

The slide features a decorative arrangement of five purple circles. Three circles are positioned in the upper right quadrant, and two are in the lower left quadrant. The top-left circle is an outline, while the other four are solid. The title text is centered horizontally and partially overlaps the top-right circles.

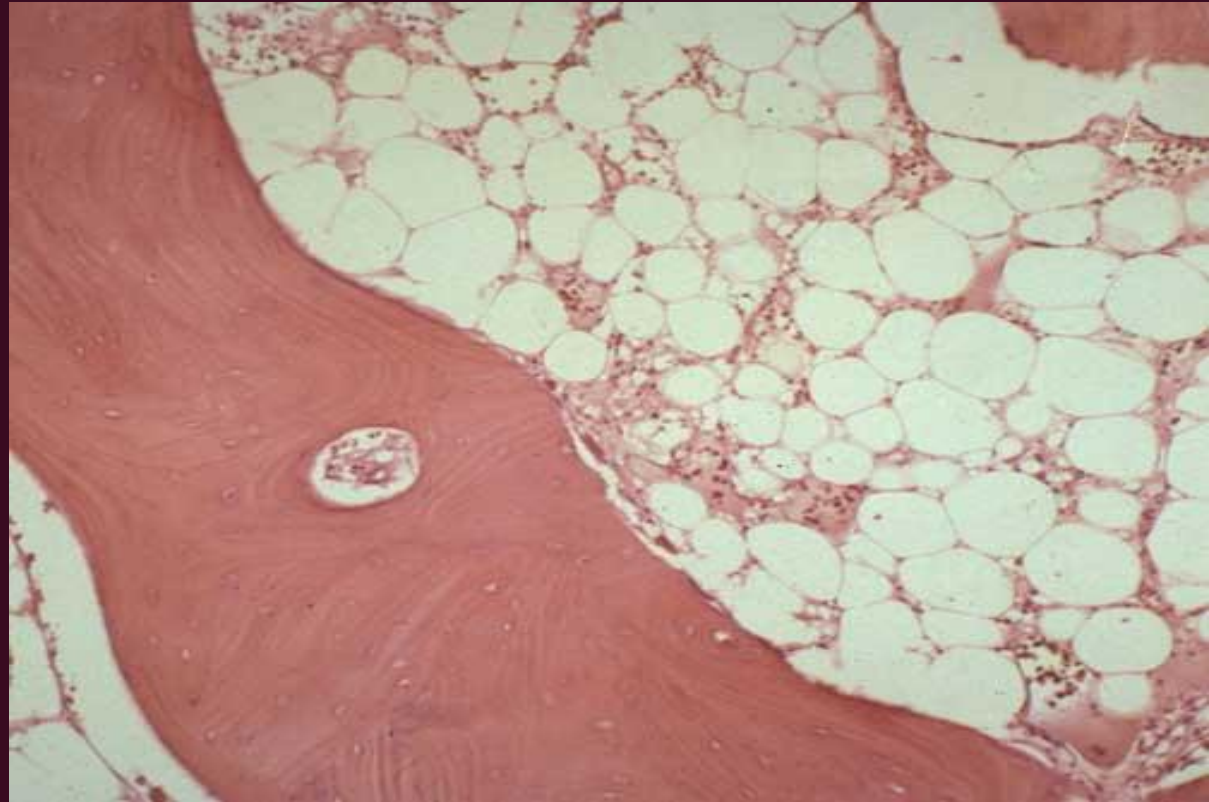
# Constitutional Aplastic Anemias


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# Overview

- Erythroid lineage only (pure red cell aplasia)
- Two cell lines (bicytopenia)
- All hematopoietic cells (aplastic anemia)
- Aplastic anemias : Constitutional and acquired disorders





## Constitutional Aplastic Anemias

- Fanconi's Anemia
- Dyskeratosis Congenita
- Shwachman-Diamond Syndrome

## Acquired Aplastic Anemias

- Idiopathic
- Drugs, toxins, infections
- PNH (clonal)



## Constitutional Red Cell Aplasia

- Diamond-Blackfan anemia



## Acquired Red Cell Aplasia

- Transient erythroblastopenia of childhood
- Parvovirus infection
- Idiopathic
- Neoplasms, immune disorders, and drugs

