Growth Adaptations, Cellular Injury, and Cell Death

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GROWTH ADAPTATIONS

I. BASIC PRINCIPLES

A. An organ is in homeostasis with the physiologic stress placed on it.
B. An increase, decrease, or change in stress on an organ can result in growth adaptations.

II. HYPERPLASIA AND HYPERTROPHY

A. An increase in stress leads to an increase in organ size.
   1. Occurs via an increase in the size (hypertrophy) and/or the number (hyperplasia) of cells
B. Hypertrophy involves gene activation, protein synthesis, and production of organelles.
C. Hyperplasia involves the production of new cells from stem cells.
D. Hyperplasia and hypertrophy generally occur together (e.g., uterus during pregnancy).
   1. Permanent tissues (e.g., cardiac muscle, skeletal muscle, and nerve), however, cannot make new cells and undergo hypertrophy only.
   2. For example, cardiac myocytes undergo hypertrophy, not hyperplasia, in response to systemic hypertension (Fig. 1.1).
E. Pathologic hyperplasia (e.g., endometrial hyperplasia) can progress to dysplasia and, eventually, cancer.
   1. A notable exception is benign prostatic hyperplasia (BPH), which does not increase the risk for prostate cancer.

III. ATROPHY

A. A decrease in stress (e.g., decreased hormonal stimulation, disuse, or decreased nutrients/blood supply) leads to a decrease in organ size (atrophy).
   1. Occurs via a decrease in the size and number of cells
B. Decrease in cell number occurs via apoptosis.
C. Decrease in cell size occurs via ubiquitin-proteosome degradation of the cytoskeleton and autophagy of cellular components.
   1. In ubiquitin-proteosome degradation, intermediate filaments of the cytoskeleton are "tagged" with ubiquitin and destroyed by proteosomes.
   2. Autophagy of cellular components involves generation of autophagic vacuoles. These vacuoles fuse with lysosomes whose hydrolytic enzymes breakdown cellular components.

IV. METAPLASIA

A. A change in stress on an organ leads to a change in cell type (metaplasia).
   1. Most commonly involves change of one type of surface epithelium (squamous, columnar, or urothelial) to another
   2. Metaplastic cells are better able to handle the new stress.
B. Barrett esophagus is a classic example.

For example: Heart
It has a function of pumping against the Systemic BP & it is in homeostasis when it deals with that physiologic stress.

If the organ has to do more work, it will become bigger in order to do the excess work. It may occur via hypertrophy or hyperplasia.

A cell has a skeleton k/a cytoskeleton & it is what gives the cell its size & its shape. If we want the cell to get bigger, we are going to have to increase the production of cytoskeleton & it is primarily made up of proteins.

cytoskeleton ↑

High yield

→ Pathologic v/s physiologic hyperplasia

epi means on top, thelium means layer

cells that line body surfaces

1. Esophagus is normally lined by nonkeratinizing squamous epithelium (suited to handle friction of a food bolus).
2. Acid reflux from the stomach causes metaplasia to nonciliated, mucin-producing columnar cells (better able to handle the stress of acid, Fig. 1.2).

C. Metaplasia occurs via reprogramming of stem cells, which then produce the new cell type.
1. Metaplasia is reversible, in theory, with removal of the driving stressor.
2. For example, treatment of gastroesophageal reflux may reverse Barrett esophagus.

D. Under persistent stress, metaplasia can progress to dysplasia and eventually result in cancer.
1. For example, Barrett esophagus may progress to adenocarcinoma of the esophagus.
2. A notable exception is apocrine metaplasia of breast, which carries no increased risk for cancer.

E. Vitamin A deficiency can also result in metaplasia.
1. Vitamin A is necessary for differentiation of specialized epithelial surfaces such as the conjunctiva covering the eye.
2. In vitamin A deficiency, the thin squamous lining of the conjunctiva undergoes metaplasia into stratified keratinizing squamous epithelium. This change is called keratomalacia (Fig. 1.3).

F. Mesenchymal (connective) tissues can also undergo metaplasia.
1. A classic example is myositis ossificans in which connective tissue within muscle changes to bone during healing after trauma (Fig. 1.4).

V. DYSPLASIA

A. Disordered cellular growth

B. Most often refers to proliferation of precancerous cells
1. For example, cervical intraepithelial neoplasia (CIN) represents dysplasia and is a precursor to cervical cancer.

C. Often arises from longstanding pathologic hyperplasia (e.g., endometrial hyperplasia) or metaplasia (e.g., Barrett esophagus)

D. Dysplasia is reversible, in theory, with alleviation of inciting stress.
1. If stress persists, dysplasia progresses to carcinoma (irreversible).

