Chemotherapy and the Skin

Objectives:

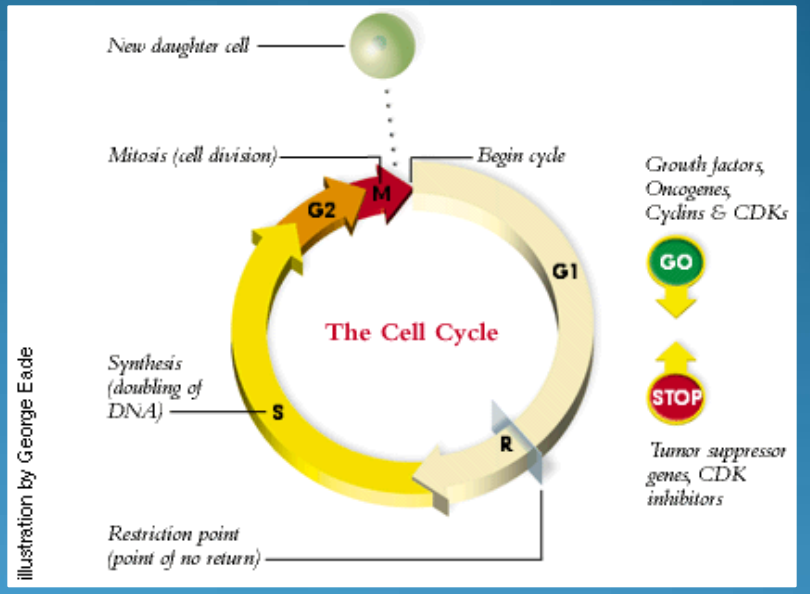
- To define chemotherapy
- To define the common classes of drugs used and mechanism of action
- To identify dermatologic side effects of chemotherapeutic drugs

Chemotherapy

- Definition: the treatment of disease by a chemical agent; originally applied to chemicals that affect the causative organism unfavorably but do not harm the patient (Dorland's Medical Dictionary)
- Common: medications used in the treatment of various cancers

Pharmacology

- Cell cycle
  - An ordered set of events that is necessary for cell growth and division
  - G1: preparation
  - S: synthesis of DNA
  - G2: preparation
  - M: mitosis



Pharmacology (cont.)

- Chemotherapy:
  - Goal is to target actively reproducing cells.
  - Combination therapies are chosen to that attack different phases of the cell cycle.
  - Balance: the drugs do not affect only actively dividing CANCER cells, but also dividing normal cells.

Pharmacology- Agents

- Cell Cycle Specific:
  - Antimetabolites: affect DNA/RNA *production* in the S-phase
    - 5-FU, 6MP, cytarabine
    - methotrexate
  - Plant Alkaloids: affect tubule *separation* in the M-phase
    - vincristine, vinblastine
    - paclitaxel, etoposide

Pharmacology- Agents

- Cell Cycle Non-Specific:
  - Alkylating: interrupt proper DNA base-pairing
    - chlorambucil
    - cyclophosphamide, ifosfamide
    - thiotepa, busulfan
    - cisplatin, carboplatin
  - Antibiotics: bind to DNA
    - doxorubicin, daunorubicin (aka anthracyclines)
    - dactinomycin
    - bleomycin

Side Effects

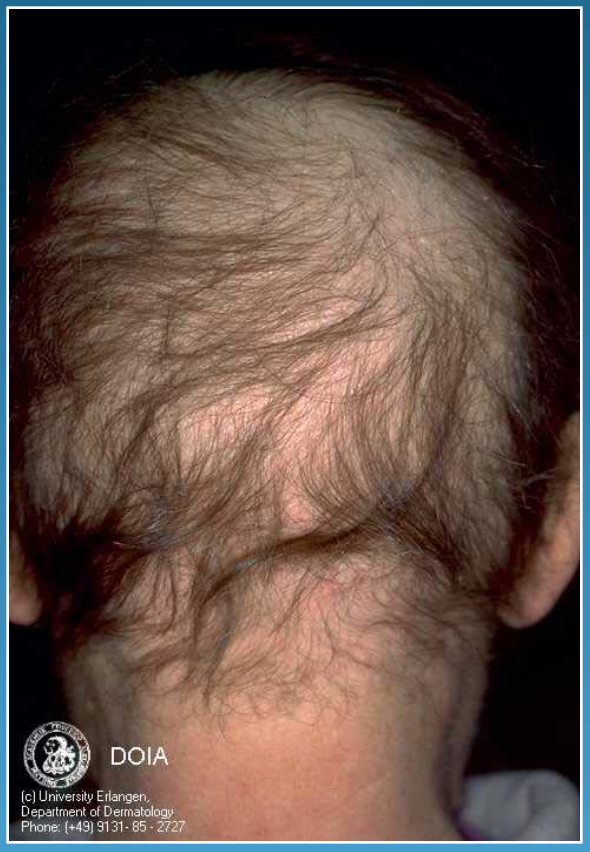
- Mechanism of action
- Clinical presentation
- Classic agents
- Prevention
- Treatment