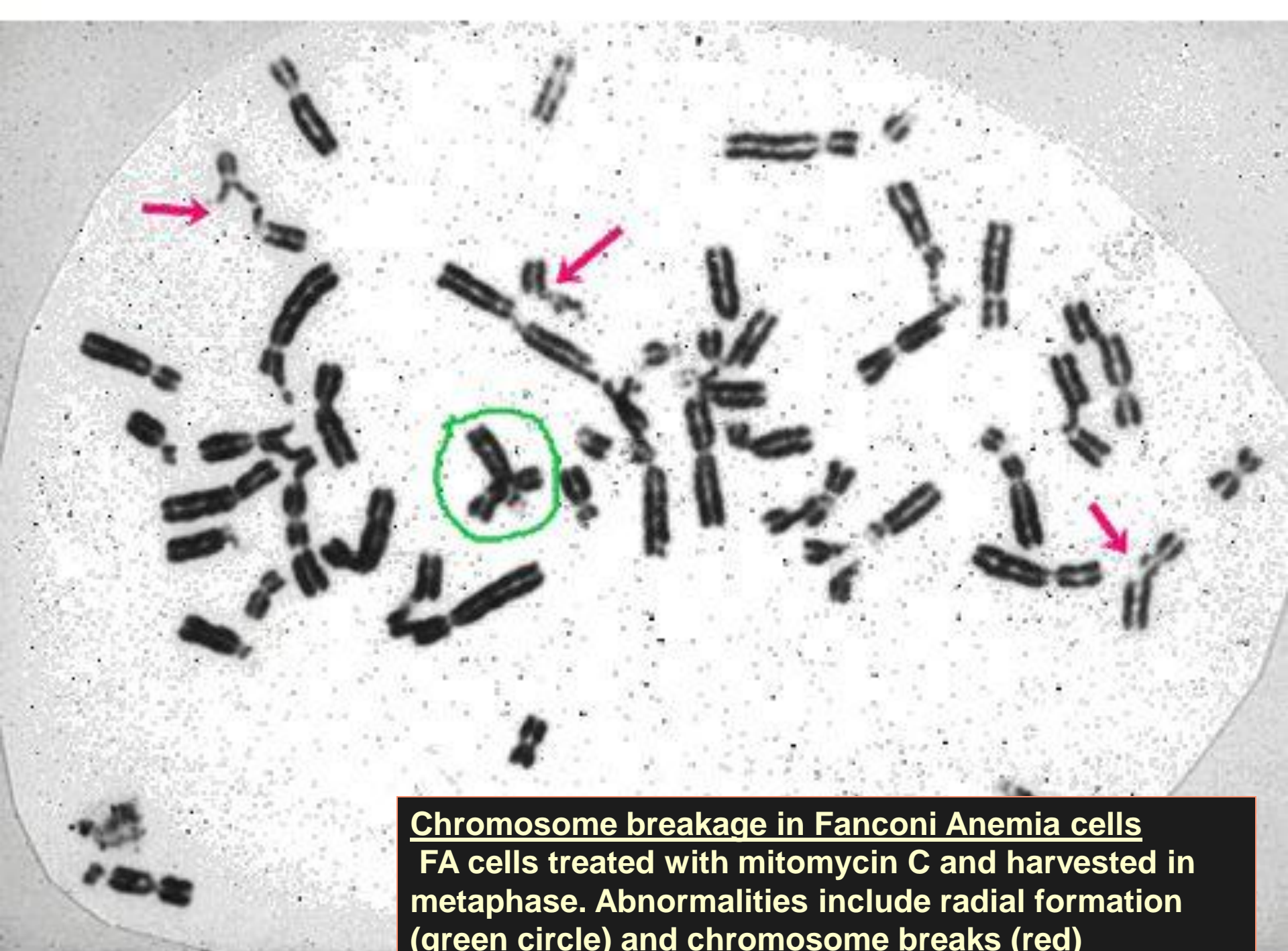
# Fanconi's Anemia (FA)



- Most frequently reported of the rare inherited bone marrow failure syndromes
- 1927: Guido Fanconi first reported 3 brothers with pancytopenia and physical abnormalities
- 1960s - cultured cells from pts with FA had increased numbers of chromosome breaks
- Breakage rate increased with DNA cross-linkers: diepoxybutane (DEB) or mitomycin C (MMC )



**Hypoplastic thumbs - Fanconi's anemia**



**Chromosome breakage in Fanconi Anemia cells**  
FA cells treated with mitomycin C and harvested in metaphase. Abnormalities include radial formation (green circle) and chromosome breaks (red)