VI. APLASIA AND HYPOPLASIA

A. Aplasia is failure of cell production during embryogenesis (e.g., unilateral renal agenesis).

B. Hypoplasia is a decrease in cell production during embryogenesis, resulting in a relatively small organ (e.g., streak ovary in Turner syndrome).

Apocrine Metaplasia

- It is one of the change that is seen in association with fibrocystic change in the breast.
- The fibrocystic changes can be associated with the future development of breast cancer, however apocrine metaplasia does not increase the risk of cancer.

Plasia means growth,
Dys means bad

The term dysplasia is only used for epithelial cells

A means without
Hypo means less

Fig. 1.1 Left ventricular hypertrophy. (Courtesy of Aliya Husain, MD)

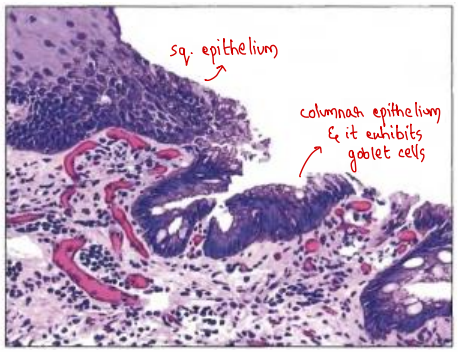
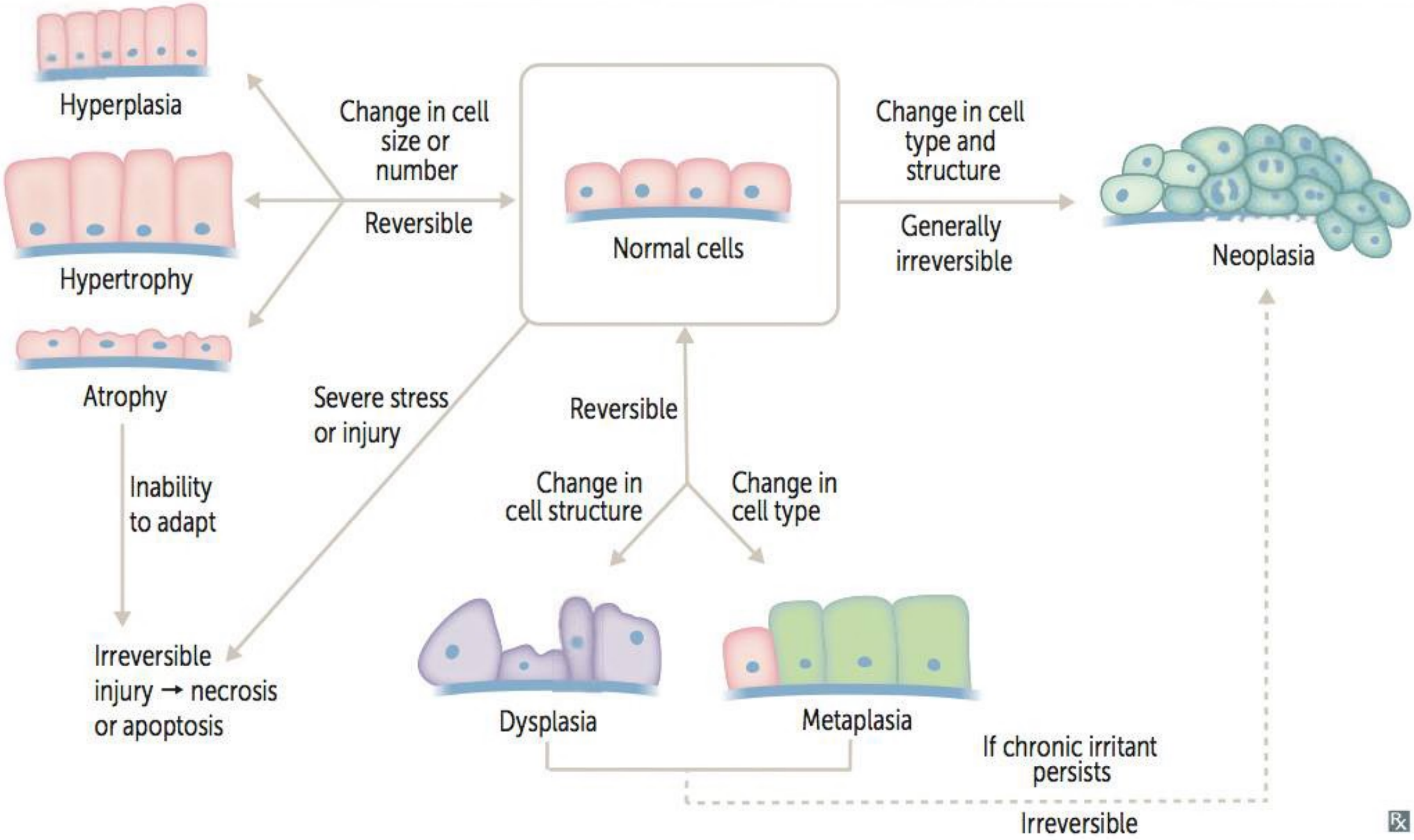


Fig. 1.2 Barrett esophagus.