Side Effects

- Alopecia
- Stomatitis
- Hyperpigmentation
- Acral erythema
- Radiation recall
- Radiation enhancement
- Photosensitivity
- Extravasation
- Inflammation of keratoses
- Neutrophilic eccrine hidradenitis
- Eccrine squamous syringometaplasia
- Lymphocyte recovery

Anagen Effluvium

- Mechanism:
  - abrupt cessation of mitotic activity in the hair matrix cells
- Clinical:
  - Diffuse loss of hair loss seen as breakage in grooming
  - Day 7-10; most prominent 1-2 months
  - Scalp hair>>body hair
  - Not totally bald
    - Remember, not all hair is in active anagen



Anagen Effluvium

Anagen Effluvium (cont.)

- Classic agents:
  - Alkylating agents (eg. cyclophosphamide, cisplatin)
  - Antimetabolites (e.g. 5FU, 6MP, methotrexate)
- Prevention:
  - Scalp hypothermia and tourniqutes? Ineffective.
  - New research on p53 inhibition
- Treatment:
  - 2% minoxidil AFTER may help re-growth. Shown to speed re-growth by 50 days.
  - None: most people will regrow hair without difficulty.
    - Some grow back different texture/color
    - PERMANENT loss has been reported with busulfan and cyclophosphamide

Telogen Effluvium

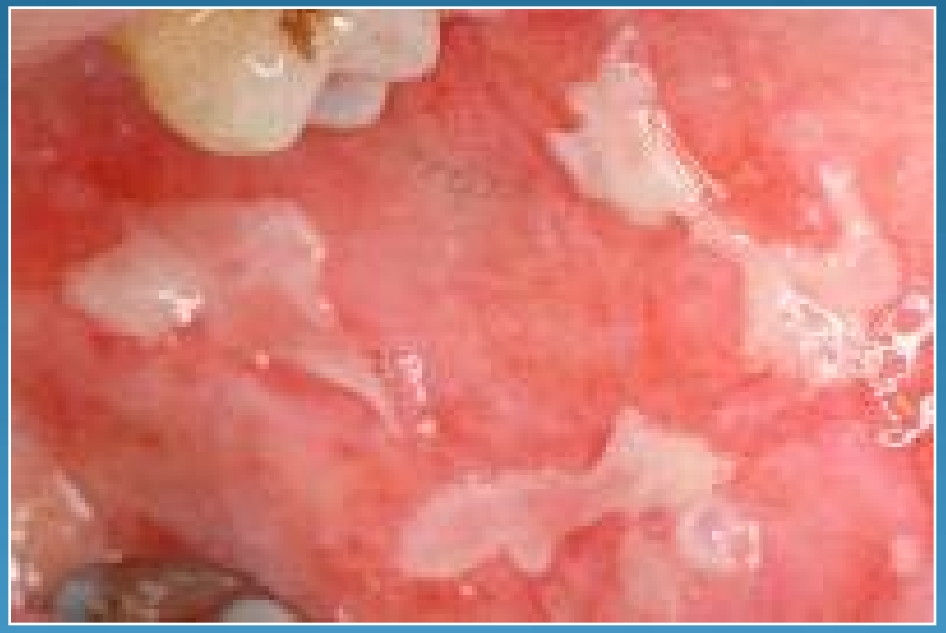
- Patients may experience an additional telogen effluvium months following their therapy secondary to stresses of treatment, infections, fevers, etc…

Stomatitis

- Mechanism:
  - Direct: drug toxicity due to high mitotic rate
  - Indirect: BM suppression with secondary hemorrhage and infection
- Clinical:
  - Direct effects, day 7-10:
    - pain, burning, dryness
    - Erythema, edema, ulceration; rarely vesiculation
  - Indirect effects, day 14 BM:
    - Fever and pain with oral lesions; FEW signs of inflammation
      - Bacterial oral flora, most common
      - Candida (thrush)
      - HSV

Stomatitis (cont.)

