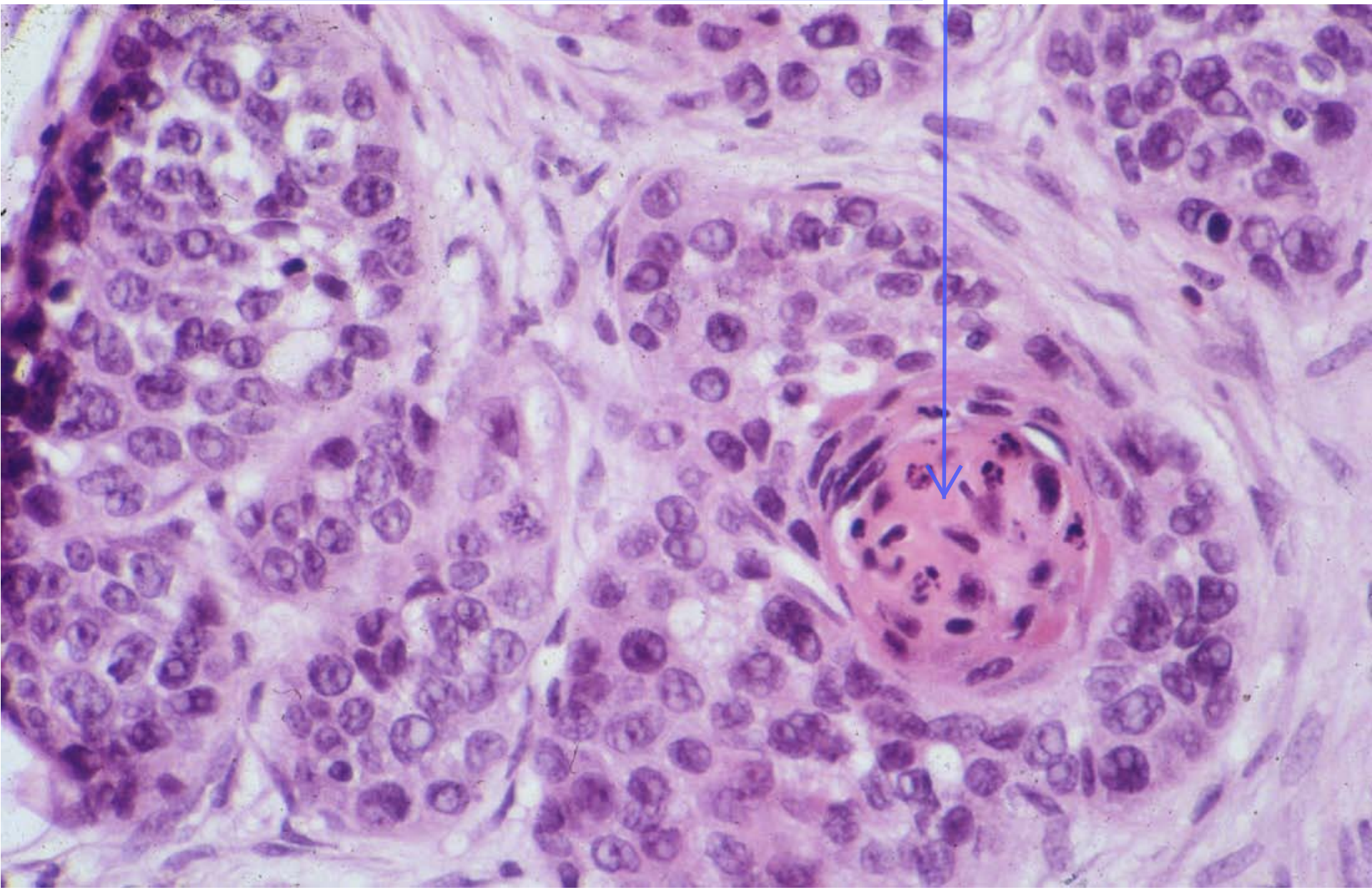
32:47



Squamous cell carcinoma arising in inverted papilloma

33:02

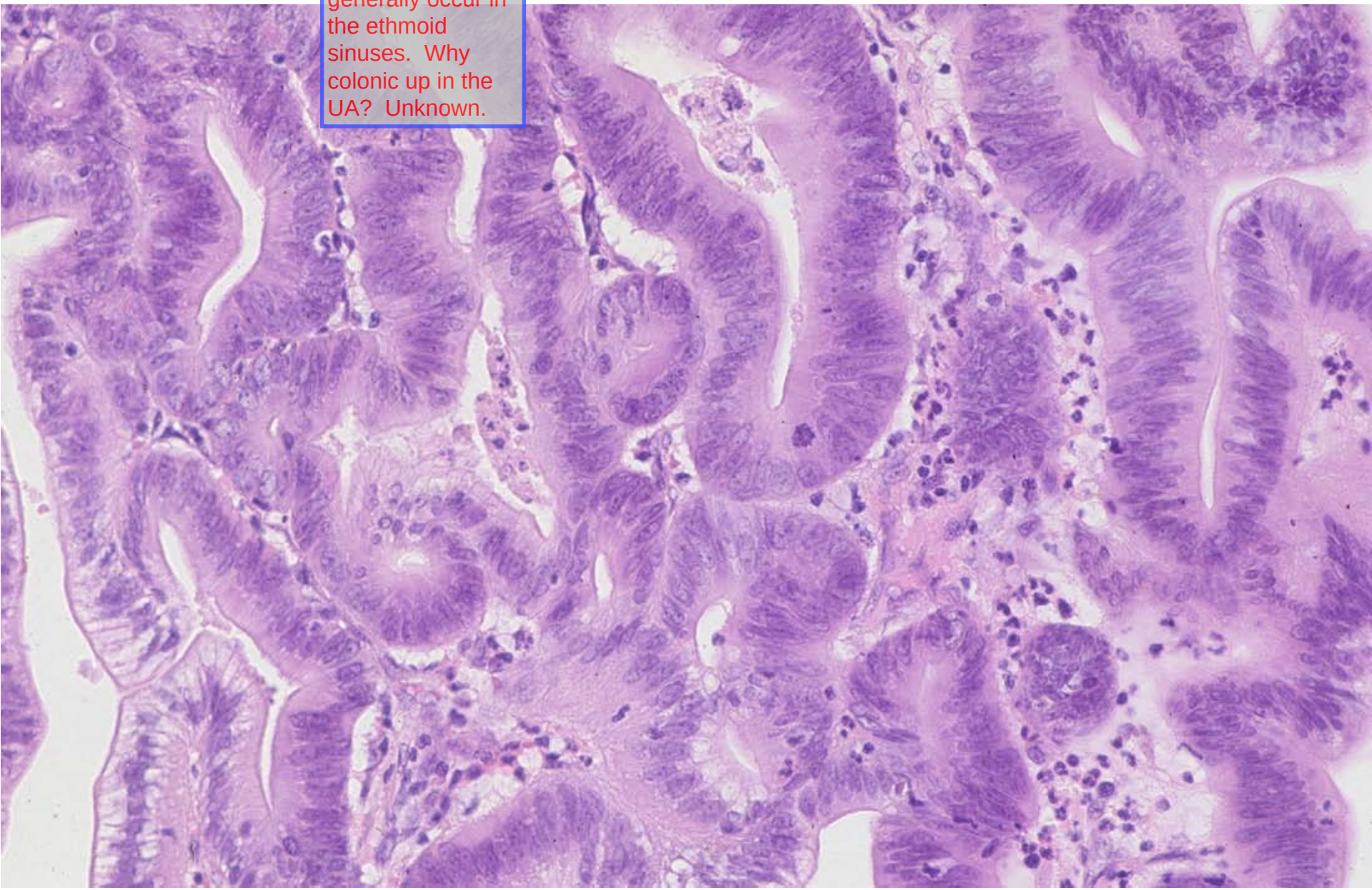
We can see this squamous pearl and so we know that it is squamous cell carcinoma.