Hyperplasia
Hypertrophy
Atrophy
Change in cell size or number
Reversible
Normal cells
Change in cell type and structure
Generally irreversible
Neoplasia
Severe stress or injury
Inability to adapt
Irreversible injury → necrosis or apoptosis
Reversible
Change in cell structure
Change in cell type
Dysplasia
Metaplasia
If chronic irritant persists
Irreversible

Cellular adaptations	Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy 2° to systemic HTN to prevent injury). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy → injury to myofibrils → HF).
Hypertrophy	↕ structural proteins and organelles → ↑ in size of cells.
Hyperplasia	Controlled proliferation of stem cells and differentiated cells → ↑ in number of cells. Excessive stimulation → pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer.
Atrophy	↓ in tissue mass due to ↓ in size (↑ cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy; ↓ protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Metaplasia	Reprogramming of stem cells → replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (→ Barrett esophagus) or cigarette smoke (→ respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia → malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).
Dysplasia	Disordered, precancerous epithelial cell growth. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia usually becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.

Metaplasia

metaplastic cells are better able to handle the new stress:

- Repeated gastric acid causes stratified squamous epithelium of lower esophagus to be replaced with columnar epithelium + goblet cells to be able to better handle stress (Barrett' esophagus)

- Repeated cigarette smoke causes respiratory ciliated columnar epithelium to be replaced by stratified squamous epithelium

Vitamin A deficiency

1. The first thing that comes to mind is night blindness
2. Patients who are vitamin A deficient can be deficient in their immune system, because vitamin A is necessary for proper maturation of cells of the immune system.
3. Its deficiency can also lead to metaplasia.
   - The conjuctiva is composed of a highly specialized squamous epithelium (transparent) & vitamin A is required to keep it that way, deficiency of vitamin A can lead to thickening of that surface, k/a keratomalacia (White colored layer)

15/17 Translocation leads to Acute Promyelocytic Leukemia

- 15/17 translocation involves the Vitamin A receptor (retinoic acid receptor)
- So, it disrupts the vitamin A receptor & that causes the cells to remain trapped in the blast state & their accumulation then leads to Pro-myelocytic leukemia
- One of the treatment of Pro-Myelocytic Leukemia is ATRA which is short for All trans retinoic acid, it is a derivative of vitamin A. This derivative has the ability to bind to the mutated receptor which then allows the cells to mature & become neutrophills.

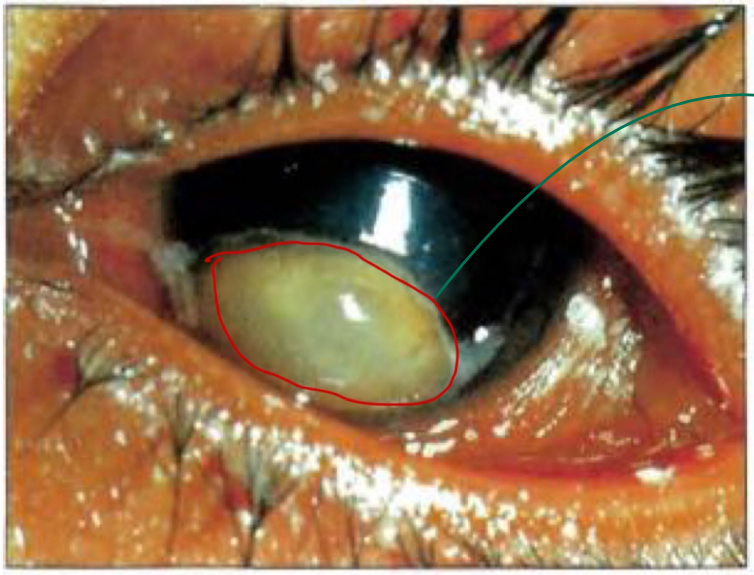


Fig. 13 Keratomalacia. (Courtesy of motherchildnutrition.org)

