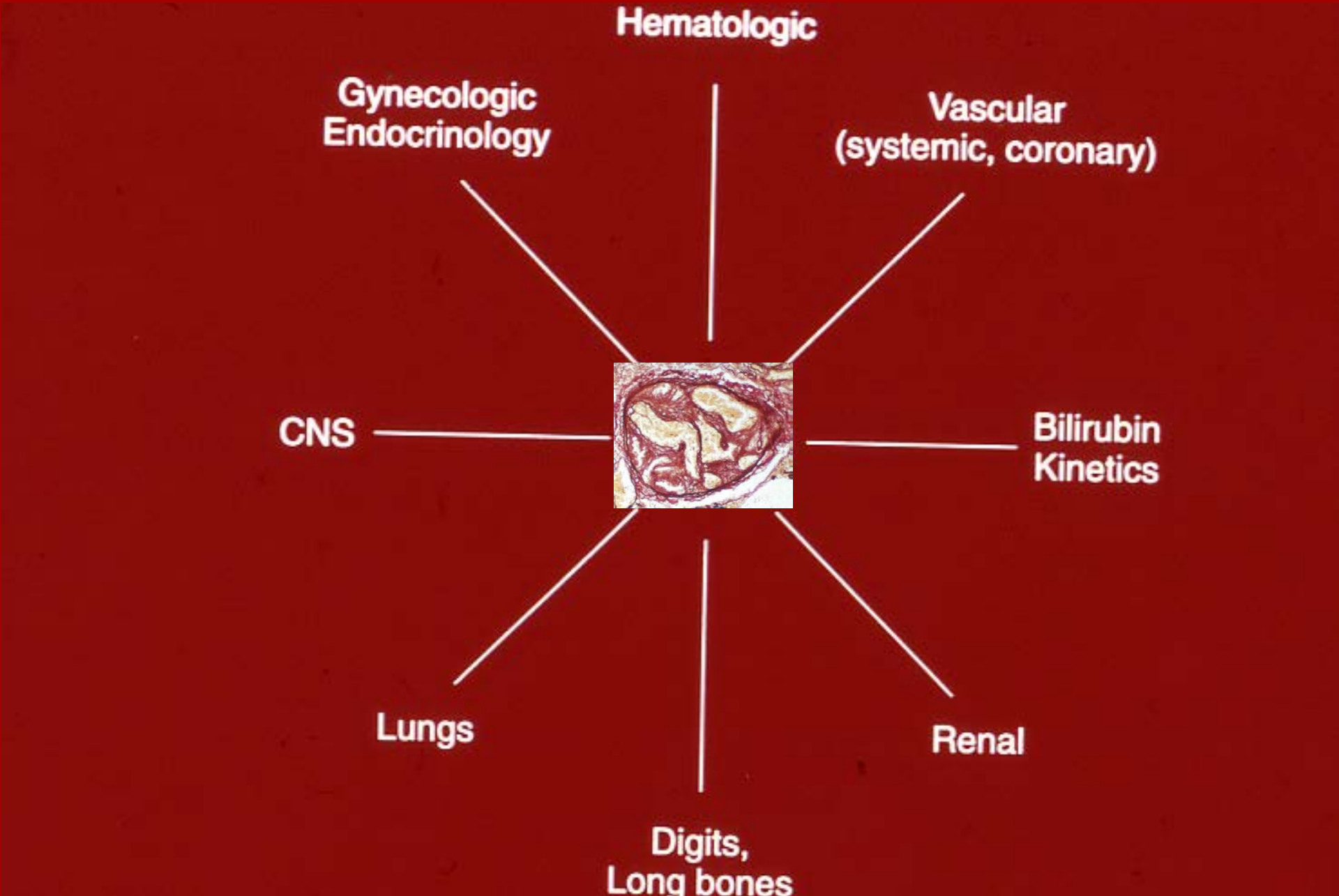
CCHD - A Multi-System Systemic Disorder



Decades Ago

The First Step

Perloff JK, Jacobsen J, Rath CE
Intravascular hemolysis and thrombocytopenia in left ventricular outflow obstruction.
Br. Heart J. 1973

The Second Step
2011

The Hematologic Disorders of Congenital Heart Disease

Hematologic Disorders

1) The red blood cell:

a) Mass

b) Iron deficiency

c) Nitric oxide

d) Bilirubin kinetics

2) Platelets/Megakaryocytes

3) Hemorrhagic diatheses:

a) Vasodilatation

b) Hemostatic defects

Increased Red Cell Mass

Primary--Polycythemia rubra vera is a malignant clonal stem cell disorder characterized by excessive proliferation of all three hematopoietic cell lines---erythroid, myeloid and megakaryocytic.