- Classic agents:
  - Antimetabolites (e.g. 5FU, 6MP, mtx)
  - Antibiotics (e.g. doxorubicin, dactinomycin)
- Prevention:
  - Oral hygiene (brush, floss, rinse with sodium bicarbonate)
  - Ice chips during therapy
  - Oral glutamine, sucralfate
- Treatment:
  - Supportive
    - Coating agents (kaopectate, MOM)
    - Anesthetic agents (benzocaine, viscous lidocaine)
    - PO pain meds (acetaminophen, codeine)
  - Culture for infection. Low threshold to treat.



Mucositis from chemotherapy

Hyperpigmentation

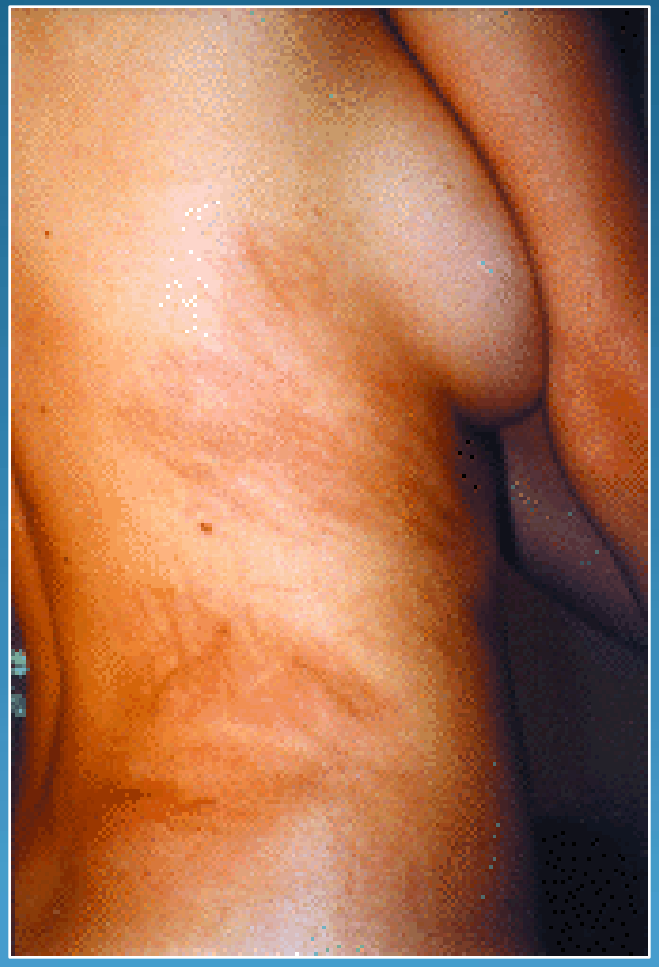
- One of the most common side effects; may affect skin, hair, nails, or mucosa
- Mechanism: varies
  - Increased blood flow with drug deposition
  - Endocrine mediated
  - Depletion of tyrosinase inhibitors
- Clinical: variable
  - Localized or diffuse
  - Under occlusive dressings

Hyperpigmentation (cont.)

- Classic agents:
  - “flag sign” of hair
    - methotrexate
  - “flagellate”: often on trunk
    - bleomycin
  - “serpentine”: overlying the vein of infusion
    - fluorouracil
  - occlusive dressing
    - thiotepa
    - BCNU, ifosfamide

Hyperpigmentation (cont.)