Vitamin A Facts

1) Ester eggs + beta carrot:
Vitamin A is derived from retinyl esters and beta-carotenes (both are in the diet)
2) Fat bunny:
Vitamin A is fat-soluble
3) Star streamers:
Retinyl esters are picked up by chylomicrons and stored inside liver **stellate** cells
4) "Be Different!" shirt:
Vitamin A is required for **differentiation** of specialized epithelia
5) Glasses + retina balloon:
Vitamin A (**retinol**) is important for **vision** (phototransduction and retinal development)
6) ---3 symbols for causes of vitamin A deficiency---
Kid 1: Party hat falling + falling cake + pancreas pouch:
Poor diet, pancreatic insufficiency
Kid 2: lifting up shirt to drop intestinal streamers:
Malabsorption (Crohn's/bariatric surgery)
Kid 3 squeezing bag of green icing:
Cholestatic liver disease
---not labeled: **kid's branch** = cystic fibrosis → fat soluble vitamin deficiencies---
7) Dark sunglasses:
Nyctalopia = impaired night vision (specifically due to deficient rhodopsin)
8) Blindfold:
Vitamin A deficiency → blindness 2/2 squamous metaplasia of the cornea
9) "Mal carrot":
Vitamin A deficiency → **keratomalacia** of the cornea
10) Unicorn:
Vitamin A deficiency → keratomalacia of the **cornea**
11) Bee toe:
Vitamin A deficiency → **bitot spots** of the cornea
12) Squamous hem + metal plate:
Sequelae of vitamin A deficiency are caused by **squamous metaplasia**
13) Frosting lung spots + squamous hem + metal plate:
Vitamin A deficiency → **pneumonia** 2/2 squamous metaplasia of bronchi
14) Pancreas pouch + squamous hem + metal plate:
Vitamin A deficiency → **squamous metaplasia** of **pancreatic** exocrine ducts
15) Short kid:
Vitamin A deficiency is a major cause of **growth retardation** worldwide

16) Kidney moss + stones:
Vitamin A deficiency → **kidney stones**
17) Party hats atop wrinkled blanket:
Topical vitamin A used to treat and prevent **wrinkles**
18) Icing on tongue:
Topical vitamin A used to treat **oral hairy leukoplakia**
19) Acne:
Topical vitamin A used to treat **acne** (inhibits follicular epidermal keratinization and shrinks sebaceous glands)
20) Icy treat:
Isotretinoin is an oral vitamin A used to treat severe cystic acne (second line)
21) "Go Pro":
All-trans-retinoic acid (ATRA) is used to treat acute promyelocytic leukemia (APL)
22) Weasel:
Vitamin A supplementation is used to treat **measles**
23) Dirty retina balloon:
Vitamin A supplementation helps in **retinitis pigmentosa**
24) Girl in parka:
Vitamin A toxicity seen in **northern climates** (e.g. Inuit who eat polar bear livers)
25) Icy treat:
Isotretinoin can also cause vitamin A toxicity
26) Vomiting + dizzy + lifting blindfold:
Acute vitamin A toxicity → **nausea**, **vomiting**, **vertigo**, and **blurred vision**
27) Ripping large liver present:
Chronic vitamin A toxicity → hepatotoxicity and hepatomegaly
28) Red lips:
Chronic vitamin A toxicity → **cheilitis** (inflammation of the lips)
29) Grabbing kid's elbow:
Chronic vitamin A toxicity → **arthralgias**
30) Bald head:
Chronic vitamin A toxicity → **alopecia**
31) Pile of carrots:
Chronic vitamin A toxicity → **hyperkeratosis**
32) Swollen head balloon:
Chronic vitamin A toxicity → **idiopathic intracranial hypertension** (pseudotumor cerebri)
33) Tarantula pinata:
Vitamin A derivatives are **teratogenic** (e.g. isotretinoin)

Mesenchymal Tissues

- Bone, blood vessels, cartilage & fats are mesenchymal in origin (also called connective tissue)

Myositis Ossificans

- In Myositis Ossificans, inflammation of the skeletal muscle results in a metaplastic production of bone in the skeletal muscle, it is usually after a trauma when the skeletal muscle is healing.
- This is not be confused with osteosarcoma, which can be ruled out by
  a. The bone adjacent is normal
  b. Distinct separation between bony metaplasia with the bone