Squamous cell carcinoma

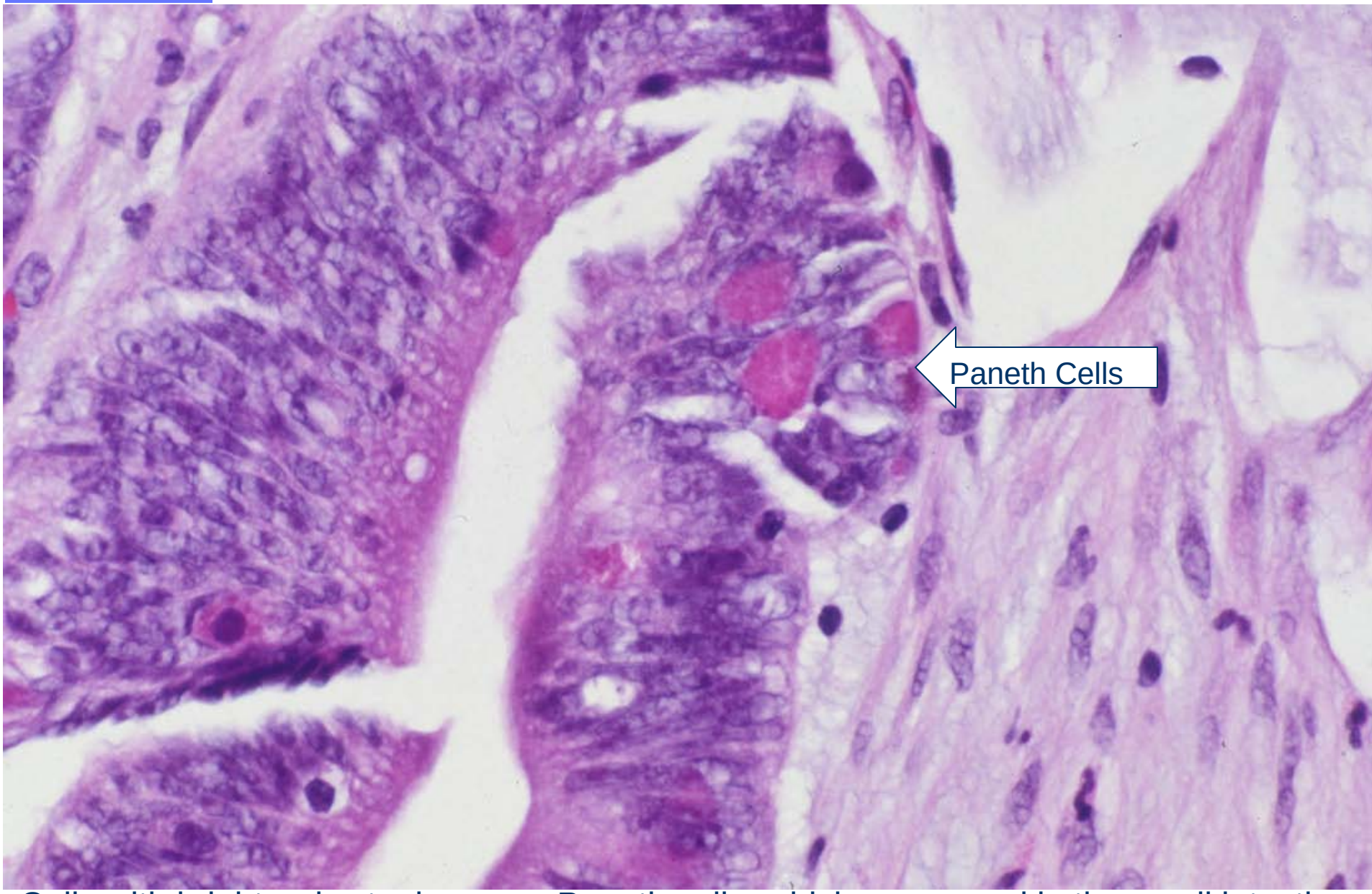
33:12

generally occur in the ethmoid sinuses. Why colonic up in the UA? Unknown.



Sinonasal colonic type adenocarcinoma

33:37



Cells with bright red cytoplasm are Paneth cells, which are normal in the small intestine and parts of the colon

34:00

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 .