Secondary--In CCHD, a desirable adaptation to hypoxemia is characterized by an isolated increase in red cell mass.

Erythropoietin

Erythropoieten is the major regulator of red cell production in the bone marrow. Its concentration is determined by oxygen availability in the renal cortex, the major site of production. The hypoxemic stimulus of CCHD elevates serum erythropoietin levels. When the increase in red cell mass is adequate to offset tissue hypoxemia, erythropoietin levels normalize.

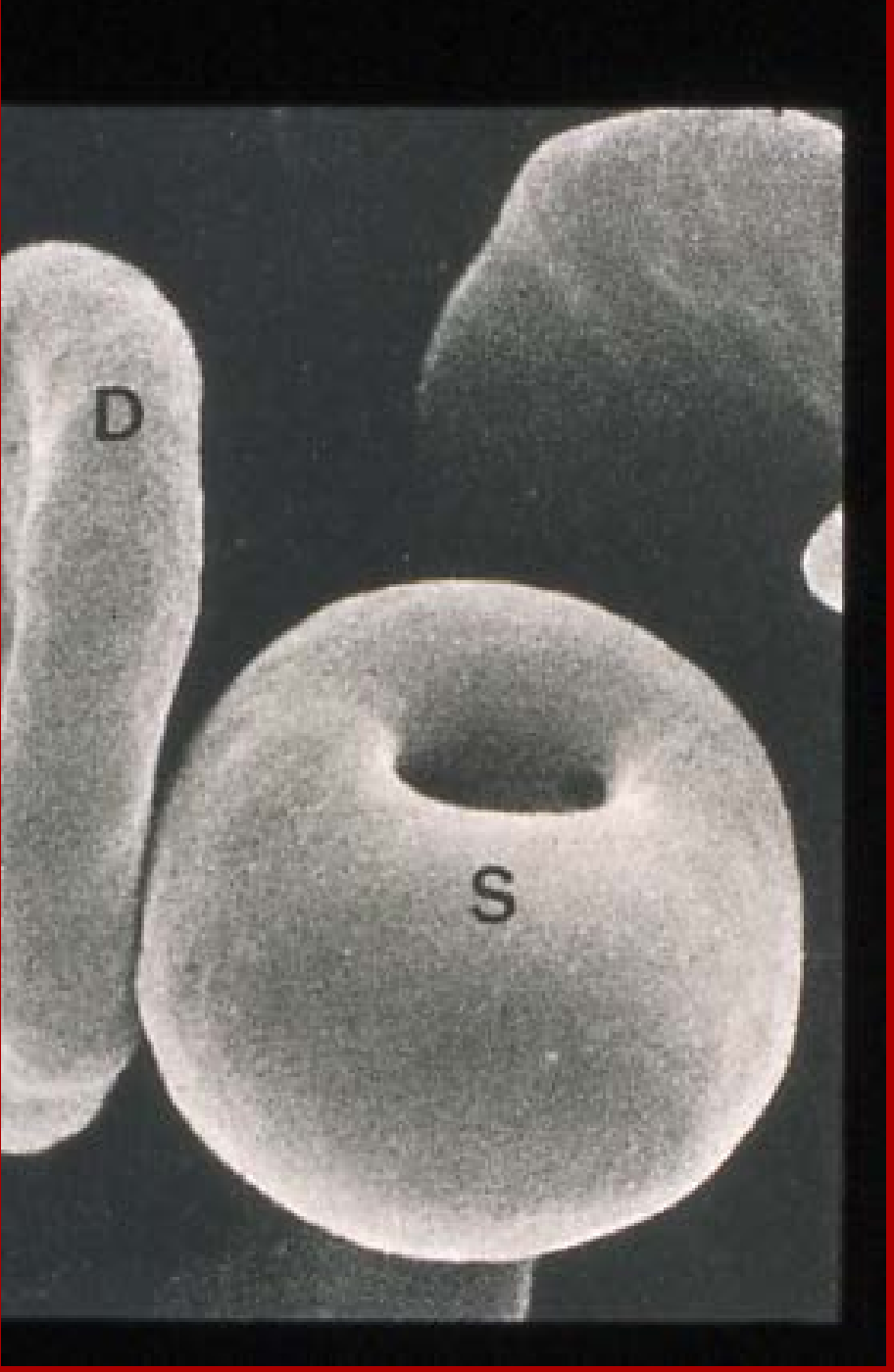
Why Does Red Cell Mass Increase in Cyanotic Congenital Heart Disease?

Nature is neither lazy nor devoid of foresight.

Galen

Erythrocytosis is a desirable compensatory adaptation to systemic arterial hypoxemia and to a decrease in tissue oxygenation.

Phlebotomy reduces red cell mass, reduces tissue oxygen delivery, and stimulates release of erythropoietin.