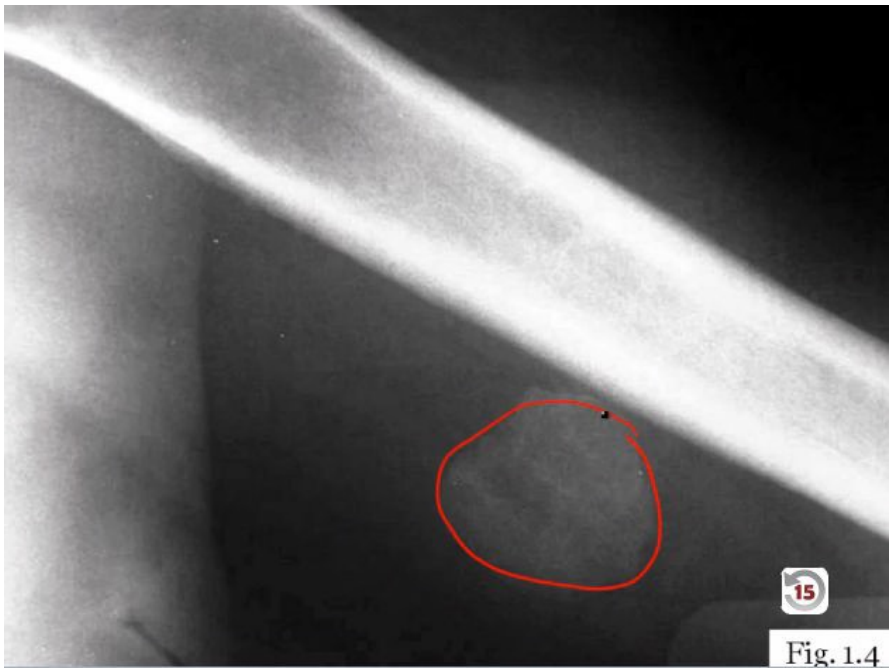


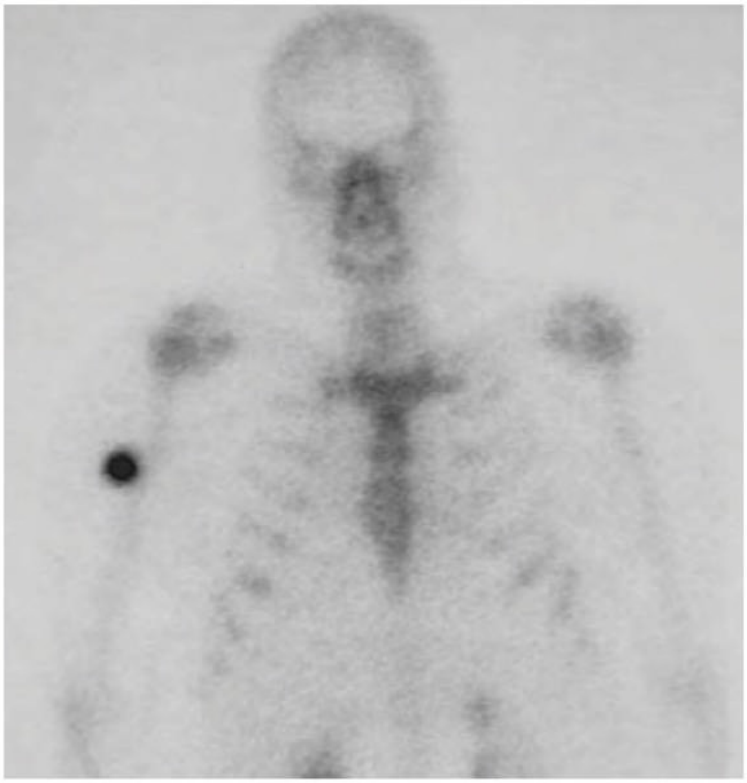
Fig. 1.4

*note it is separated from the bone-its in the muscle (it is not an osteosarcoma)

What musculoskeletal disorder is characterized by metaplasia of skeletal muscle to bone?
- Myositis ossificans

- The non-hereditary form (myositis ossificans traumatica) is due to trauma to muscle causing bone to form

- hereditary (myositis ossificans progressiva) is due to an autosomal dominant mutation in the activin type 1 receptor, causing endothelial cells to transform to mesenchymal cells and then to bone



Figures 17-88 and 17-89 Myositis ossificans, MRI and bone scan
The rounded lesion (▲) of the upper arm adjacent to the humerus in the T1-weighted MR image in the *left panel* is a tumorlike mass within skeletal muscle called *myositis ossificans.* It is a benign form of connective tissue metaplasia that results from a florid healing response to injury. In the *right panel,* the lesion appears as a discrete "hot spot" in soft tissue in a bone scan.