34:39

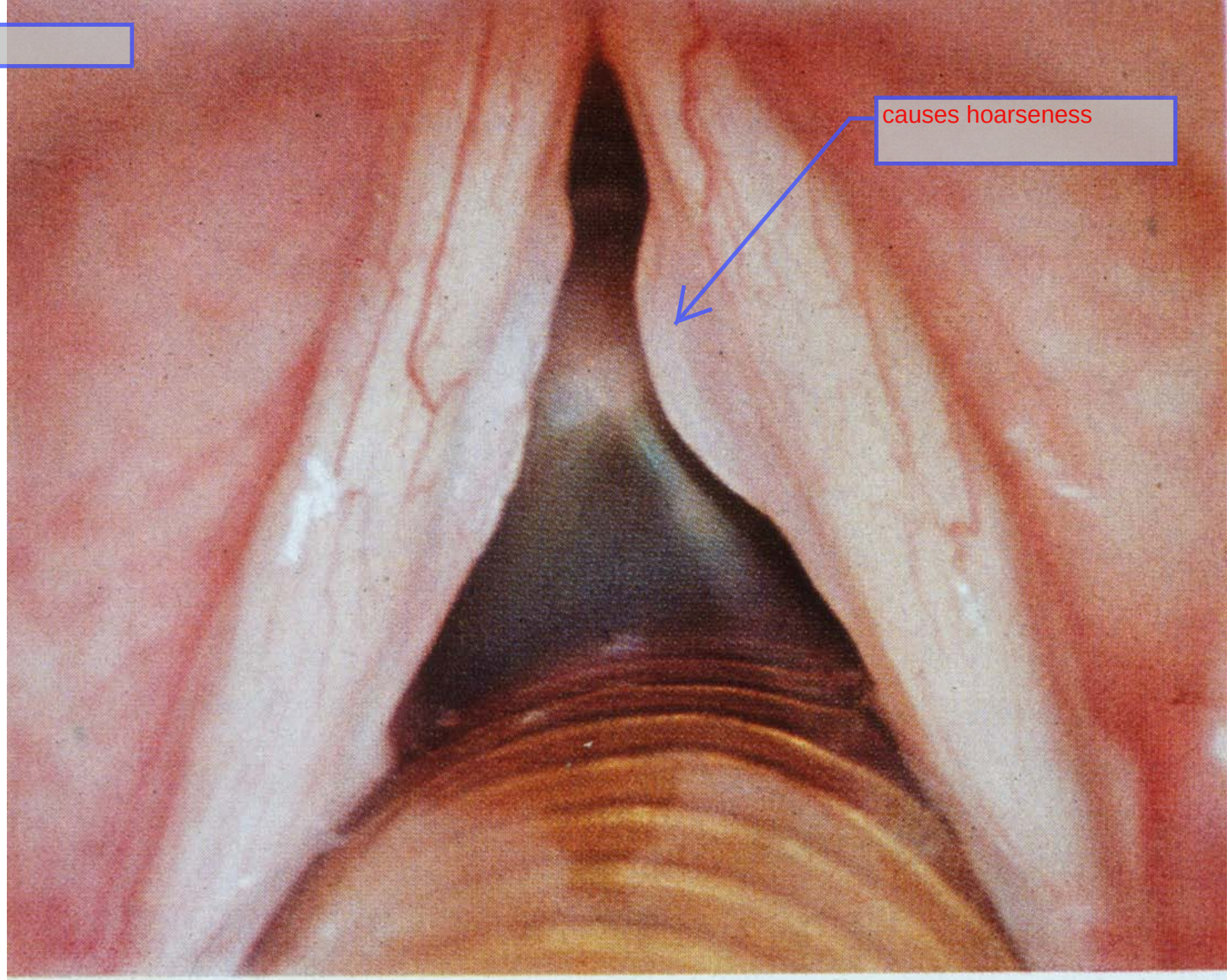
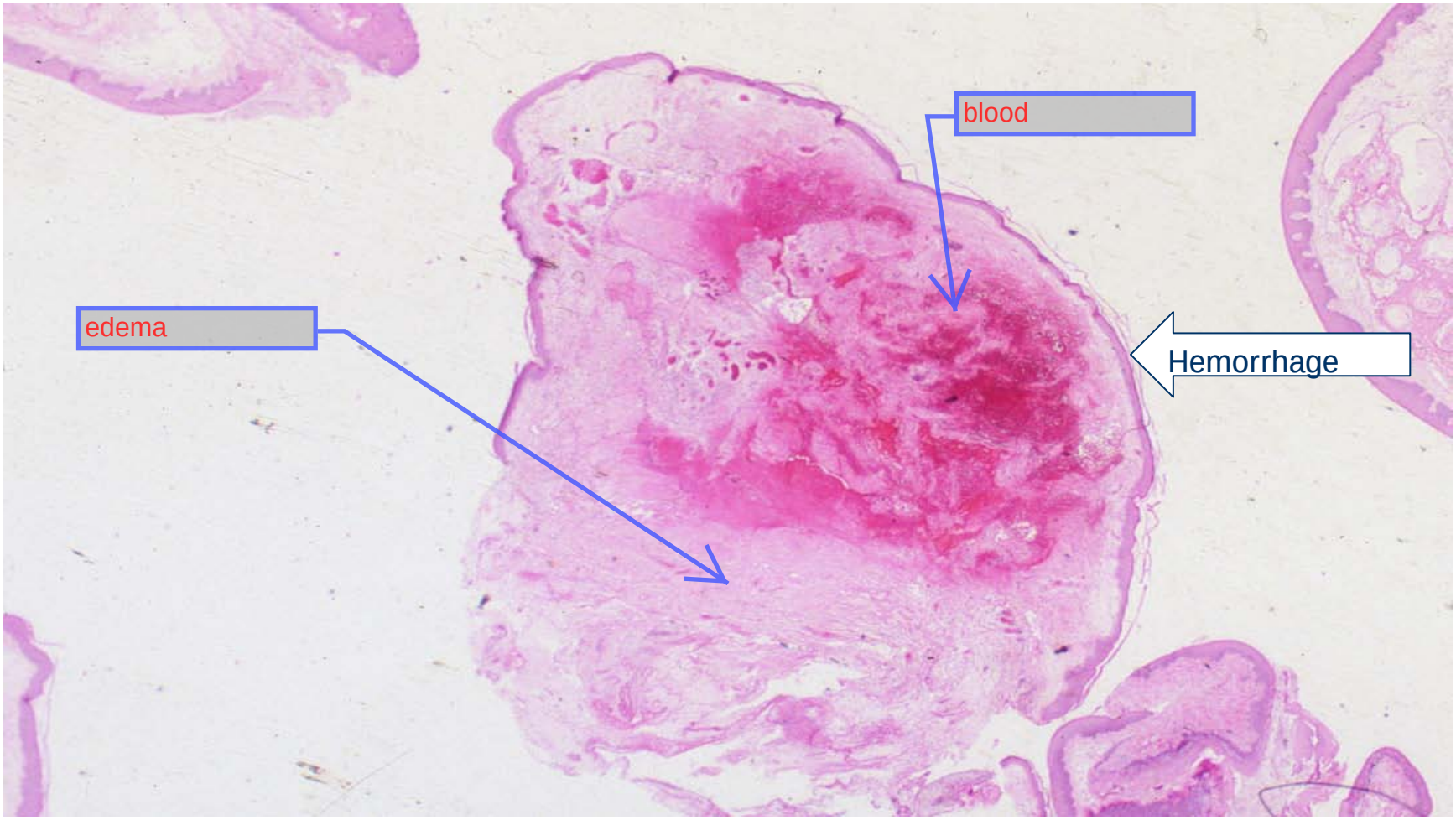


Fig. 95. Gross asymmetry in mature vocal cord nodules.

