Infectious/Immunological Diseases

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OPTH 727

In this lecture we will go over a “hodgepodge” of diseases that didn’t fit well in any other lecture. Most of these relate to the immune system or affect multiple organ systems. Specifically, we will…

- Touch on main causes of immune compromise
- Go over oral manifestations of HIV

- Talk about deep fungal infections (those with orofacial manifestations)
  - You did not get much of this in microbiology classes

- Immunologic diseases
  - Genetic

Main causes of immune compromise?

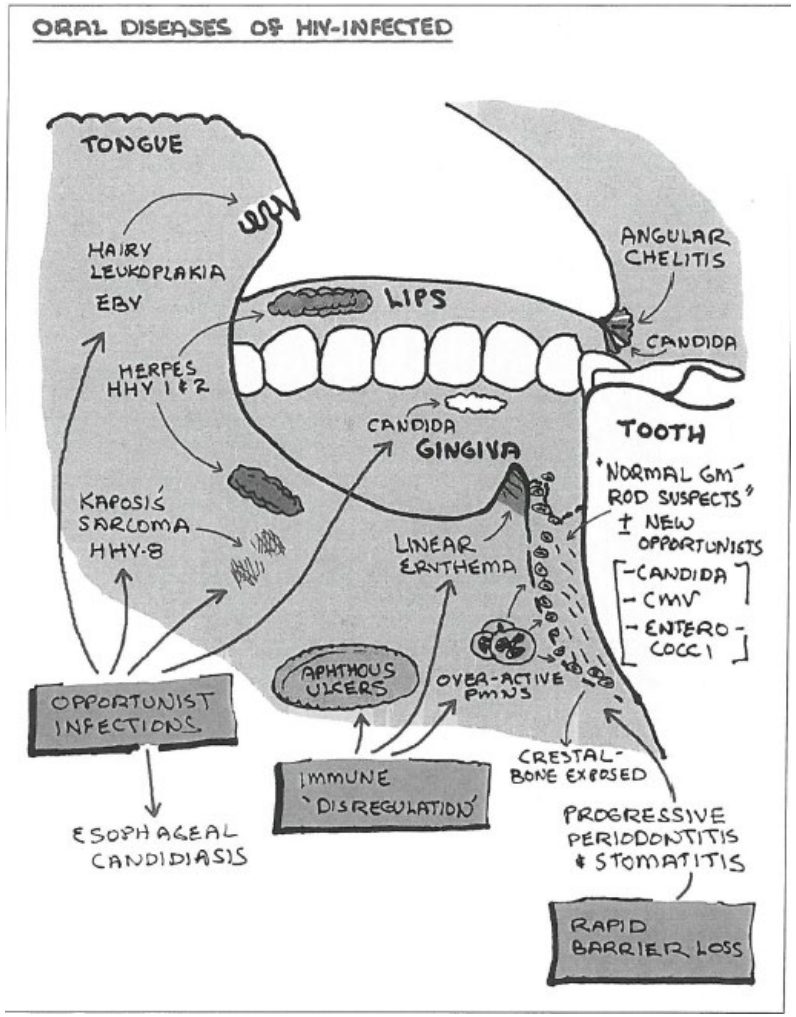
I expect that you may know this, already. I keep reviewing it because understanding immune compromise, i.e. its causes, and its oral sequelae is one of the most important biomedical concepts for our profession.

- HIV/AIDS
- Certain blood cancers (e.g. leukemia)
  - Malignant bone marrow cells crowd out proliferation of functional blood cells – leading to reduction of functional blood cells.
- Other white blood cell disturbances (dyscrasias)
  - Reductions in neutrophils (neutropenia, agranulocytosis, etc.)
- Uncontrolled diabetes
  - Vascular disturbances (angiopathy) will compromise the blood supply to tissues – leads to ischemia and tissue death. Microorganisms may colonize these areas of dead tissue, which has no ability to defend itself.
- Medications
  - Chemotherapeutics for cancer treatment
    - Drugs kill rapidly dividing cells (i.e. cancer cells)
    - Often kill other rapidly diving cells in body, i.e. white blood cells → leads to immune suppression
  - Immunosuppressive drugs
    - Following organ transplant – drugs given to prevent organ rejection
    - Many inflammatory diseases are treated with steroids (which are immunes uppressants) or other non steroidal immunosuppressant drugs
- Liver/spleen dysfunction: these are important
- Nutritional deficiencies (more common outside USA)

- Note: there are genetic causes of immune compromise (see later slides): these are more rare, but they could be asked on a board examinations. The most common causes of immune compromise are acquired (not inherited) and listed above.