Iron Deficiency

When deformable biconcave discs become non-deformable iron deficient microspherocytes, whole blood viscosity increases 100 times at a hematocrit of 70%.

Precautions

Micro-hematocrit centrifugation in the presence of erythrocytosis results in plasma trapping and false elevation of hematocrit levels. Hematocrit should therefore be based on *automated electronic particle counts*.

The standard amount of citrate anticoagulant added to a normal blood sample is excessive because plasma volume is decreased in the presence of erythrocytosis. The amount of citrate must therefore be adjusted.

Chronic Hypoxaemia and Decompensated Erthrocytosis in CCHD

Rosove, Perloff et al, The Lancet 1986

Compensated Erythrocytosis--Physiologic adaptation to tissue hypoxemia is established with equilibrium hematocrits and an iron replete state.

Decompensated Erythrocytosis-- Iron replete equilibrium hematocrits and physiologic adaptation to tissue hypoxemia are not established.

Beneficial Effects of Erythrocytosis

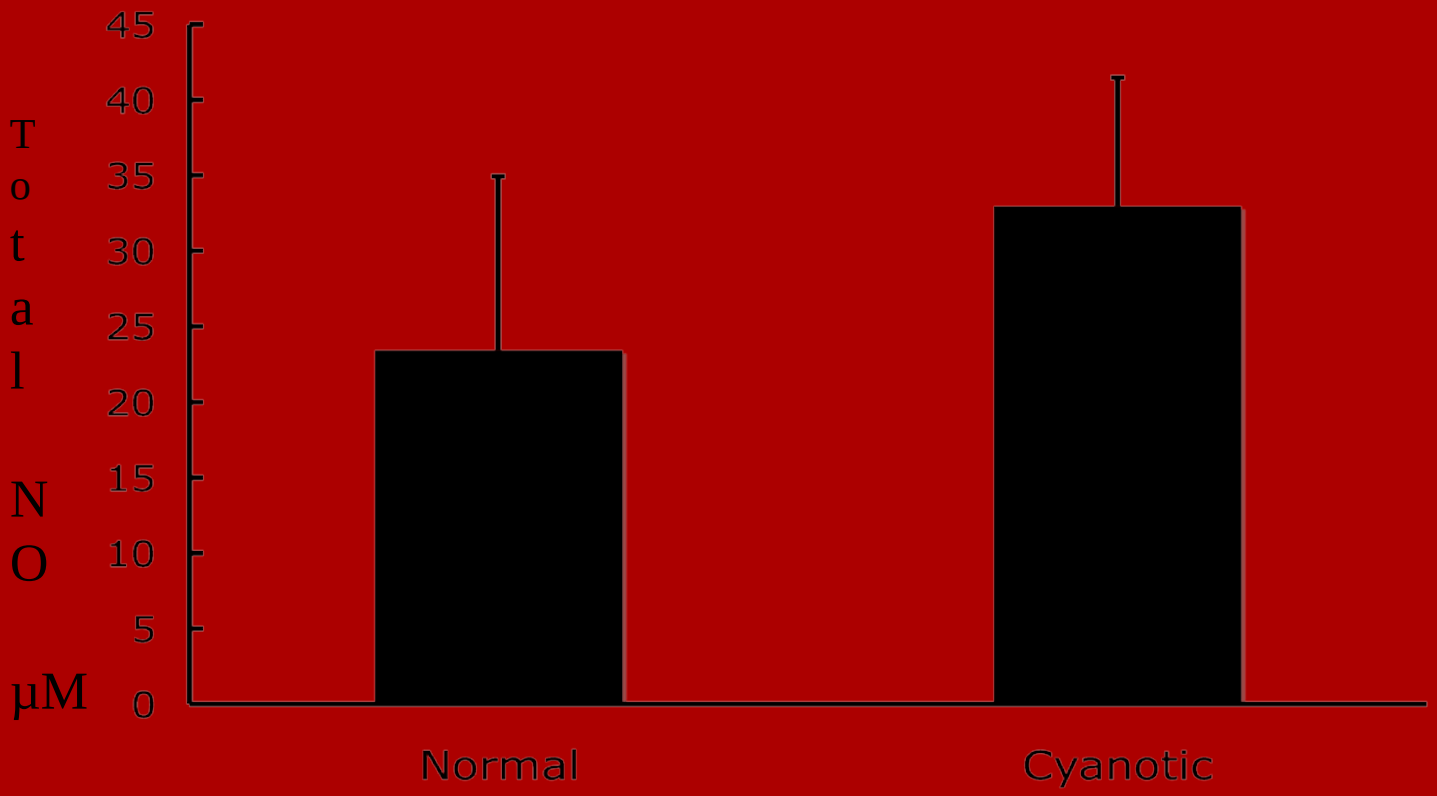
The erythrocytosis accompanying CCHD is a beneficial adaptive response to systemic arterial hypoxemia, serving to increase oxygen delivery to metabolizing tissues.