35:05

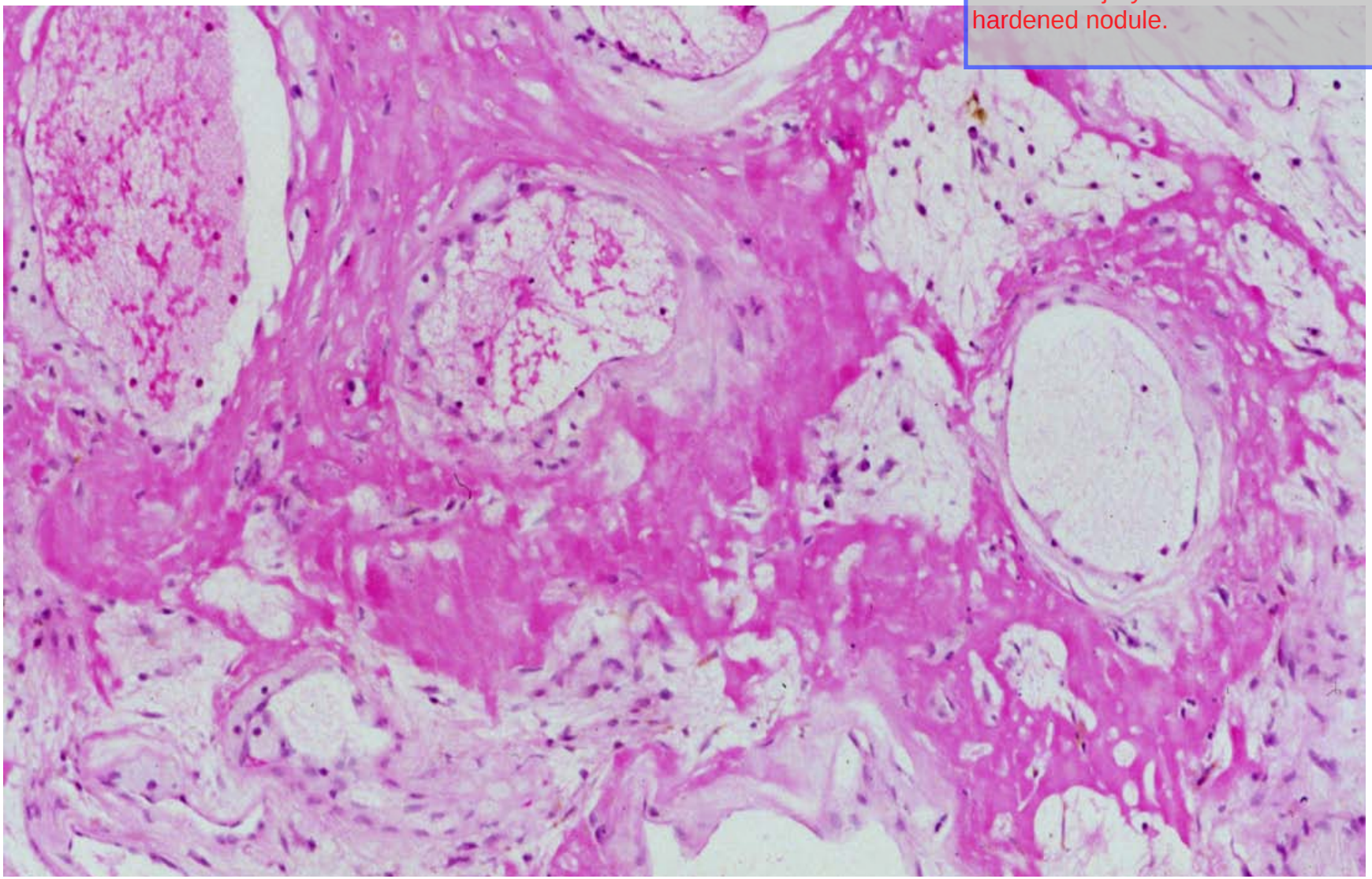
Vocal cord polyp



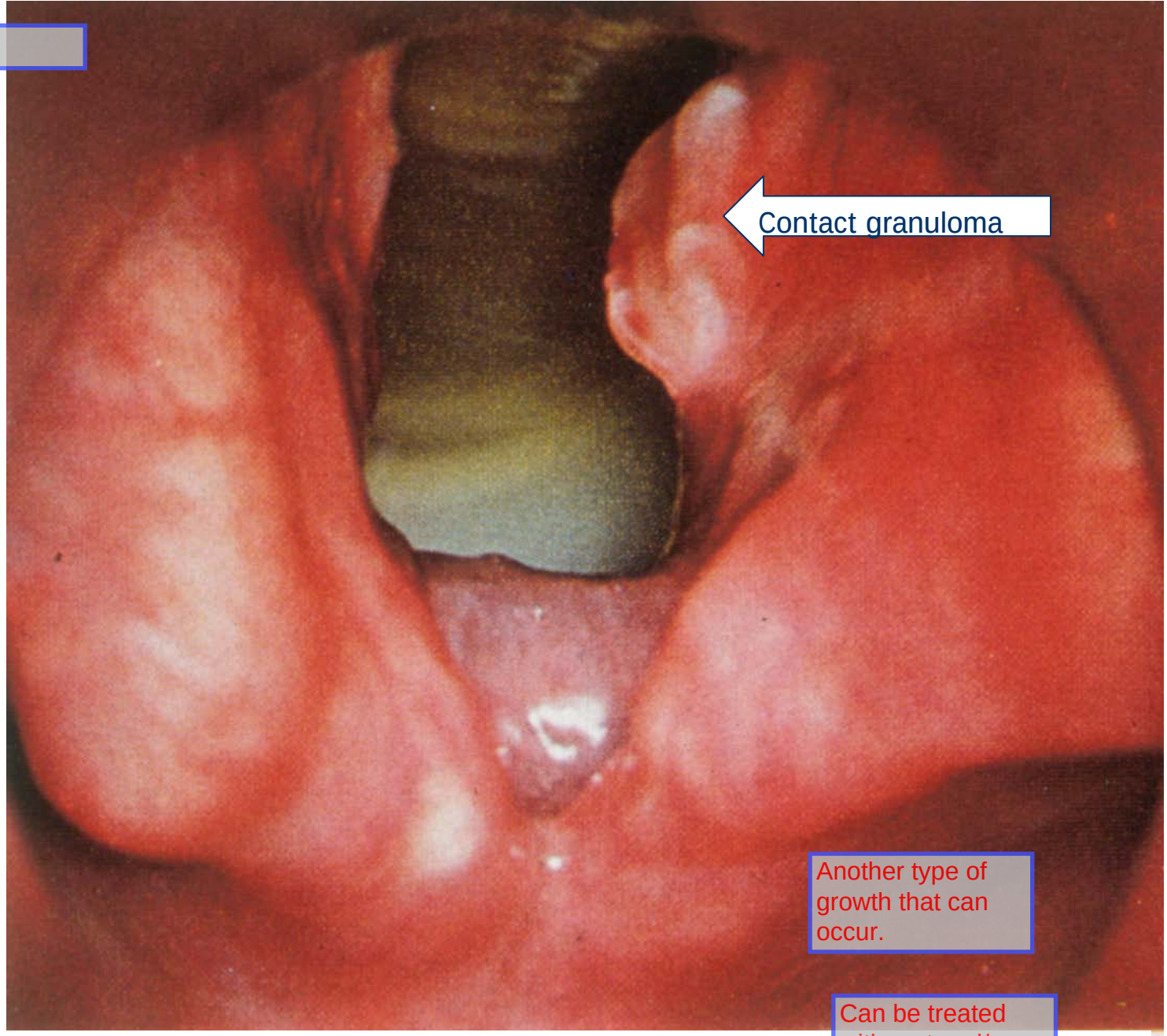
35:25

Vocal cord polyp with edema and hyalinization

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



35:45



Another type of growth that can occur.