# Fanconi's Anemia



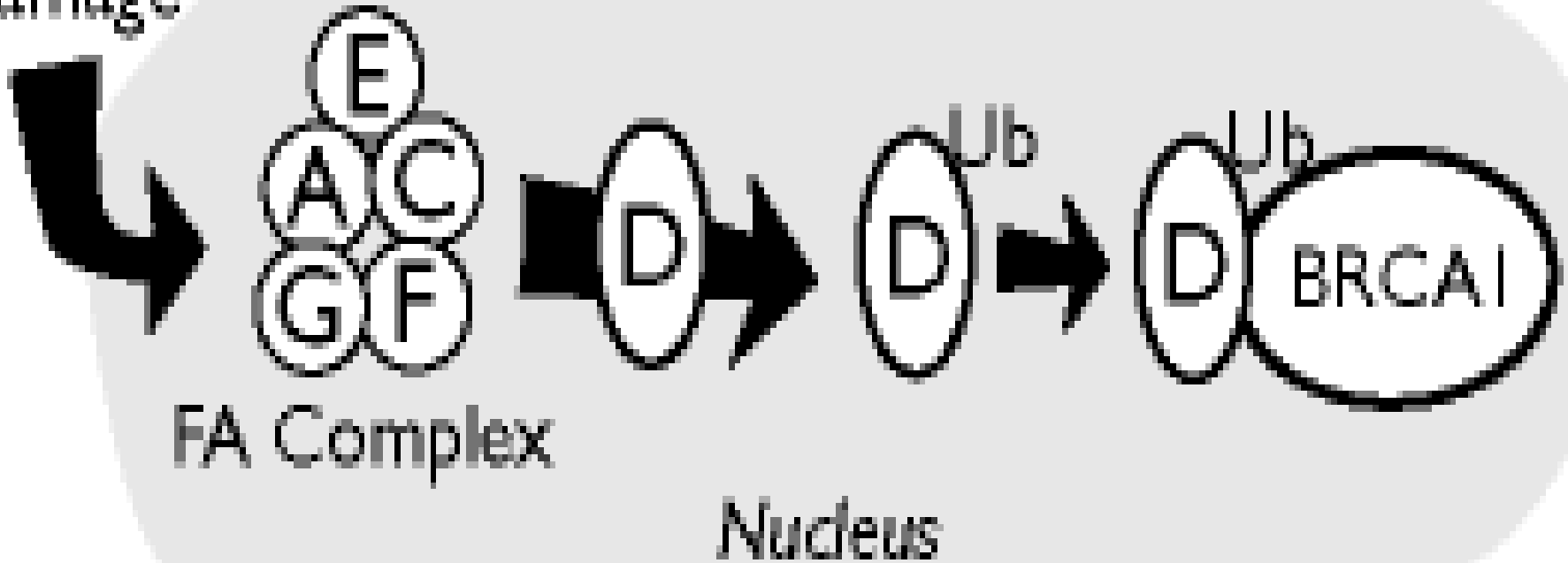
- Molecular diagnostics further improved specificity of FA diagnosis
- FA accounts for 25% of the cases of aplastic anemia seen at large referral centers.
- Approximately 25% of known patients with FA do not have major birth defects.