Oxygen delivery is further increased by systemic vasodilatation in response to elaboration of endothelial NO which is increased by the shear stress of the erythrocytotic perfusate.

Nitric Oxide

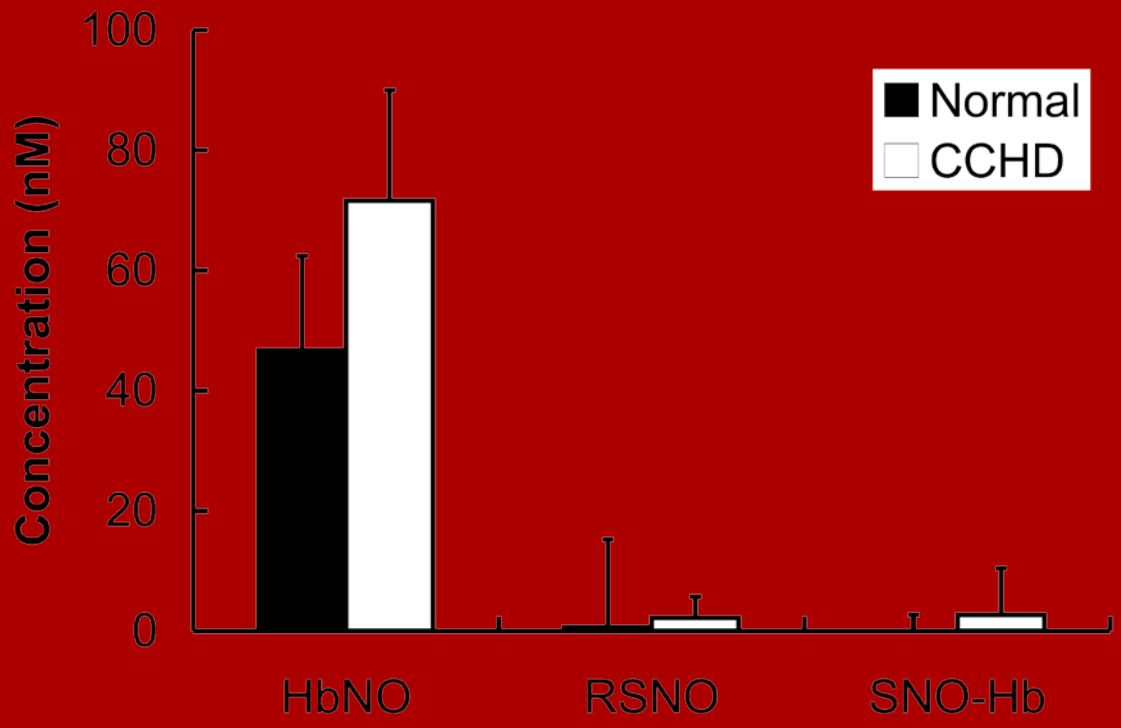
The molecule diffuses from vascular endothelium according to Fickian principles. *Abluminal* diffusion regulates blood flow by activating soluble guanylate cyclase in medial smooth muscle cells. However, a significant fraction of NO diffuses *luminally* where it is regulated by the extremely high reaction rate with red cell hemoglobin, rendering the effective luminal concentration zero.

Han and Perloff



Total NO is increased in the plasma of adults with CCHD.

Tae, Perloff, Liao



Red cell nitrosyl-hemoglobin (HbNO) concentration is increased in adults with CCHD.

Luminal diffusion of NO culminates in rapid inactivation by red cell Hg. An increase in red cell mass in CCHD results in increased NO inactivation, less abluminal diffusion, and less vasodilatation.

Han, Perloff, Liao

Nitric Oxide and Red Blood Cell Deformability

Red cell deformability is enhanced by physiologic concentrations of NO, facilitating oxygen release and delivery of oxygen to metabolizing tissue.

Gilbert's Disease

An Experiment of Nature

An inborn error of bilirubin metabolism characterized by a benign elevation of unconjugated bilirubin without liver disease or hematologic abnormalities.

Bilirubin Kinetics

- Bilirubin is formed from the breakdown of heme, a process that is excessive in the presence of the erythrocytosis of CCHD, and that coincides with a substantial increase in unconjugated bilirubin which is a natural anti-oxidant that is antiatherogenic.