Can be treated with rest and/or resection

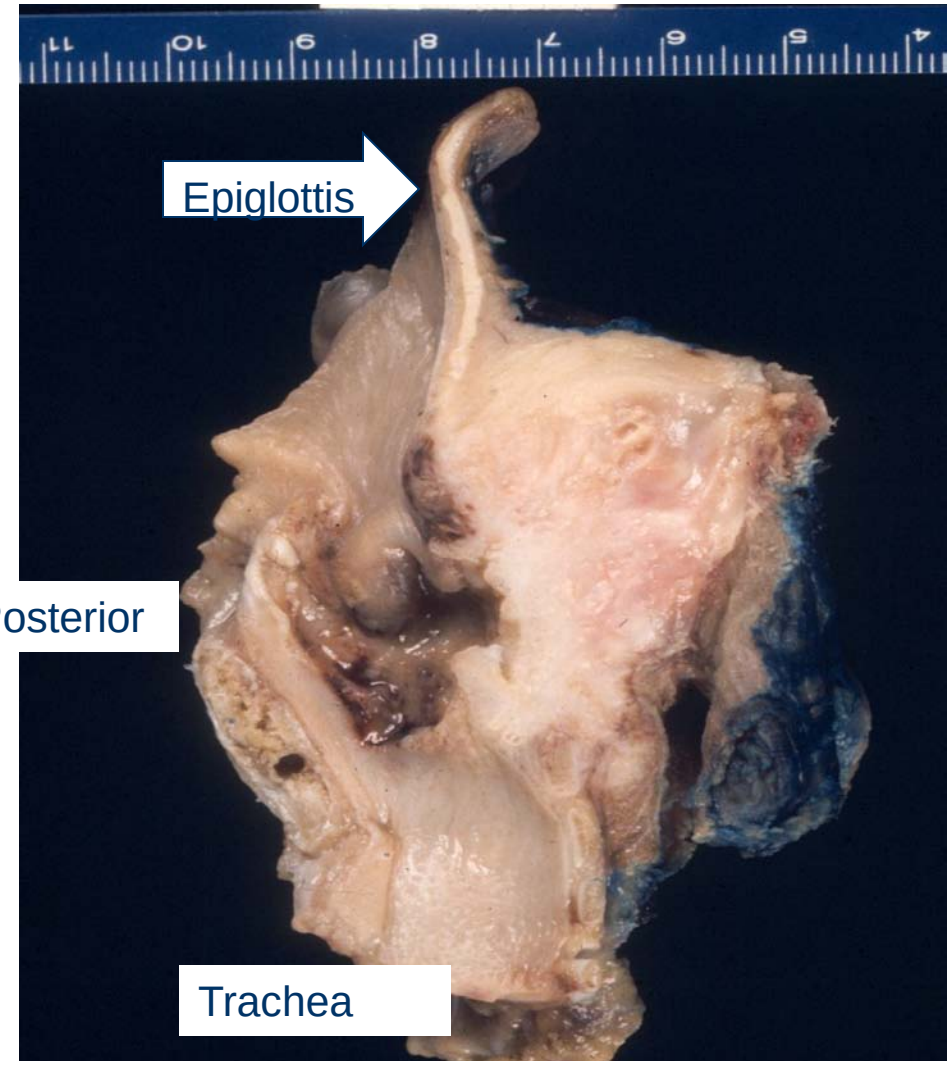
Contact Granuloma

Laryngeal Carcinoma

- 99% squamous cell carcinoma
- Most are males over 60
- Alcohol and smoking are factors

36:31

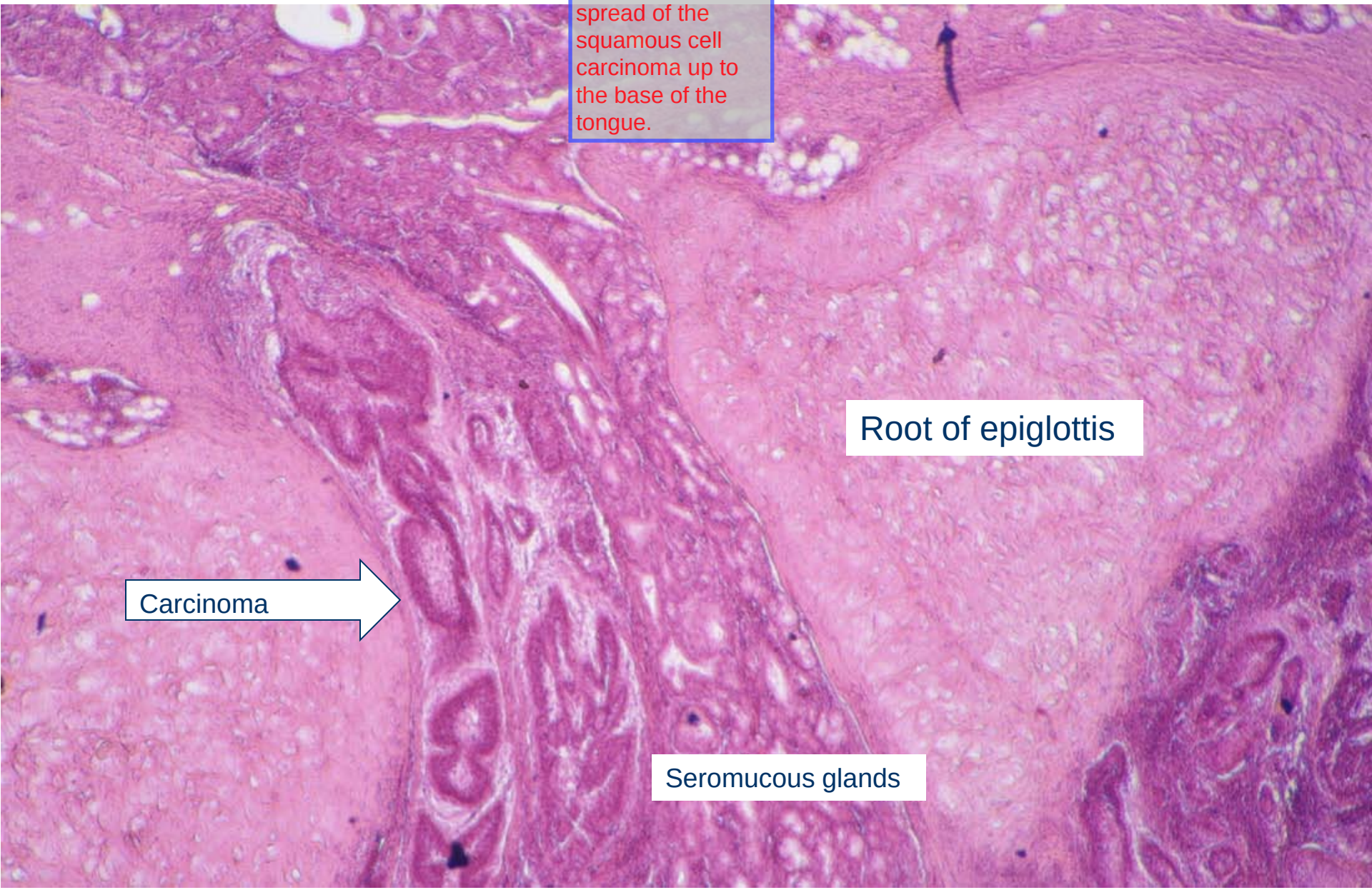
Squamous cell carcinoma of the larynx



Far-advanced carcinoma that has basically destroyed the true and false cords.