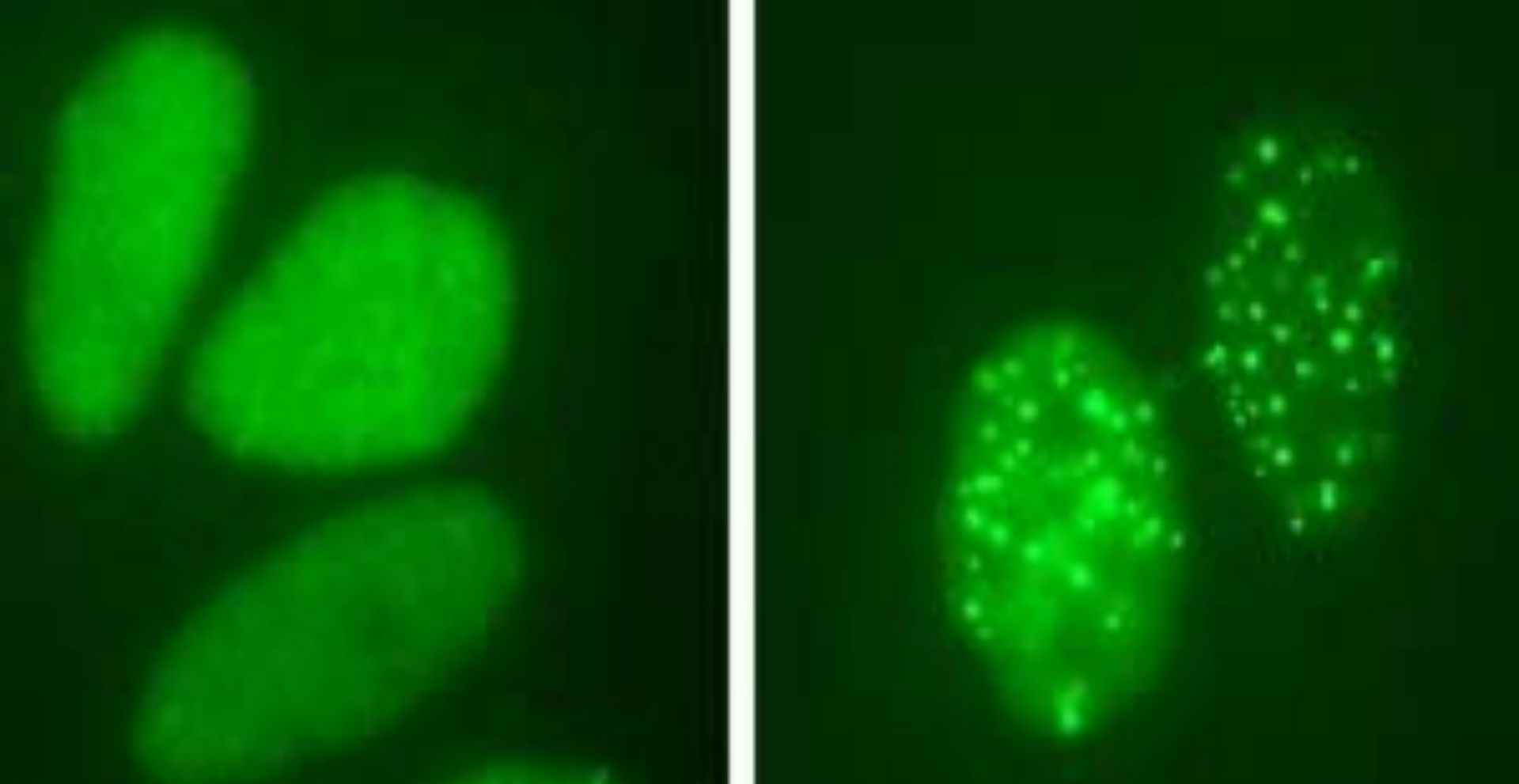
# Fanconi's Anemia

- Autosomal recessive
- Mutations in one of the 11 different genes known to be responsible for FA, genes are *FANCA* through *FANCI*
- A, B, C, E, F, G, and L → nuclear complex → inactivation D2 protein and is involved in DNA damage response

DNA  
Damage



A newly identified protein (D) link between FA protein complex and DNA-repair machinery. In response to DNA damage the FA complex allows one ubiquitin (Ub) to be added to D. Ubiquitinated D then moves to nuclear foci that contain BRCA1, a protein that is defective in the majority of inherited breast cancers and is thought to play a role in DNA repair.



Fluorescence microscopy shows that D, usually diffusely located throughout the nucleus (top left), concentrates into nuclear foci after DNA damage (top right). Adapted from originals from the Alan D'Andrea laboratory.

# Fanconi's Anemia

- Exact link between mutations and phenotype is not clear
- FA cells susceptible to damage by oxygen free radicals.
- FA cells have a defect in cell cycle regulation.
- The hematopoietic stem cell is defective in FA.
- A defect in the DNA-damage response pathway
- FA is a premalignant disorder

# Fanconi's Anemia: Frequency

- **US:** 1 per 300 people.
- Ashkenazi Jews: 1 per 90 people
- **Internationally:** Carrier frequencies are similar to those in the United States, depending on the population

# Fanconi's Anemia: Lab Studies

- CBC shows trilineage pancytopenia (mid-childhood) or only red blood cells that are macrocytic for age.
- Thrombocytopenia or leukopenia may precede full-blown aplasia.
- Chromosome breakage - examined in short-term cultures of PB lymphocytes in the presence of DNA cross-linkers (DEB or MMC)