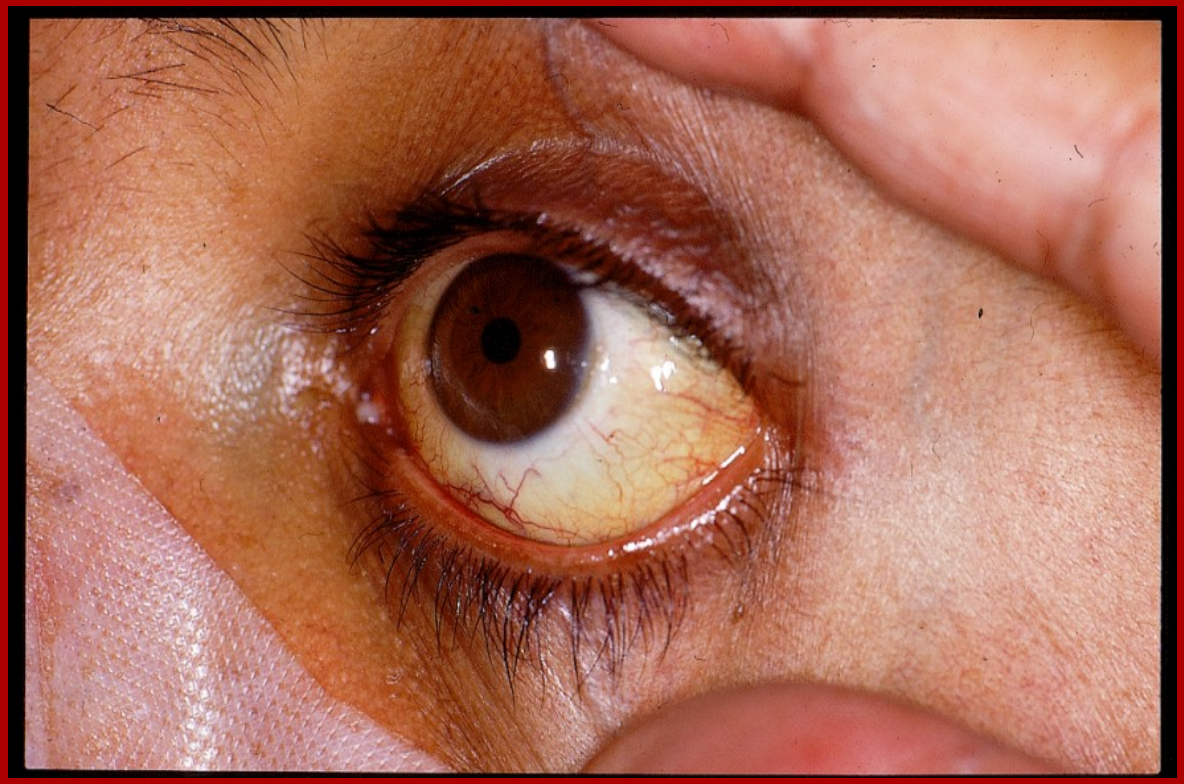
Jaundice in CCHD

Typical total bilirubin level in CCHD

3.7

Reference Level

0-1.0 mg/dL




935-10329

Blood Letting

Ancient History

An Anachronistic Benefit of Bloodletting

When Madame de Manenon became the consort of Louis IV, her physician removed one or two ounces of blood several times a week so madame would not blush so readily at the stories told in the French royal court.

Current Criteria for Phlebotomy

Phlebotomy should be reserved for temporary relief of hyperviscosity symptoms, and should not be based on hematocrit *per se* irrespective of level. The assumed risk of stroke due to cerebral arterial thrombosis in CCHD has not materialized whether erythrocytosis is iron replete or iron deficient.

Technique of Phlebotomy

The amount of blood removed is the minimum needed to achieve symptomatic relief of hyperviscosity symptoms, generally one unit followed by isovolumetric saline replacement.

Oral hydroxyurea blunts phlebotomy-induced rebound of erythropoietin.

Iron Deficiency

A Caveat

Iron deficiency in CCHD sometimes occurs without hyochromia or microcytosis because a coexisting elevation of homocystine causes an increase in both red cell size and color.