Oral manifestations of HIV

From Dr. Tom Maier's notes



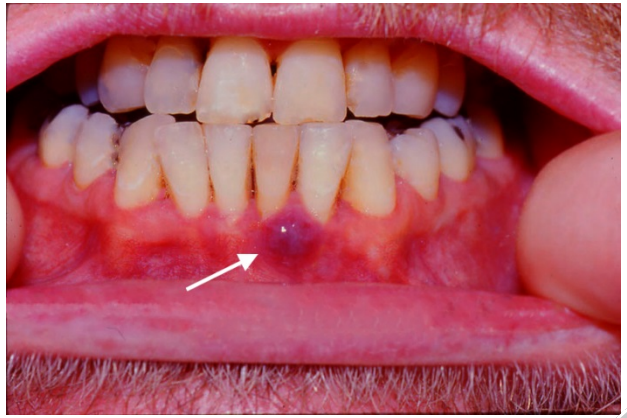
My take on oral manifestations of HIV/AIDS

- Basically, all infectious agents go "gangbuster"
  - HHV 1 (and 2)
    - Herpetic gingivostomatitis- much more severe
  - HHV8 –
    - Kaposi's Sarcoma (see next page)
  - HPV
    - Numerous wart like lesions
  - C.albicans
    - Candidiasis
  - Necrotizing Gingivostomatitis
    - Like what you might see in leukemia, neutropenia, agranulocytosis
  - More advanced periodontitis
  - Oral hairy leukoplakia (EBV mediated)
  - CMV mediated disease

- In addition…
- Generalized lymphadenopathy (cervical)
- Osteomyelitis
- Increased cancer rate
  - Lymphoma (many types are virally mediated- EBV)
  - Squamous cell carcinoma
- Deep fungal infections (see later slides)
- Molluscum contagiosum (poxvirus)

Kaposi's sarcoma

- Unusual vascular neoplasm
- Purple nodules, papules, macules
- HHV8 associated
- Associated with immune compromise
  - HIV/AIDS
  - Organ transplant patients
  - Immunosenescence
    - Seen in elderly
      - When you get old… the immune system doesn't work like it should
    - Often seen in Italian or Mediterranean men



Deep fungal diseases

“Deep” fungal infections

- Histoplasmosis
- Blastomycosis
- Paracoccidiomycosis
- Coccidiomycosis
- Cryptococcus
- Mucormycosis (Mucor)
- Aspergillosis

Q: Why do we call these “deep”?

A: More common fungal infections affect superficial tissues, i.e. skin (athletes foot, jock itch, etc.) or mucous membranes (candidiasis, a.k.a. yeast infections).

“Deep” fungal infections are aptly named because the primary infection site are… “deeper” – usually, the respiratory system, i.e. lungs or nasal cavity.

-mycosis… usually means fungal infection… but not always

These are fungal

- Histoplasmosis
- Blastomycosis
- Paracoccidiomycosis
- Coccidiomycosis

- Cryptococcosis
- Mucormycosis (Mucor, Zygomycosis)
- Aspergillosis

Please know this slide… you need to know which of the disease entities on this page are fungal infections and which are not. The entities that are not fungal infections… what are they?

On the other hand:
"Mycosis fungoides"
is not a fungal infection. It is a T-cell lymphoma (a type of blood cancer) found on the skin.

Actinomycosis – is a bacterial infection. Actinomycetes (bacteria) when clumped together looks like fungus under the microscope.