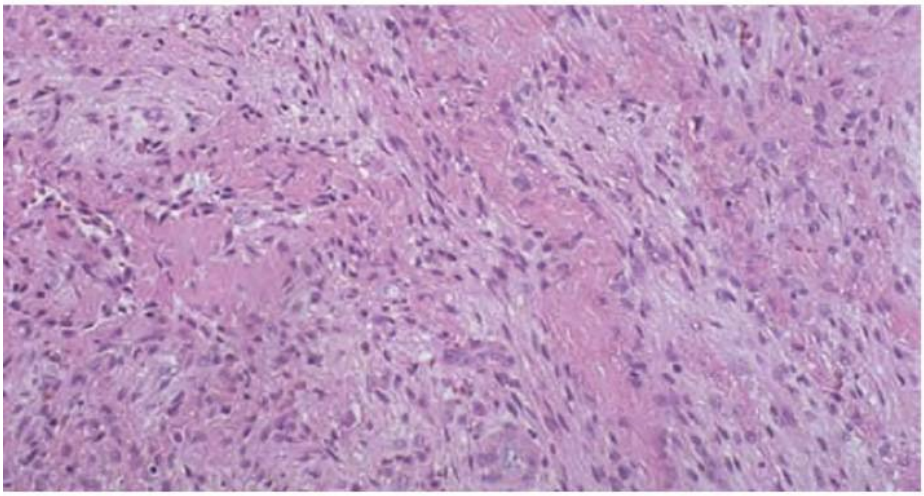


Figure 17-90 Myositis ossificans, microscopic
Myositis ossificans is an uncommon condition and occurs not within bone, but in adjacent muscle; lesions can reach several centimeters in size. Shown here is the central core of exuberant, cellular granulation tissue that can mimic a sarcoma. The correct diagnosis is suggested by radiographs. In contrast to a true neoplasm, this lesion decreases in size over time. It can cause pain and local irritation.