36:56

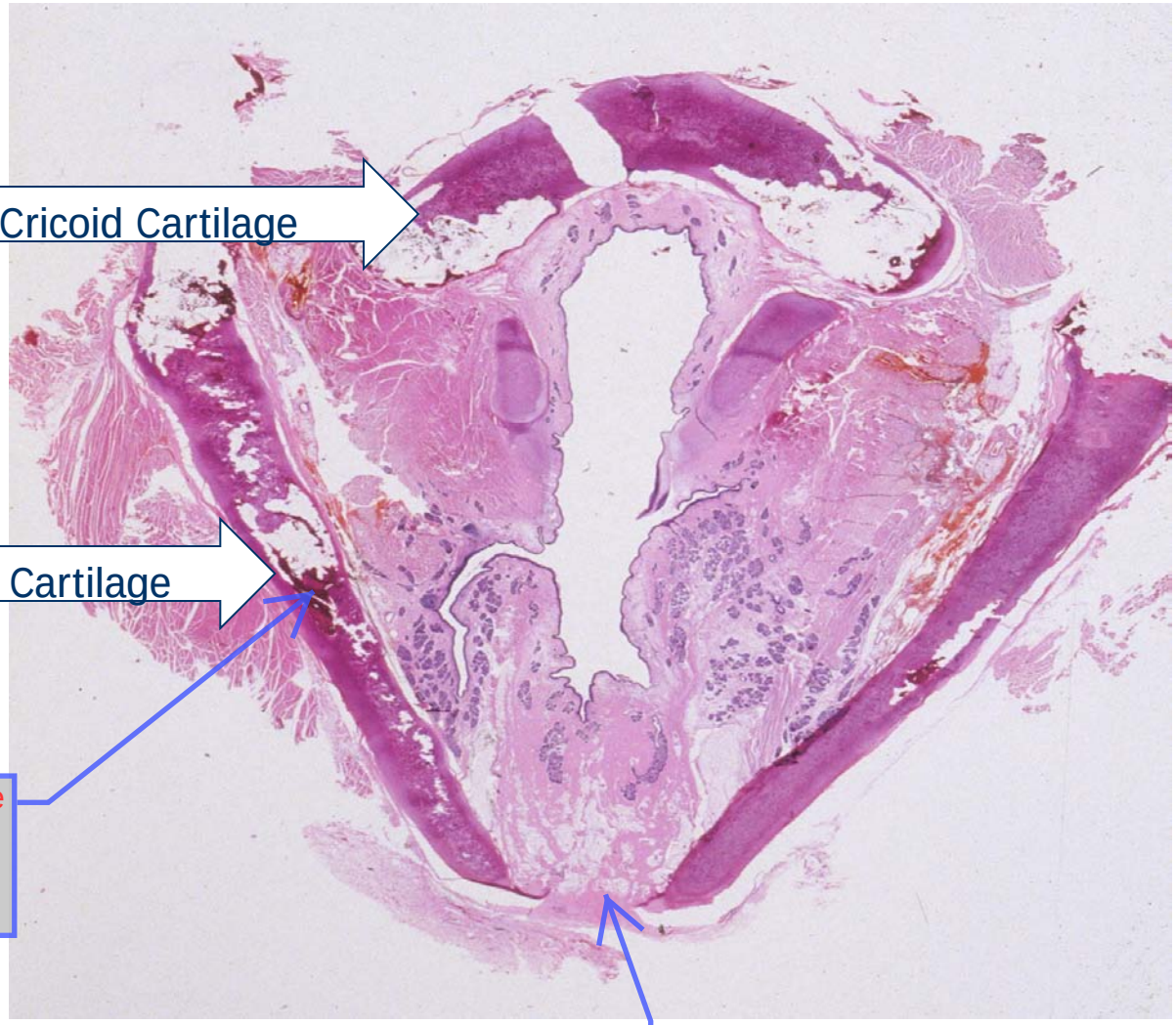
This allows the spread of the squamous cell carcinoma up to the base of the tongue.



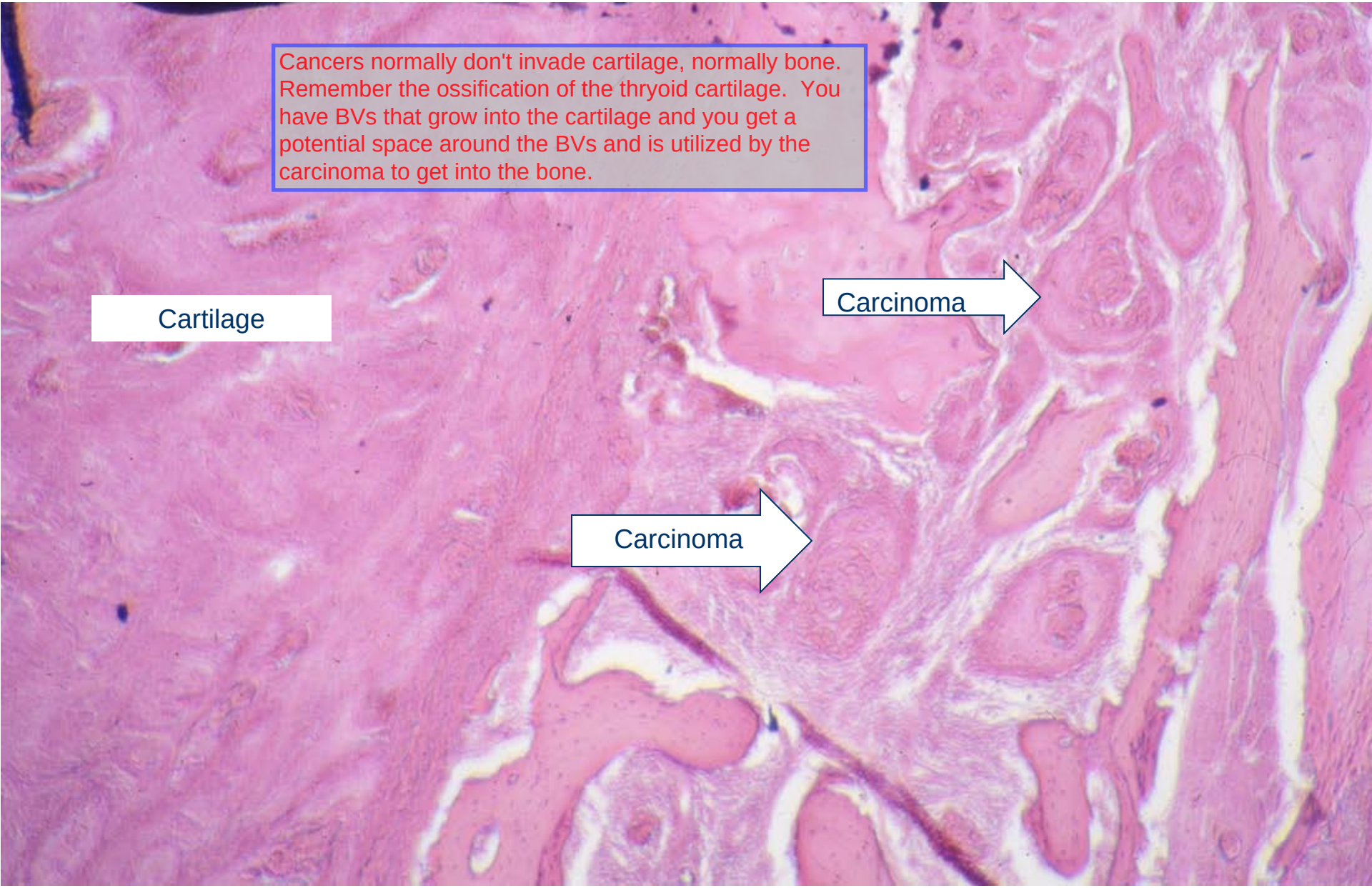
Carcinoma infiltrating in between cartilaginous roots of epiglottis