"Deep" fungal infections

- Histoplasmosis
  - *Histoplasma capsulatum*
  - Ohio/Mississippi river valley
  - Very common- 500K new cases in USA every year
- Blastomycosis
  - Eastern half of USA
  - *Blastomyces dermatitidis*
- Paracoccidiomycosis
  - Central and South America
  - M:F ratio is 15:1 (estrogen has protective effect)
  - *Paracocciodioides brasilienis*
- Coccidiomycosis
  - Southwestern USA and Mexico
  - Also known as "valley fever"
  - *Coccidioides immitis*

For exam, you DO NOT need to know the disease-specific information to the left of the dashed blue line

Commonalities with the four diseases on this page

1. Causative fungal spores found in soils (often from excrement of particular animals)- Diseases are region specific.

2. Fungal spores usually enter body through inhalation. Primary site of infection is usually lungs.

3. Primary infection – causes self-limiting flu-like disease or no disease at all

4. Immunocompromise may lead to more serious disease. Immune compromise could lead to more severe respiratory disease; or could lead to
fungi entering blood stream (septicemia); or could lead to distribution to other tissues (dissemination)

Dissemination to oral cavity or skin leads to oral blisters, ulcers, or swellings (these may look similar to oral cancer)

5. Granulomatous inflammation. A histological presentation of the disease that helps in diagnosis.

Potential board question? Which diseases lead to granulomatous inflammation? Answer: tuberculosis (caseating), Crohn's disease, sarcoidosis, deep fungal infections, foreign body reactions and a few others.

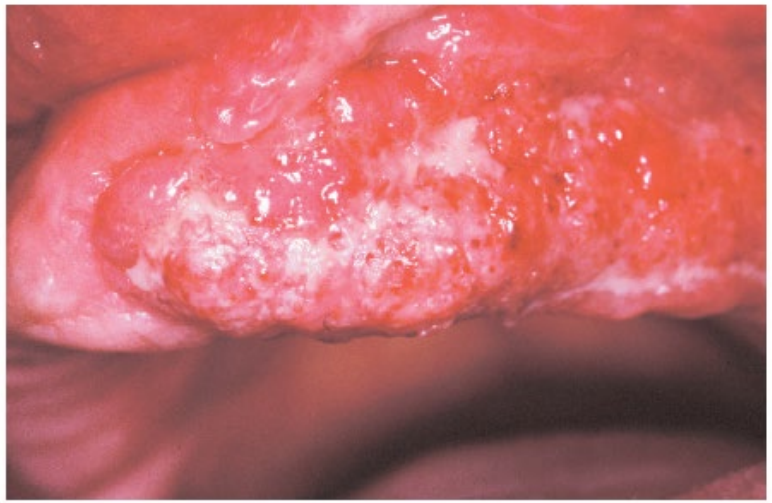
• **Fig. 6-19 Histoplasmosis.** This chronic ulceration of the ventral and lateral tongue represents an oral lesion of histoplasmosis that had disseminated from the lungs. The lesion clinically resembles carcinoma; because of this high-risk site, biopsy is mandatory.

• **Fig. 6-18 Histoplasmosis.** This ulcerated granular lesion involves the mandibular labial vestibule and is easily mistaken clinically for carcinoma. Biopsy established the diagnosis. (Courtesy of Dr. John Werther.)

• **Fig. 6-29 Coccidioidomycosis.** This ulcerated nodule involving the mid-dorsal tongue represents disseminated coccidioidomycosis. (Courtesy of Dr. Craig Fowler.)

• **Fig. 6-22 Blastomycosis.** This granular erythematous plaque of cutaneous blastomycosis has affected the facial skin. (Courtesy of Dr. William Welton.)

• **Fig. 6-25 Blastomycosis.** Granular exophytic and indurated mass on the buccal mucosa.



• **Fig. 6-27 Paracoccidioidomycosis.** This granular, erythematous, and ulcerated lesion of the maxillary alveolus represents infection by *Paracoccidioides brasiliensis.* (Courtesy of Dr. Ricardo Santiago Gomez.)

Take home point: oral manifestations of deep fungal infections mimic the appearance of oral cancer

Cryptococcosis – deep fungal infection

- *Cryptococcus neoformans (mostly)*
- Similar in many ways to other deep fungal infections
  - Inhalation of spores (pigeon excrement), produces flu-like illness
    - Spores have worldwide distribution- not region specific
- Associated with HIV/AIDS epidemic
  - 10-15% of AIDS patients
  - Dissemination to brain (meninges)
    - Cryptococcal meningitis – Can be fatal
  - Orofacial manifestations-
    - Papules on skin

• **Fig. 6-30 Cryptococcosis.** These papules of the facial skin represent disseminated cryptococcal infection in a patient infected with human immunodeficiency virus (HIV). (Courtesy of Dr. Catherine Flatz.)