- Nail pigmentation
  - Brown banding: daunorubicin
  - White banding: cyclophosphamide
  - General hypermelanosis: 5FU, hydroxyurea
- Generalized hyperpigmentation
  - “Busulfan Tan” (spares palms)
- Pigment on gingiva
  - cyclophosphamide
  - Busulfan

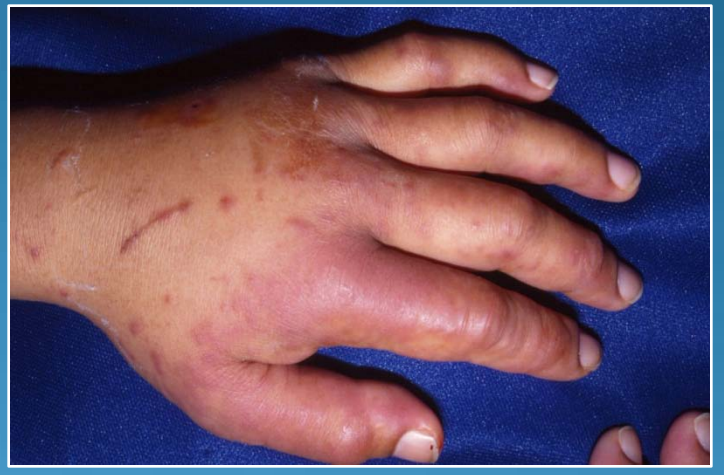


Flagellate hyperpigmentation with bleomycin

Acral Erythema

- A.k.a. hand-foot syndrome, erythrodysesthesia, Burgdorf's
- Mechanism:
  - Direct toxic effect, accumulating in acral sites
  - Self-limited variant of GVHD
- Clinical:
  - Prodrome of dysesthesia
  - 2-4 days later: pain, edema, well-demarcated erythema beginning on lateral borders
  - Significant desquamation
  - Hands > feet
  - Bullous variant (cytarabine, methotrexate)
  - Hyperpigmentation and PPK in black patients

Acral Erythema



Acral Erythema (cont.)

- Classic Agents: “A, B, C, D, et F”
  - A: acral erythema or…
  - B: “Burgdorf’s Syndrome”
  - C: cytarabine
  - D: doxorubicin (liposomal especially!)
  - Et
  - F: fluorouracil

Acral Erythema (cont.)

- Prevention:
  - Decrease dose of medicine
  - Decrease time of contact
  - Cool extremities during treatment
- Treatment:
  - Make the diagnosis
    - Can be confused with GVHD, and can occur in the same patient.
    - Serial biopsies
  - Stop medicine
  - Pyridoxine (B6) supplementation
  - Elevation cool compresses, wound care

Radiation Effects

- Recall:
  - Therapeutic irradiation
  - UV light exposure

- Current:
  - Enhancement of irradiation
  - Photosensitivity

Radiation Recall

- Mechanism:
  - DNA repair defect
  - Altered microvascualture
- Clinical:
  - Inflammatory reaction at exact site of prior radiation; erythema, edema, +/- vesiculation
  - Reaction seen hours to days after drug administration
    - Radiation occurred 8 days-15 YEARS prior!

Radiation Recall (cont.)

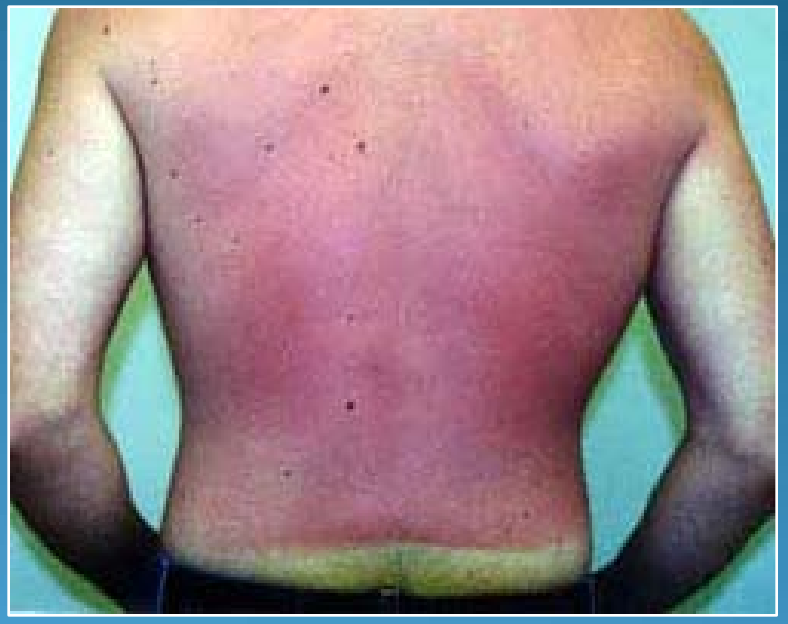
- Classic Agents:
  - doxorubicin
  - dactinomycin
- Prevention:
  - increase time between treatments
  - Decrease the initial radiation dose
- Treatment:
  - Clears spontaneously with cessation of drug
  - Symptomatic; may benefit from short course of systemic steroids