# Fanconi's Anemia: Lab Studies

- Flow cytometry : cells cultured with nitrogen mustard and other clastogens demonstrates an arrest in G2/M.
- Increased HbF for age as a manifestation of stress erythropoiesis.
- Red cell ADA increased in with Diamond-Blackfan anemia, normal in FA.
- Serum EPO levels : markedly increased

# Fanconi's Anemia – Bone Marrow

- Bone marrow aspirate and biopsy
  - \* Hypocellularity, loss of myeloid and erythroid precursors and megakaryocytes (with relative lymphocytosis)
  - \* Full-blown aplasia with a fatty marrow
  - \* Signs of myelodysplastic syndrome
  - \* Cytogenetic clone in a high and increasing proportion over time may suggest an evolution to leukemia



# Fanconi's Anemia



- Prenatal FA diagnosis:
- Chromosome breaks in cells obtained in utero from chorionic villus biopsy, amniocentesis, or cord blood (by cordocentesis)
- Identification of FA gene mutations in DNA extracted from fetal cells.

# Fanconi's Anemia - Treatment

- Treatment is recommended for significant cytopenias
  - HB < 8 g/dL
  - Platelets < 30,000/mL
  - Neutrophils < 500/mL.
- First line of therapy is stem cell transplantation
- Androgens: If transplantation is not an option, 50-75% of patients respond

# Fanconi's Anemia - Complications

- Hemorrhages, infections, leukemia, myelodysplastic syndrome, liver tumors, and other cancers.
- Leukemia 100 out of 1200 reported in the literature; 95% of cases are AML
- Myelodysplastic syndrome was reported in approximately 75 patients

# Fanconi's anemia – Prognosis/Tx

- Aplastic anemia - medications, blood products, and stem cell transplantation increases the life expectancy beyond projected median of age 30
- Cancer prevention and screening to identify early malignancies

# Dyskeratosis Congenita (DKC)

- Zinsser-Engman-Cole syndrome
- Progressive BM failure syndrome.

oral leukoplakia

nail dystrophy

reticulated skin hyperpigmentation

# DKC - Early mortality



- Bone marrow failure
- Infections
- Fatal pulmonary complications
- Malignancy

# DKC - Pathophysiology

- Subtypes: X-linked recessive, autosomal dominant, and autosomal recessive
- Related to telomerase dysfunction
- *DKC1* and *TERC* genes encode proteins in the telomerase complex, responsible for maintaining telomeres at the ends of chromosomes.