Mucormycosis- deep fungal

- Opportunistic infection
  - Almost always seen in immune compromised
  - Often leads to fulminant disease
    - What does fulminant mean? Sudden onset of severe disease.
- Deadly, destructive, dangerous!!!
- Primary infection – nasal cavity
  - Highly destructive – infection spreads rapidly
  - Black, necrotic tissue often on palate

• **Fig. 6-31 Mucormycosis.** Diffuse tissue destruction involving the nasal and maxillary structures caused by a *Mucor* species. (Courtesy of Dr. Sadru Kabani.)

• **Fig. 6-32 Mucormycosis.** The extensive black, necrotic lesion of the palate represents mucormycotic infection that extended from the maxillary sinus in a patient with poorly controlled type I diabetes mellitus. (Courtesy of Dr. Michael Tabor.)

Aspergillosis- deep fungal infection

- Two types: “non-invasive” and “invasive”
- Non-invasive disease –
  - Not serious – nasal symptoms – stuffiness, etc
- Invasive disease –
  - Usually in immune compromised
  - Disseminated disease
  - Lungs, nasal cavity, other organs

- Infection often obtained in hospitals – Nosocomial
  - Especially bad if patient is hospitalized due to immune compromise

Immunological Diseases

Genetic diseases that lead to severe immune compromise (these are all very rare).

Take home message: know that these 4 entities are genetic diseases that may lead to immune compromise from the time of infancy (some presentations may be severe). Also know that "transient hypogammaglobulinemia of infancy" is when an infant is slow to start making its own immunoglobulins – leading to immune compromise in infancy. This is NOT genetic.

- Bruton's agammaglobulinemia
  - X-linked
  - B-cells not produced
    - Leads to lack of antibodies (more specifically, gamma globulins)
- SCID (severe combined immunodeficiency), "bubble-boy" disease
  - Many different mutations/clinical presentations/inheritance patterns
    - Some X-linked, some autosomal recessive, etc…
  - Usually leads to deficiency of B and T cells
- Chediak-Higashi Syndrome
  - Genetic disease that leads to decrease in phagocytosis
  - Specifically – leads to reduced neutrophil function
  - Leads to high susceptibility to bacterial infections
    - Other clinical manifestations: albinism and early onset periodontal disease
- Wiskott-Aldrich syndrome
  - X-linked
  - Eczema, thrombocytopenia (low platelet count), immune deficiency (reduced immunoglobulin production)

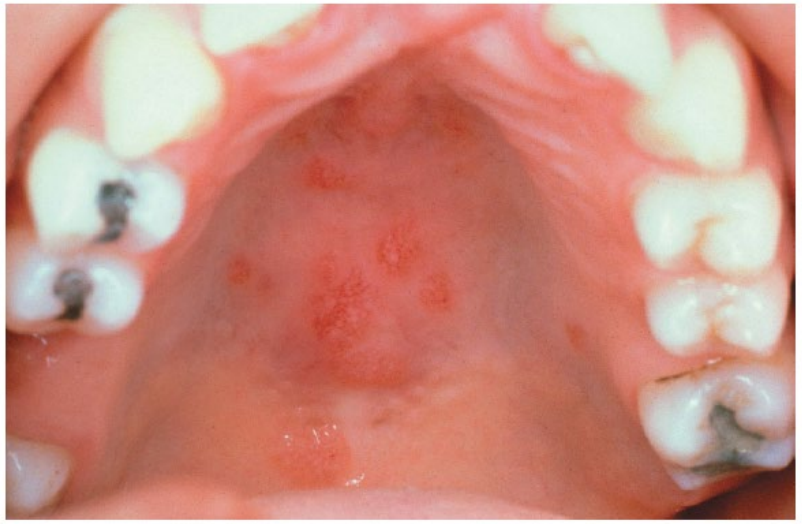
Sarcoidosis

- Multi-system disorder
- Unknown cause (is it auto-immune, inflammatory? But it is not infectious)
  - Females and AA more commonly affected
- Many organs may be affected (including skin and oral cavity)
  - Lungs most commonly affected
    - May produce symptoms such as fatigue, shortness of breath, fever
  - Sarcoidosis is often a disease of exclusion… i.e. Need to rule out other diseases
- Orofacial manifestations:
  - Macules/nodules may be seen in oral cavity and perioral skin.
    - Biopsy will show noncaseating granulomatous inflammation