37:39

Axial Section of Larynx



37:58



Carcinoma in thyroid cartilage

39:04

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 the true cord, you would present earlier bc 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.

39:40

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

Uses this to show that the cell doesn't have to have direct contact with the smoke to have issues.

40;06

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

Note this number is high.

Reference: IARC Monogr Eval Carcinog Risks Hum 2004;83:1-1438

40:18

Smoking and Upper Airway Carcinoma

Depends on the amount you smoke.

- 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

- Reference: J Natl Cancer Inst 2007;99:777-89

40:35

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

41:48

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

42:37

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

AA can also be made by oral bacteria with poor hygiene.

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

43:10

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

Already talked about the synergism.

- Cancer Epidemiol Biomarkers Prev 2006;15 (2196-2202)

43:18

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

GST metabolizes some of the carcinogens of tobacco. Some people don't have GSTM1 = more likely to get CA from smoking. Some people don't have GSTT1 = decrease CA likelihood.

43:48

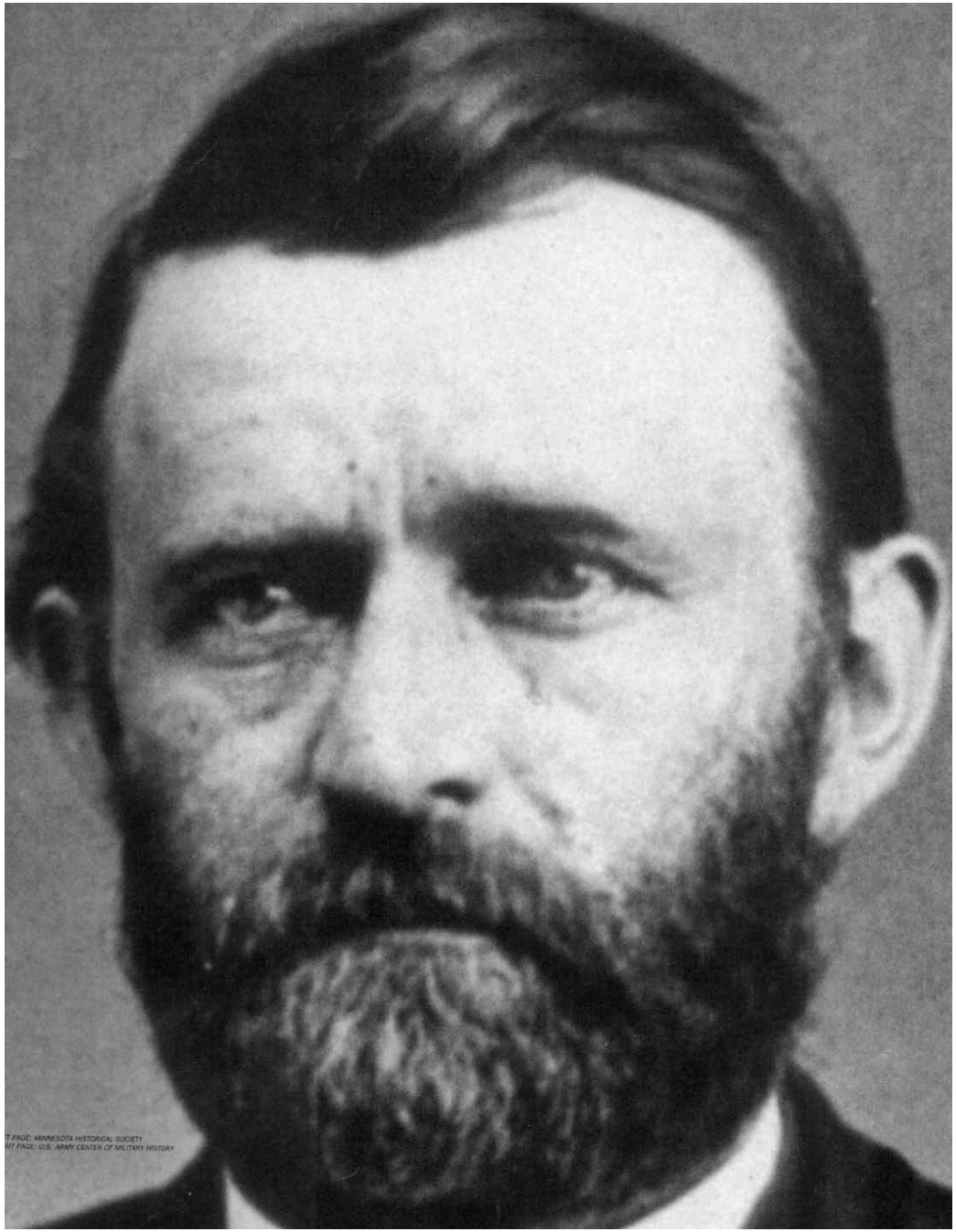
Diet and H&N Cancer

Just read this.

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

- J Cancer Res Clin Oncol (2008)134:93-100

44:06



Grant. Smoked and drank a lot. Developed laryngeal CA.