UV Recall

- Mechanism:
  - Actinically damaged skin may have more fragile vascular tissue
- Clinical:
  - Enhancement of former sunburn site
  - Sunburn must have occurred between 1-5 days prior to drug administration
  - Reaction will subside gradually despite continued treatment

UV Recall (cont.)

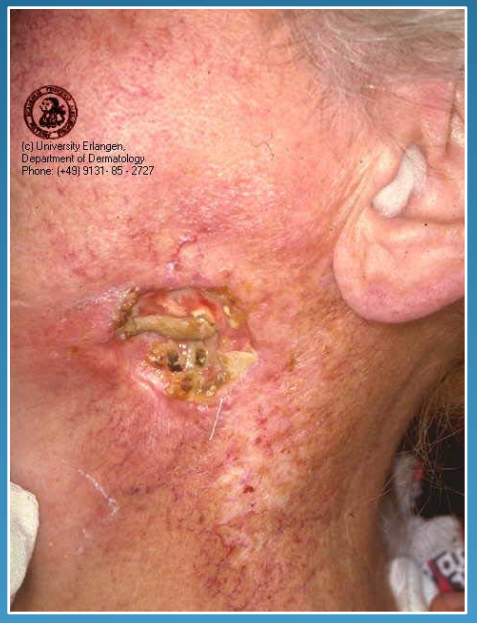
- Classic Agents:
  - Methotrexate!!!
  - Suramin
  - Taxanes (e.g. paclitaxel)
- Treatment:
  - Symptomatic
  - Leucovorin is no help



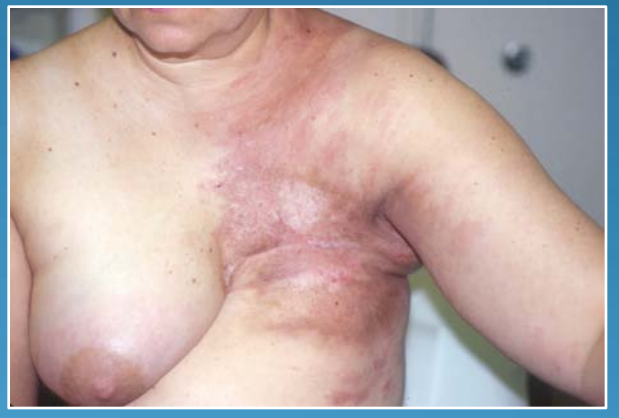
Radiation Enhancement

- Mechanism:
  - Synergy of radiation and chemo side effects
    - increased blood supply
    - increased percentage of cells in S-phase
    - interference with repair enzymes
- Clinical:
  - BAD radiation dermatitis: erythema, edema, vesiculation, ulceration
  - Drug and radiation occur within 7 days of each other

Radiation Enhancement



Acute ulceration



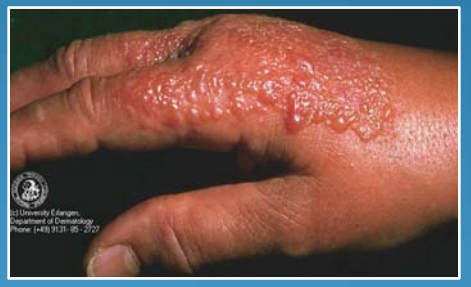
Chronic fibrosis

Radiation Enhancement (cont.)