Sarcoidosis

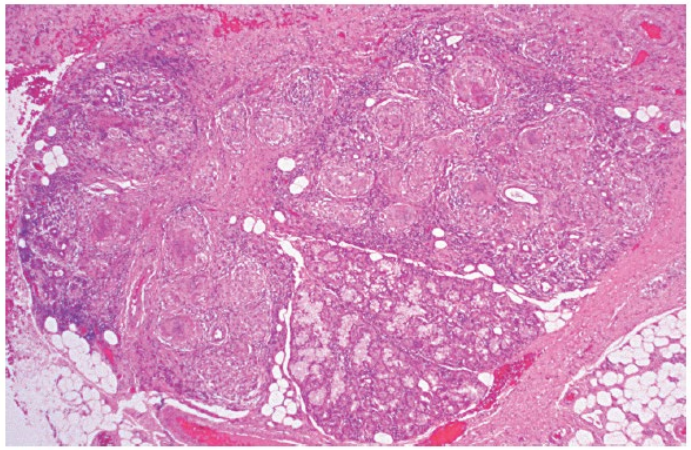
This disease will be covered more in oral pathology courses…

• **Fig. 9-14 Sarcoidosis.** Violaceous indurated plaques of the right malar area and bridge of nose. (Courtesy of Dr. George Blozis.)



• **Fig. 9-15 Sarcoidosis.** Multiple erythematous macules of the hard palate. (Courtesy of Dr. George Blozis.)

• **Fig. 9-16 Sarcoidosis.** Erythematous macules with central hyperkeratosis of the lower labial mucosa.



• **Fig. 9-17 Sarcoidosis.** Photomicrograph of a labial minor salivary gland demonstrating granulomatous inflammation characterized by circumscribed collections of histiocytes, lymphocytes, and multinucleated giant cells.

A case of hereditary angioedema

Angioedema

- Characterized by diffuse edematous swelling of soft tissues
  - Usually affects submucosal/subcutaneous tissues (face commonly affected)
    - May affect respiratory/GI tract – which would be much more serious (respiratory failure)
- An increase in vascular permeability is most common cause
  - The most common cause of angioedema is mast cell degranulation… which leads to histamine release… i.e. IgE mediated hypersensitivity.
    - Mast cell degranulation may be precipitated by many things… foods, other materials, heat, cold, stress, medications (especially ACE inhibitors)
  - Angioedema may also result from activation of complement pathway
    - Hereditary angioedema
      - Lack of C1 esterase inhibitor
      - Disease leads to greater transformation of C1 to C1 esterase
    - There are othr acquired forms of complement mediated angio-edema (will not cover these)

Raynaud's Phenomena

- Results from exaggerated vasoconstriction of arteries and arterioles in the extremities (hands and feet).
  - Restricted blood flow induces attacks of pallor (paleness) or cyanosis (blue) of the hands and feet.

- Primary vs. Secondary Raynaud's phenomenon
  - Primary Raynaud's phenomenon
    - Caused by exaggerated central and local vasoconstriction in response to cold or emotion.
    - Very common…affects 3-5% of population
      - Women more than men- often young women
    - Primary Raynauds usually not much of a problem

  - Secondary Raynaud's phenomenon
    - When Raynaud's is associated with another vascular/immunological disease
      - Systemic lupus erythematosus (SLE)
      - Scleroderma
      - Buerger disease (a type of vasculitis)
      - Atherosclerosis
    - Important point… because Raynaud's phenomenon may be the first clinically noticeable manifestation of the above diseases… someone with Raynauds should get evaluated.