# DKC - Pathophysiology

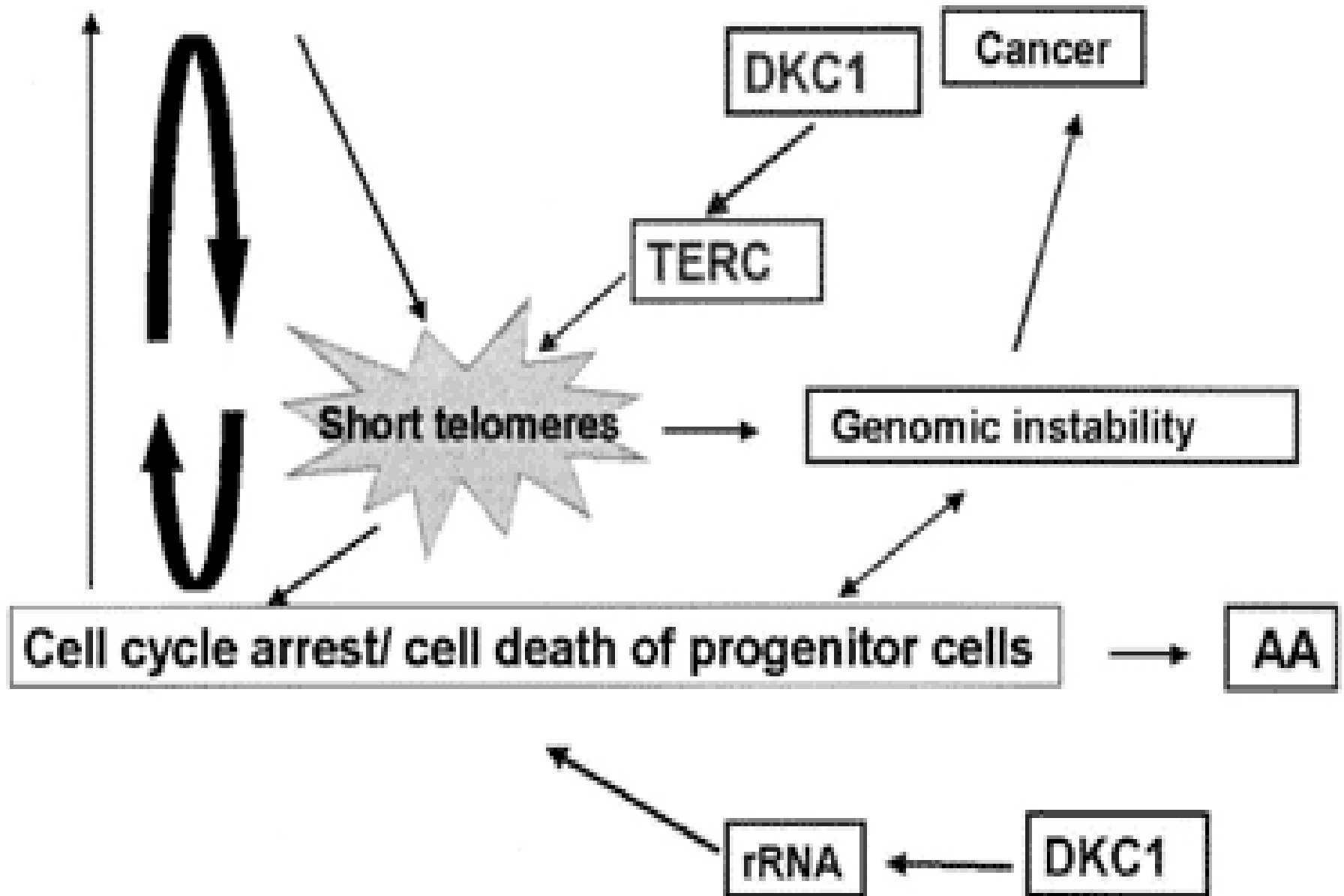
- Telomeres are repeat structures at ends of chromosomes, stabilizing chromosomes
- With cell division, the length of telomeres is shortened and the enzyme telomerase compensates by maintaining telomere length in germline and stem cells
- Critical role in preventing cellular senescence and cancer progression.



# DKC - Pathophysiology

- Reduced telomerase activity and abnormally short tracts of telomeric DNA
- Rapidly proliferating tissues with the greatest need for telomere maintenance (eg, bone marrow) are at greatest risk for failure

# Constant increased recruitment of stem cells into cell cycle

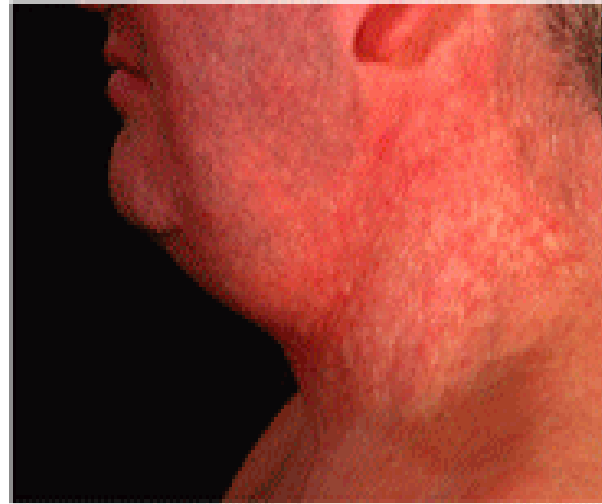


# DKC

- **Internationally:** 1 in 1 million people, M: F = 3:1
- **Mortality/Morbidity:** 70% with BM failure or from its complications at a median age of 16 years.
- 11% died of sudden pulmonary complications; a further 11% died of pulmonary disease in the bone marrow transplantation (BMT) setting.
- 7% died of malignancy (eg, Hodgkin lymphoma, pancreatic carcinoma)
- **Age:** first decade of life; skin hyperpigmentation and nail changes typically appearing first.