- Classic Agents:
  - cyclophosphamide combos
  - dactinomycin
  - doxorubicin
  - 5-FU
- Prevention:
  - Decrease the drug dose if radiation expected
- Treatment:
  - Self limiting reaction; local wound care only
  - May have long term sequelae of atrophy or fibrosis

Photosensitivity

- Mechanism:
  - photoTOXIC reaction
- Clinical:
  - Exaggerated sunburn; erythema, edema, pain, stinging, tenderness
  - Face, V-of-neck, dorsum of hands
  - Photo-onycholysis of finger nails



Photosensitivity (cont.)

- Classic agents:
  - dacarbazine
  - 5-FU
  - vinblastine
  - flutamide: thought to be photoALLERGIC
- Prevention:
  - Sun precautions counseling
- Treatment:
  - Sunscreens, protective clothing

Inflammation of Keratoses

- Mechanism:
  - Increased abnormal DNA in these lesions
  - Form of “radiation recall”
- Clinical:
  - Inflammatory, pruritic, hyperkeratotic papules
  - Apparent within 1 week of starting drug
  - May actually make lesions regress

Inflammation of Keratoses (cont.)

- Classic agents:
  - Systemic 5-FU
  - cytarabine, fludarabine
  - dactinomycin, doxorubicin (like recall)
- Treatment:
  - None; the inflammation may actually be beneficial
  - Symptomatic treatment with topical steroid

Neutrophilic Eccrine Hidradenitis

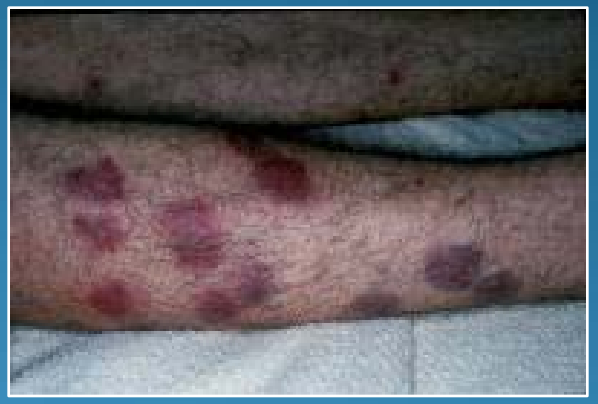
- Mechanism:
  - Direct toxic effect: concentration of drug in the sweat glands
- Clinical: (in classic, chemo-associated)
  - Nonspecific “fever and a rash”
  - Erythematous/violaceous macules, papules, or plaques
  - Asymptomatic or tender
  - Rash after 2 days-3 weeks of drug

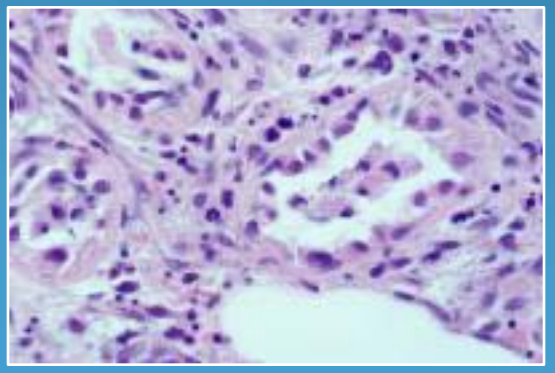
NEH (cont.)

- Classic Agents:
  - cytarabine
  - cyclophosphamide
  - doxorubicin
  - bleomycin
- Prevention:
  - 60% of patients have recurrence
  - Dapsone, NSAIDS
- Treatment:
  - Need to make diagnosis; get biopsy
  - No therapy needed, self-limited

NEH (cont.)

- Histopathology:
  - Dense neutrophilic infiltrate in and around eccrine units
  - Necrosis of eccrine epithelial cells





Eccrine Squamous Syringometaplasia

- Mechanism:
  - Concentration of drug in sweat glands
  - Non-inflammatory *spectrum* of NEH
  - ? These conditions may be primary sweat galnd processes?
- Clinical:
  - Nonspecific rash, similar to NEH
  - Begins 2-39 days after starting therapy

Eccrine Squamous Syringometaplasia

- Classic Agents:
  - None; caused by virtually any chemotherapeutic
- Treatment:
  - None
  - Make the diagnosis with biopsy

Lymphocyte Recovery

- Mechanism:
  - In BMT patients, return of the few immunocompetent lymphocytes to the circulation
- Clinical:
  - Day 6-21 of BMT ablation therapy
  - Erythematous macular/papular rash that becomes confluent; may be erythrodermic
  - Fever for first 2-3 days; cultures negative
  - Desquamation with defervescence

Lymphocyte Recovery (cont.)