Kaemmerer, et al.
Am J Cardiol 2005

Metabolic Effects of Iron Deficiency

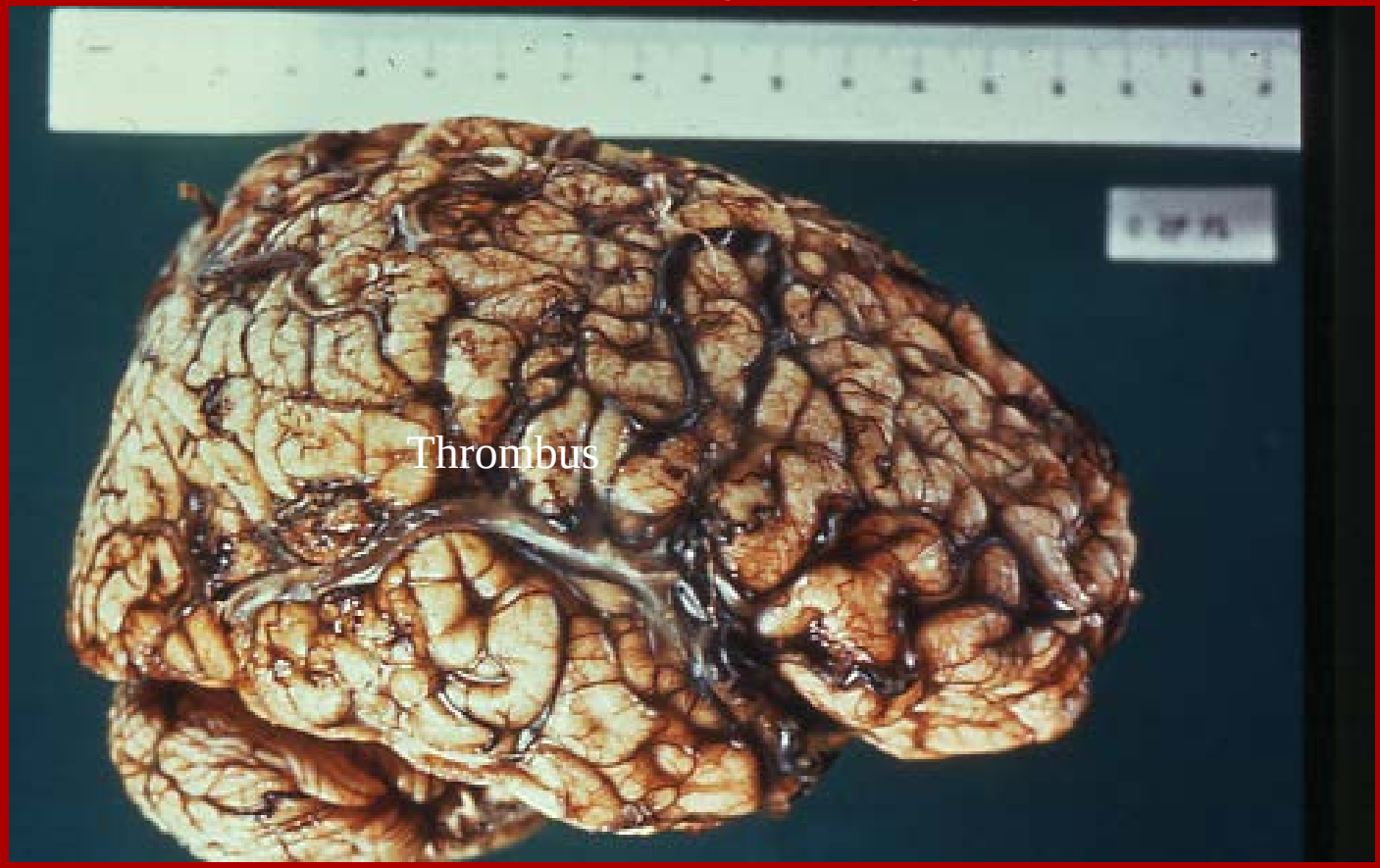
Iron is an integral part of myoglobin and of certain mitochondrial enzymes, and plays an important role in oxidative metabolism. Because of the *metobolic effect* of iron, the myalgias and muscle weakness of iron deficiency disappear promptly after administration of intravenous iron dextran, i.e. before iron stores are replete.

Management of Iron Deficiency

Because erythropoietin levels are elevated in patients with phlebotomy-induced iron deficiency, administraton of iron results in a rapid rise in red cell mass. Accordingly, the therapeutic dose of iron should be small, and monitoring should be frequent. Iron should be stopped at the first discernible rise in hematocrit.