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

46:51

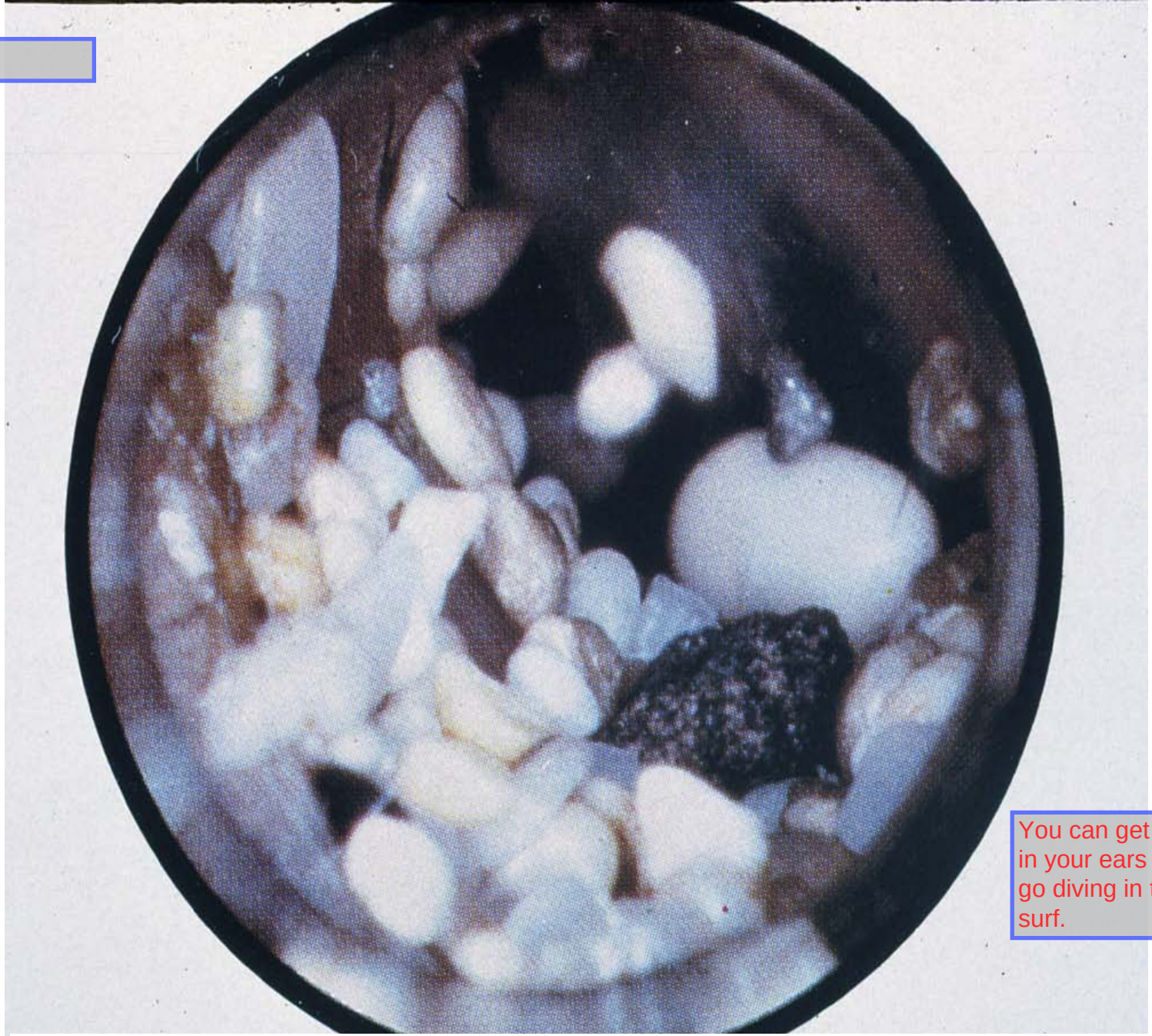
The Ear

Remember that the ear is connected to the UA system through the eustachian tube.

- Deafness
  - Aging
  - Exposure to Loud sounds
- Tinnitus (“ringing in the ears”)

The Musical Note

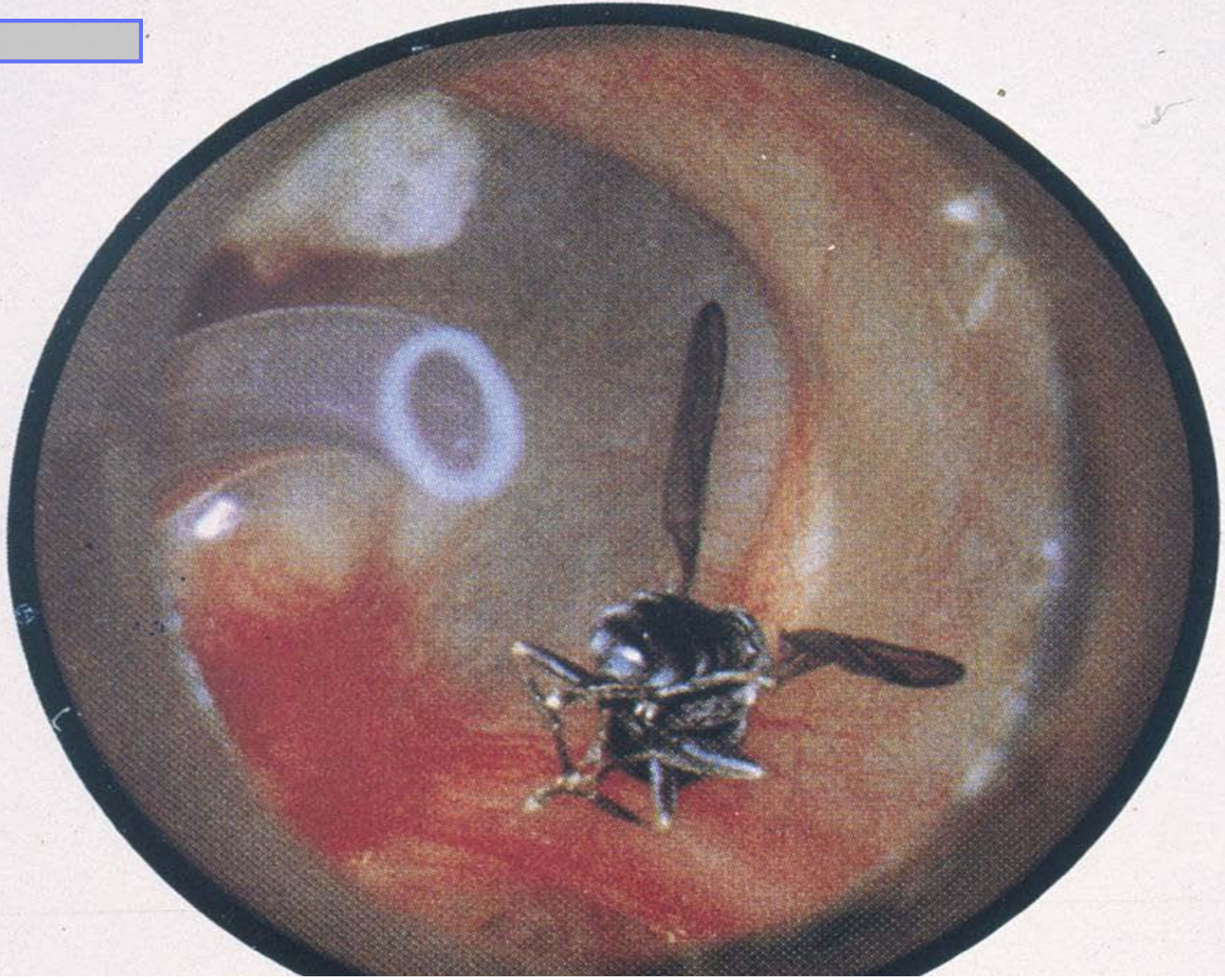
47:36



You can get rocks in your ears if you go diving in the surf.

External Ear Canal after a visit to the beach

47:55



External Ear Canal

The Buzz

48:05

Good summary.

Summary

- 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 recfognize that the orbit and brain are bost close to the UA and so anything (infection ot 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 my 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.