- Classic Agents:
  - None in particular
  - cytarabine, daunorubicin, cyclophosphamide, etoposide, vincristine
- Treatment: ???

Extravasation

- Mechanism:
  - Direct infiltration of agent into surrounding tissues
  - Vesicant: toxic injury
  - Irritant: inflammatory reaction
- Clinical:
  - Vesicant:
    - Early: mild erythema and slight “tingling”
    - Late: necrosis, eschar, ulceration
  - Irritant: aching, tightness, phlebitis

Extravasation (cont.)

- Classic Agents:
  - Most drugs can do this. Most can be both irritant or vesicant!
  - Vesicant: antibiotics (doxorubicin, daunorubicin, dactinomycin)
  - Irritant: doxorubicin, daunorubicin
- Prevention:
  - Procedural accuracy!
- Treatment:
  - Stop infusion immediately
  - Surgical consult
  - Elevation and cold packs
    - EXCEPT vinca alkaloids…HOT packs only!

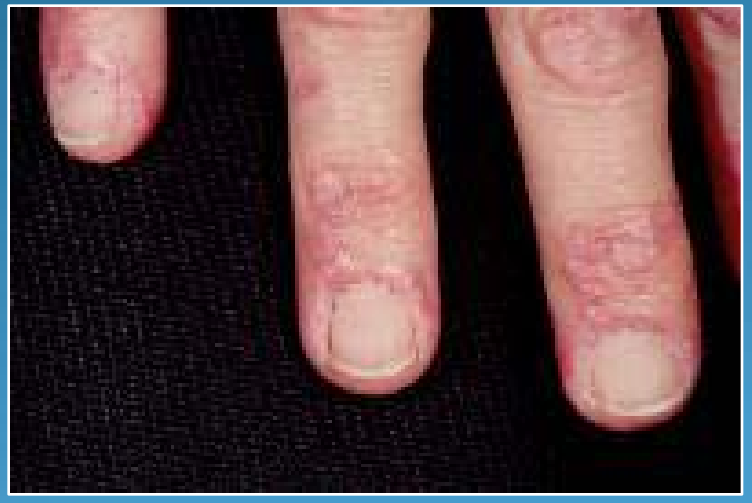
Extravasation (cont.)

- Treatment Antidotes:
  - dox/daunorubicin, mitomycin = DMSO
  - vinca alkaloids, etoposide = hyaluronidase
  - dacarbazine, cisplatin, mechlorethamine = sodium thiosulfate
- Do NOT use local steroid injection or sodium bicarbonate

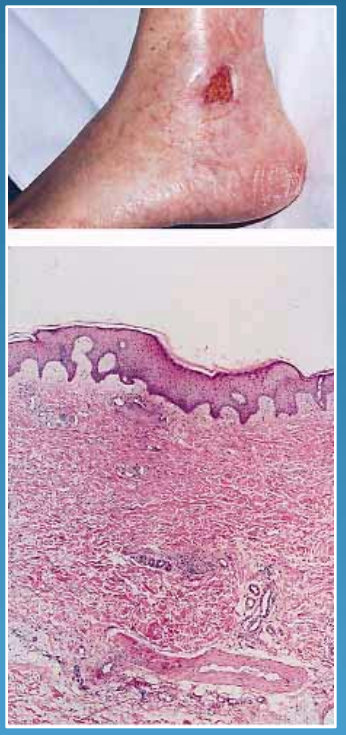
Miscellaneous Reactions:

- Folliculitis = dactinomycin
- Flushing = any!
- Sclerodermoid = bleomycin, docetaxel
- Raynauds = bleomycin
- Leg Ulcers = hydroxyurea
- Dermatomyositis = hydroxyurea
- Pulmonary fibrosis = bleomycin, methotrexate
- Hypersensitivity = L-asparaginase
- Sweet's = GCSF

Hydroxyurea



Dernatomyositis



Leg ulcer

Other reactions