# DKC – Skin Findings

- Tan-to-gray hyperpigmented or hypopigmented macules and patches in a mottled or reticulated pattern.
- Alopecia of the scalp, eyebrows, and eyelashes
- Premature graying of the hair
- Hyperkeratosis of the palms and soles
- Adermatoglyphia (loss of dermal ridges on fingers and toes)

**a****b****c****d****e****f**

**Abnormal skin pigmentation (a, b, c), premature hair greying (a), leukoplakia and premature loss of teeth (d), nail dystrophy (e, f).**

# DKC – Nail Findings



- Nail dystrophy : 90% of patients, fingernails before toenails
- Ridging and longitudinal splitting → small, rudimentary, or absent nails.

# DKC – Mucosal Findings

- Mucosal leukoplakia → verrucous → ulceration may occur.
- Dysphagia
- Dysuria
- Phimosi

# DKC



- Increased risk of malignancy

- Malignant mucosal neoplasms

- \* Squamous cell carcinoma of the mouth, nasopharynx, esophagus, rectum, vagina, or cervix

- \* Within sites of leukoplakia

- Adenocarcinoma of the gastrointestinal tract, bronchial and laryngeal carcinoma.



# DKC – Lab studies

- Screen for BM failure, pulmonary disease, neurologic disease, and mucosal malignancies.
- CBC count, CXR, pulmonary function tests, and stool tests for occult blood.
- Mutational analysis : *TERC* gene and in the *TERT* gene, the gene for telomerase reverse transcriptase
- Genetic testing for *DKC1*

# DKC - Treatment

- Short-term tx for BM failure
  - anabolic steroids
  - granulocyte macrophage colony-stimulating factor
  - granulocyte colony-stimulating factor
  - EPO
- Long term – stem cell transplant

# Shwachman-Diamond Syndrome (SDS)

- Pancreatic insufficiency, bone marrow dysfunction, and short stature.
- In 1964, Shwachman, Diamond, Oski, and Knaw first reported the syndrome at Harvard Medical School.
- SDS is the 2<sup>nd</sup> most common cause of inherited pancreatic insufficiency
- M:F = 1.7:1.

# SDS

- Emaciated, abdominal distension, hypotonia and hepatomegaly
- Short stature with a normal growth rate
  - Clinodactyly
  - Syndactyly
  - Supernumerary metatarsals
  - Coxa vara deformity
  - Genu and cubitus valgus
  - Dental abnormalities



Metaphyseal irregularities proximally and distally in the femur with secondary growth abnormality in the left lower femur

# SDS - Lab Studies



- CBC : Neutropenia, anemia, and thrombocytopenia
- Neutrophil function studies: Neutrophil migration defect
- HB F - elevated in approximately 75% of cases
- Iron studies: Iron deficiency secondary to malabsorption.
- A 72-hour fecal fat measurement
- Periodic BM evaluation

# SDS

- Predilection for developing marrow failure and leukemic transformation (occurs in 5-33% of patients with SDS)
- AML, ALL, and juvenile CML
- BM : hypocellularity with maturation arrest in the myeloid series and fat infiltration. Megakaryocytes – normal to decreased.

# SDS



- All pts have varying degrees of pancreatic insufficiency
- Pancreatic acinar cells do not develop in utero, replaced by fatty tissue.
- In contrast to cystic fibrosis, the pancreatic ductal architecture is spared; thus, an intact anion secretion and fluid flow occurs.
- Pancreatic lipase secretion increases slightly with age

# SDS - Pathophysiology

- Definitive pathogenic defect responsible for the associated hematologic abnormalities in persons with SDS is unknown.
- 50% have pancytopenia
- Neutropenia may be mild, moderate, or severe.
- Defective neutrophil chemotaxis



# SDS- Pathophysiology

- Defective neutrophil chemotaxis : defect in chromosome 7
- Mutations in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene - chromosome 7 - in up to 75%
- Unusual surface distribution of concanavalin A on neutrophils may reflect a cellular cytoskeletal defect.
- Hematologic abnormalities may be due to a stem cell : decreased CFU-GM and CFU-E growth potential in culture

# SDS - Frequency



- **In the U.S.:** Approximately 3% of childhood pancreatic dysfunction; 1 in 10,000-200,000 births.
- **Internationally:** More than 200 cases of SDS have been reported in the literature

# SDS - Mortality/Morbidity

- Prognosis uncertain
- Recurrent bacterial infections
- Bone marrow failure and leukemic transformation

# SDS – Treatment



- Pancreatic enzyme supplementation
- Prevention or treatment of serious and/or invasive infections with early attention to febrile illnesses
- Correction of hematologic abnormalities when possible
- Prevention of orthopedic deformities