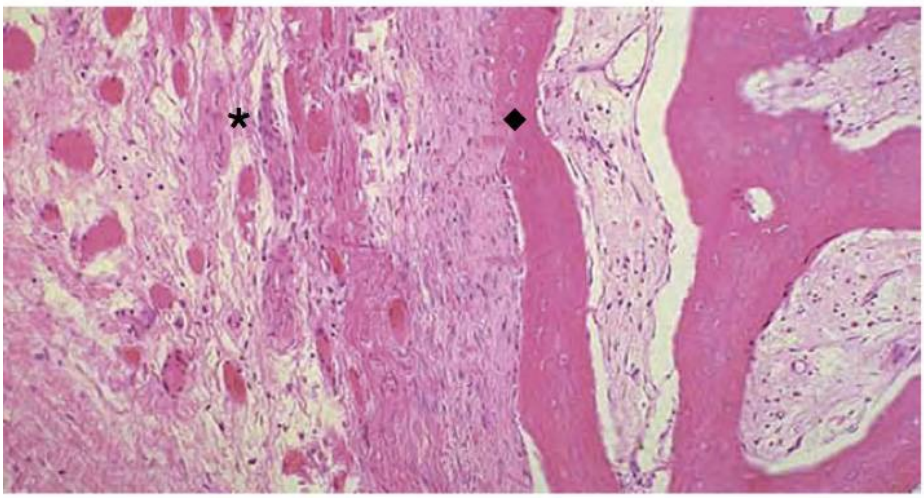


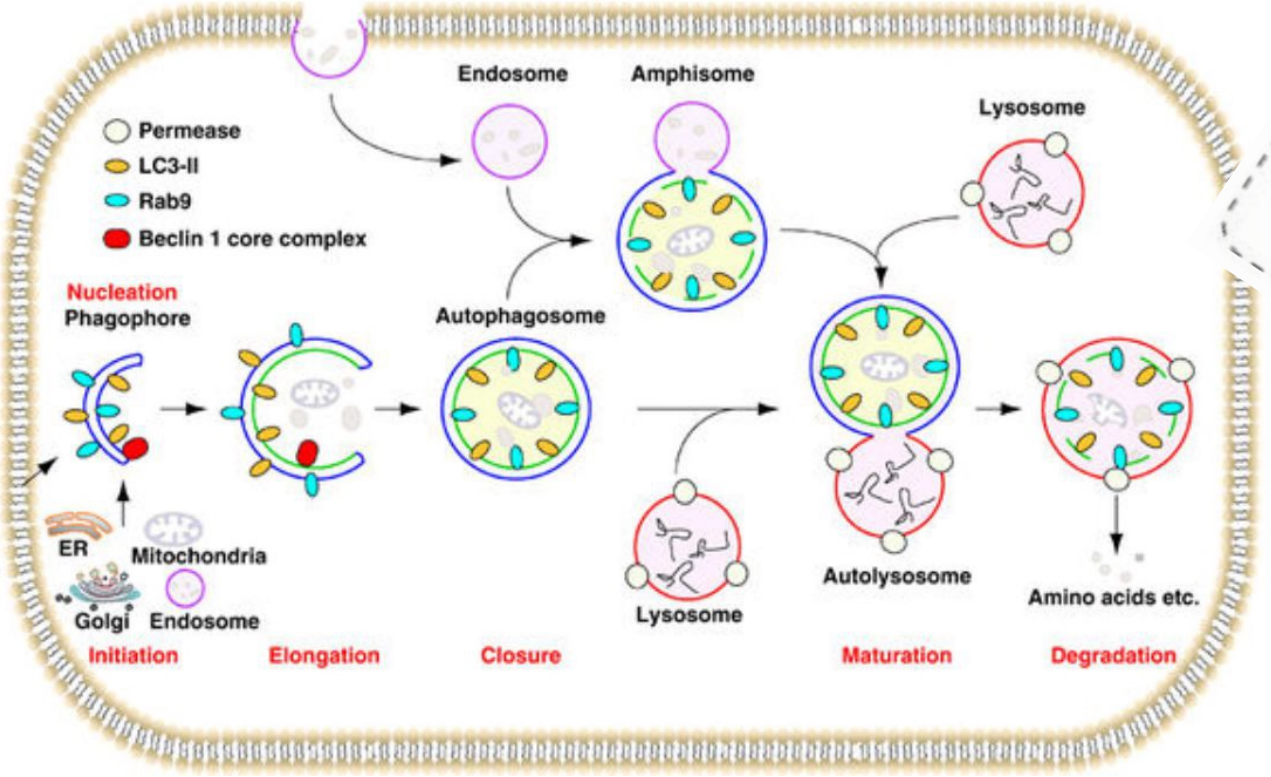
Figure 17-91 Myositis ossificans, microscopic
Peripheral to the cellular core (★) of the lesion is a zone of reactive new bone formation with a rim (◆) of dense trabecular bone appearing here on the right. This outer shell of bone blends with adjacent muscle fibers visible here on the left. The whole process eventually calcifies and shrinks over weeks to months.