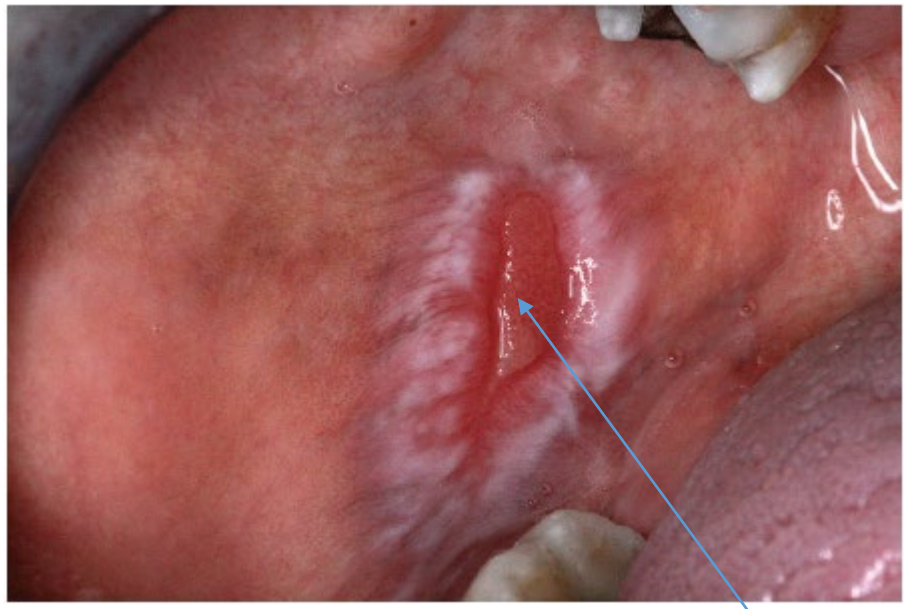
Key question… what is more concerning… primary or secondary Raynaud's?

Lupus Erythematosus (Lupus)

- Lupus is a classic immunological mediated condition
  - Numerous autoantibodies produced against various antigens
  - Deposition of immune complexes in tissues cause disease

- Two main types of Lupus
  - Systemic Lupus Erythematosus (SLE)… next slide will discuss in more detail
    - Far more serious
    - Multisystem disease
    - Usually, when someone says “Lupus”, they are talking about the Systemic type
    - Much more common in women
  - Chronic cutaneous lupus erythematosus
    - Disease manifests in skin/mucous membranes (oral)
    - Note: in SLE; skin/mucous membrane involvement is also seen

Lupus - orofacial manifestations (seen in both the chronic cutaneous and systemic lupus)



Lichenoid lesions

Malar rash

Systemic Lupus Erythematosus (SLE)

- Serious multisystem disease
- Systemic signs include fatigue, malaise, fever, weight loss
- Many organ systems **<u>may</u>** be affected (clinical presentation differs for each patient)
  - Cardiopulmonary
    - Pericarditis
  - Renal
    - Nephrotic disease
    - Renal failure

  Most serious
  - Hematological, neurological, musculoskeletal also possible
  - Oral/cutaneous- important because they may be the first visible signs of disease.
    - Malar rash (see photo on next page)
    - Lichenoid/erythematous oral involvement (see photo on next page)
- Diagnosis of SLE is based on:
  - Serology- analysis of auto-antibodies
    - The presence of certain autoantibodies may distinguish SLE from other autoimmune diseases.
  - Biopsy of skin-
    - Immune complexes deposited in basement membrane zone.

Scleroderma (systemic sclerosis)

- Rare group of autoimmune diseases
- Affect skin, connective tissues, blood vessels and many internal organs
- Unknown cause
  - Adult onset
  - Women far more commonly affected than men
- Common characteristics:
  - Skin thickening/hardening – due to immune attack and subsequent fibrosis
    - Sclero = hard…. Derma = skin
    - Hands and face are often affected (see next slide)
  - Raynauds phenomenon also seen.
- More serious when internal organs are involved.
  - Pulmonary fibrosis
    - Pulmonary hypertension and heart failure

• **Fig. 16-122 Systemic Sclerosis.** The tense, shiny appearance of the skin is evident. Note that the fingers are fixed in a clawlike position, with some showing shortening as a result of acro-osteolysis.

• **Fig. 16-126 Systemic Sclerosis.** Diffuse widening of the periodontal ligament space is often identified on evaluation of periapical radiographs.

• **Fig. 16-124 Systemic Sclerosis.** The involvement of the facial skin with abnormal collagen deposition produces a masklike facies. Note the loss of the alae of the nose.

Common clinical symptoms – scleroderma (aka systemic sclerosis)

- acro-osteolysis – shortening of fingers in claw like position
-"mask-like" facies
- Microstomia with limited mouth opening
- Widened PDL

• **Fig. 16-125 Systemic Sclerosis.** Same patient as depicted in Fig. 16-124. Because of the associated microstomia, this is the patient's maximal opening.