Cerebral Venous Thrombotic Stroke

Increased risk in infants with
iron deficient erythrocytosis



Hyperviscosity Symptoms

Headache, faintness, dizziness.
Lightheadedness, slow mentation.
Impaired alertness, a sense of distance
or dissociation.
Paraesthesiae, tinnitus, anorexia.
Blurred vision, double vision, scotomata.
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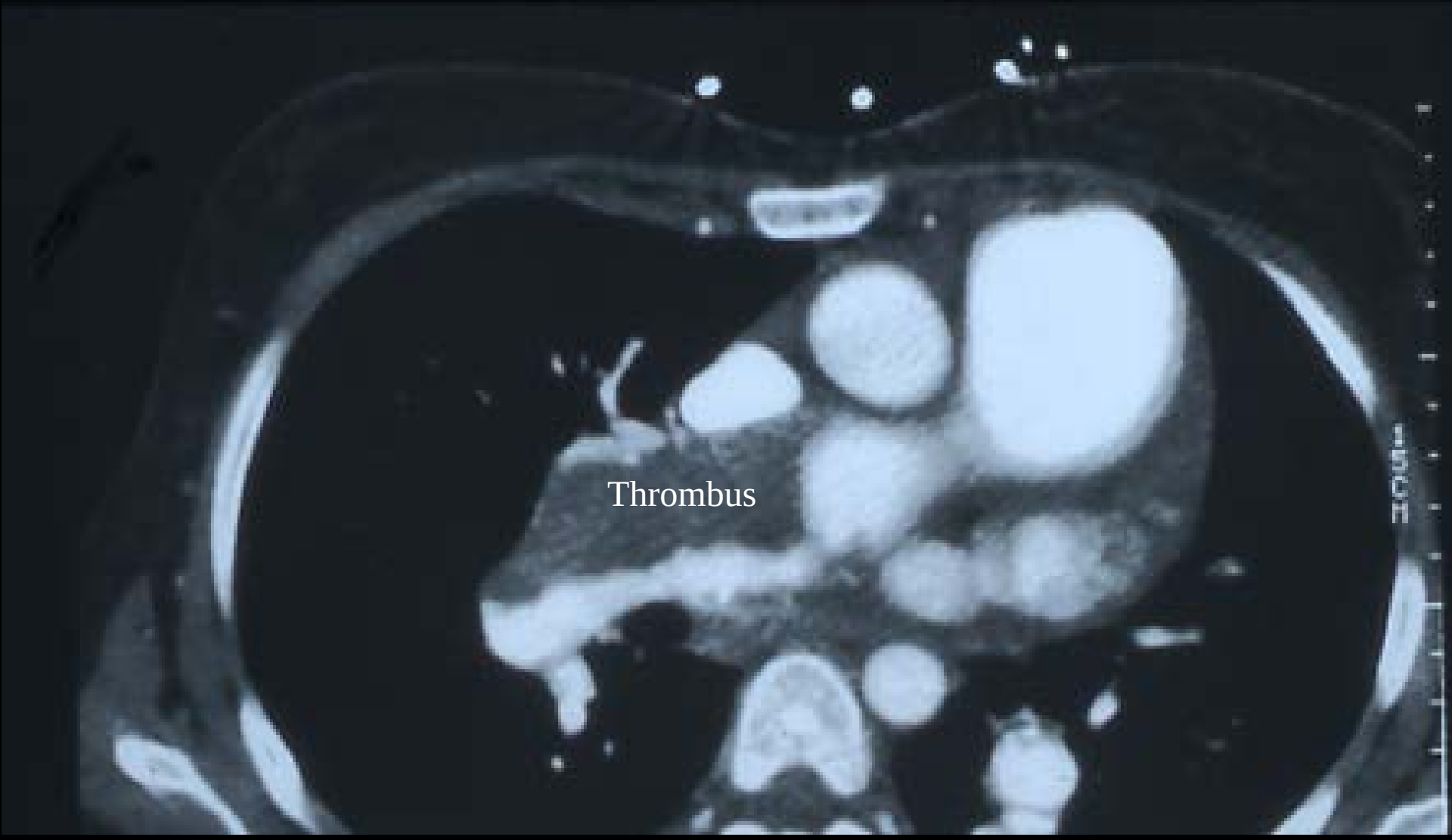
Symptoms of Iron Deficiency