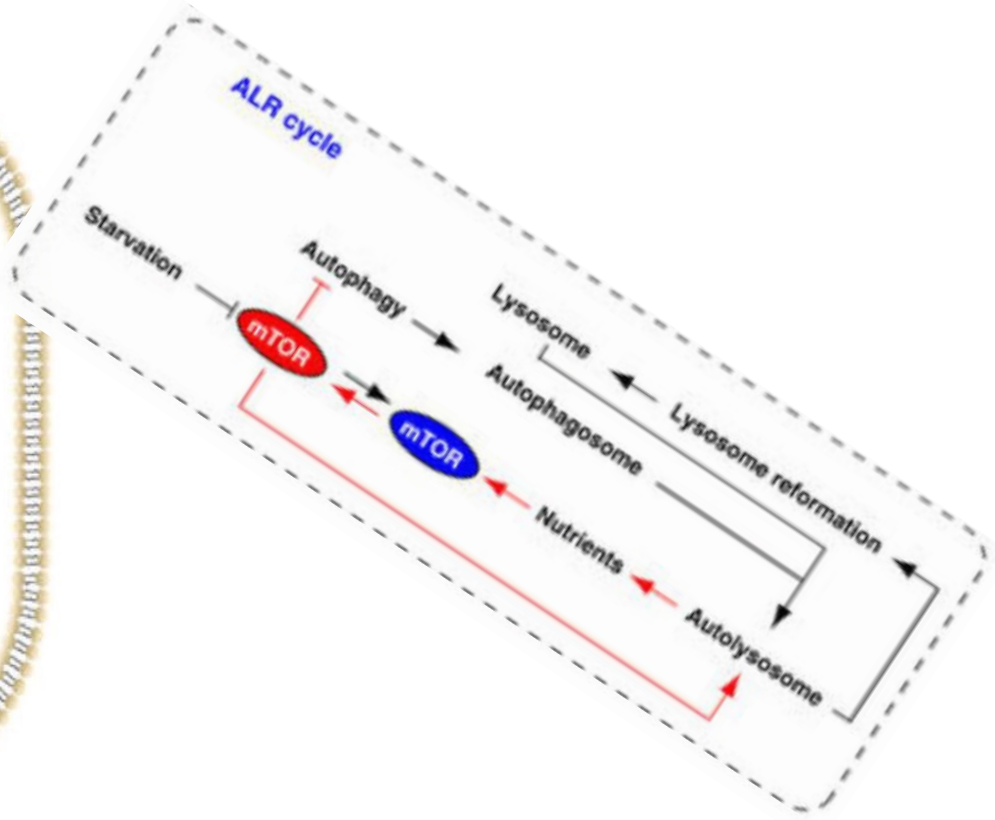
Atrophy

1. Atrophy via decrease in cell size may occur via autophagy of cellular components

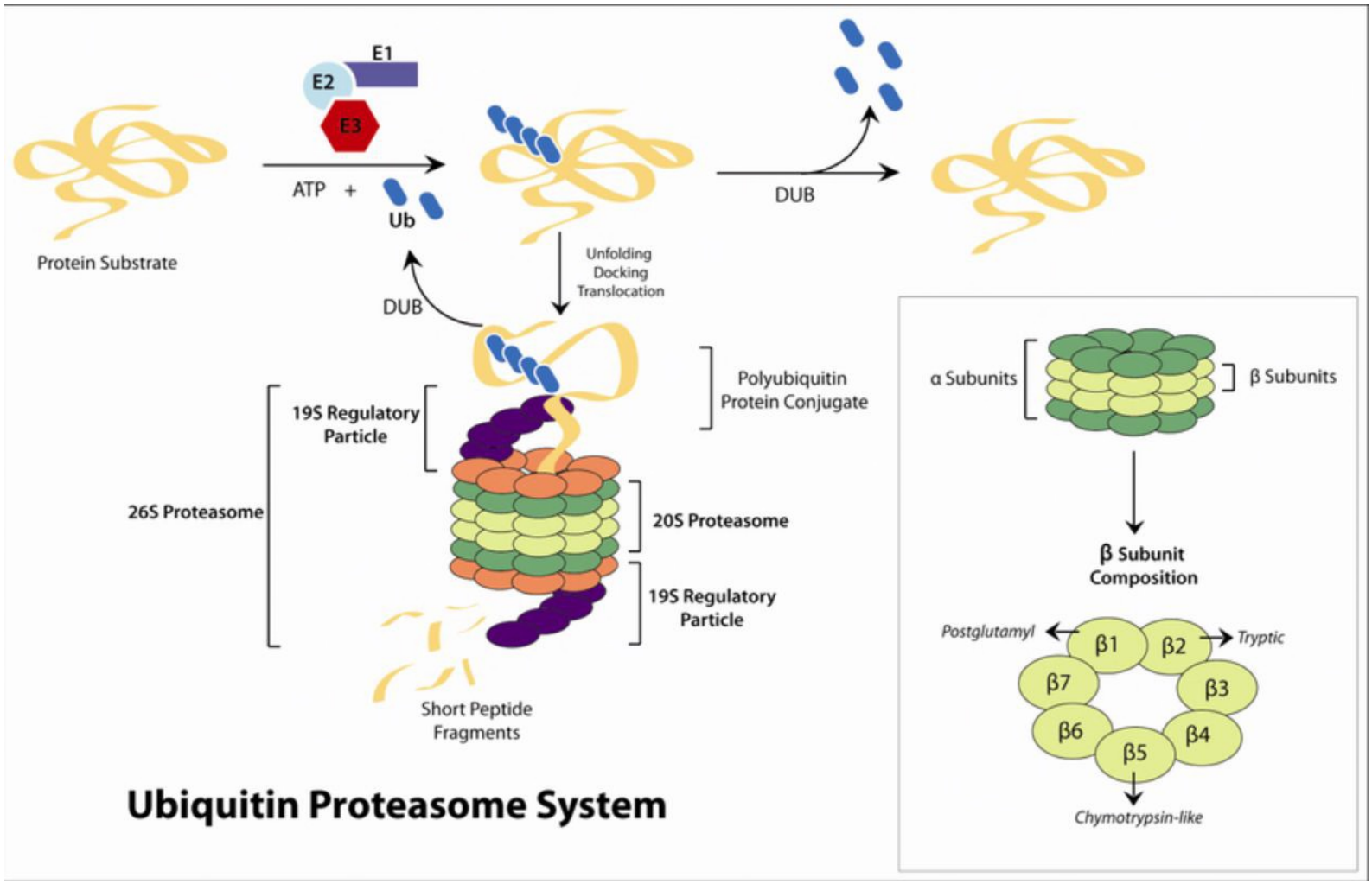
This process is mediated by the Beclin-1 core complex; which helps generate autophagic vacuoles that consume cellular organelles, these combine with lysozymes whose hydrolytic enzymes break down organelles for nutrients

Autophagy is a response to a state of cellular starvation, this is recognized by Akt and results in inhibition of mTOR, relieving inhibition of autophagy





2. Atrophy via decrease in cell size may occur via ubiquitin-proteasome degradation of cytoskeleton
- The Proteasome is an intracellular tagging system that allows for degradation of misfolded / unwanted / used up / damaged intermediate filaments of the cytoskeleton are "tagged" with ubiquitin and destroyed by proteasomes



Atrophy via decrease in cell number occurs via apoptosis

- This is an ATP-dependent programmed cell death, responding to the presence of pro-death signals or the lack of survival signals