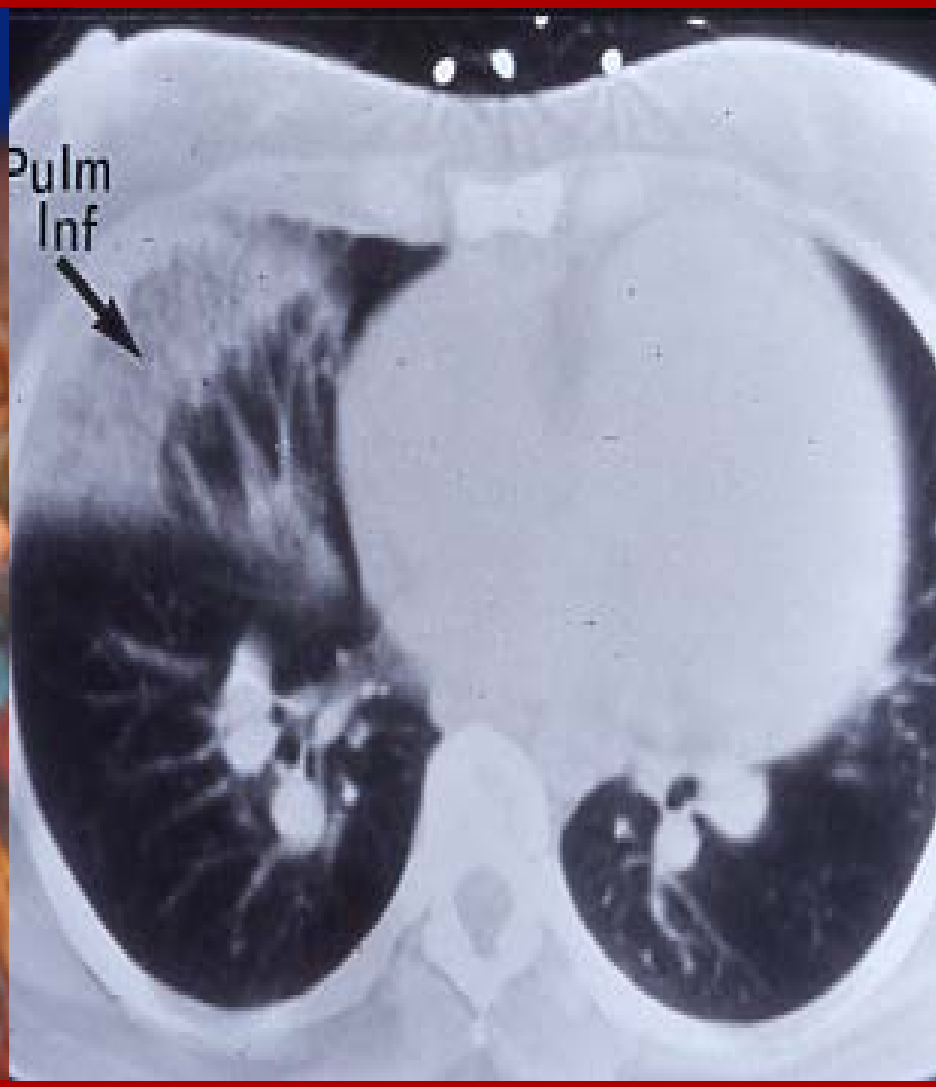
Myalgias, muscle weakness.
Fatigue, lassitude, lethargy.

Proximal Pulmonary Arterial Thrombosis in Eisenmenger Syndrome



Massive Proximal Pulmonary Arterial Thrombus in Eisenmenger Syndrome

Intra-pulmonary Embolization from Proximal Thrombus

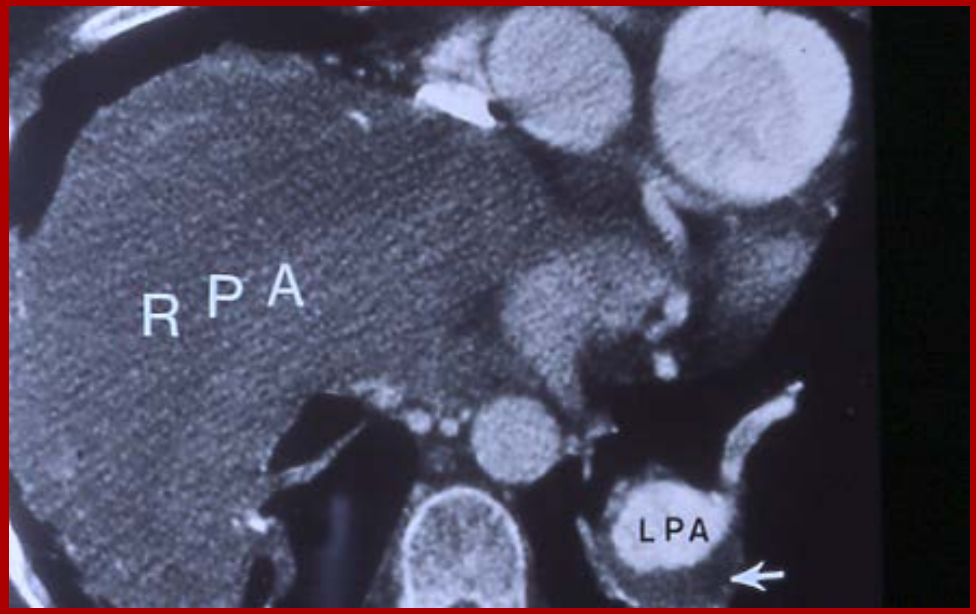


“The temptation to use the anticoagulant drugs may be great. On the basis of the present studies, their use would appear to be fraught with danger.”

Hartman RC. A Hemorrhagic Disorder Occurring in Patients with Cyanotic Congenital Heart Disease.

Bull Johns Hopkins Hospital 1952

Proximal Pulmonary Arterial Thrombosis
A Therapeutic Dilemma



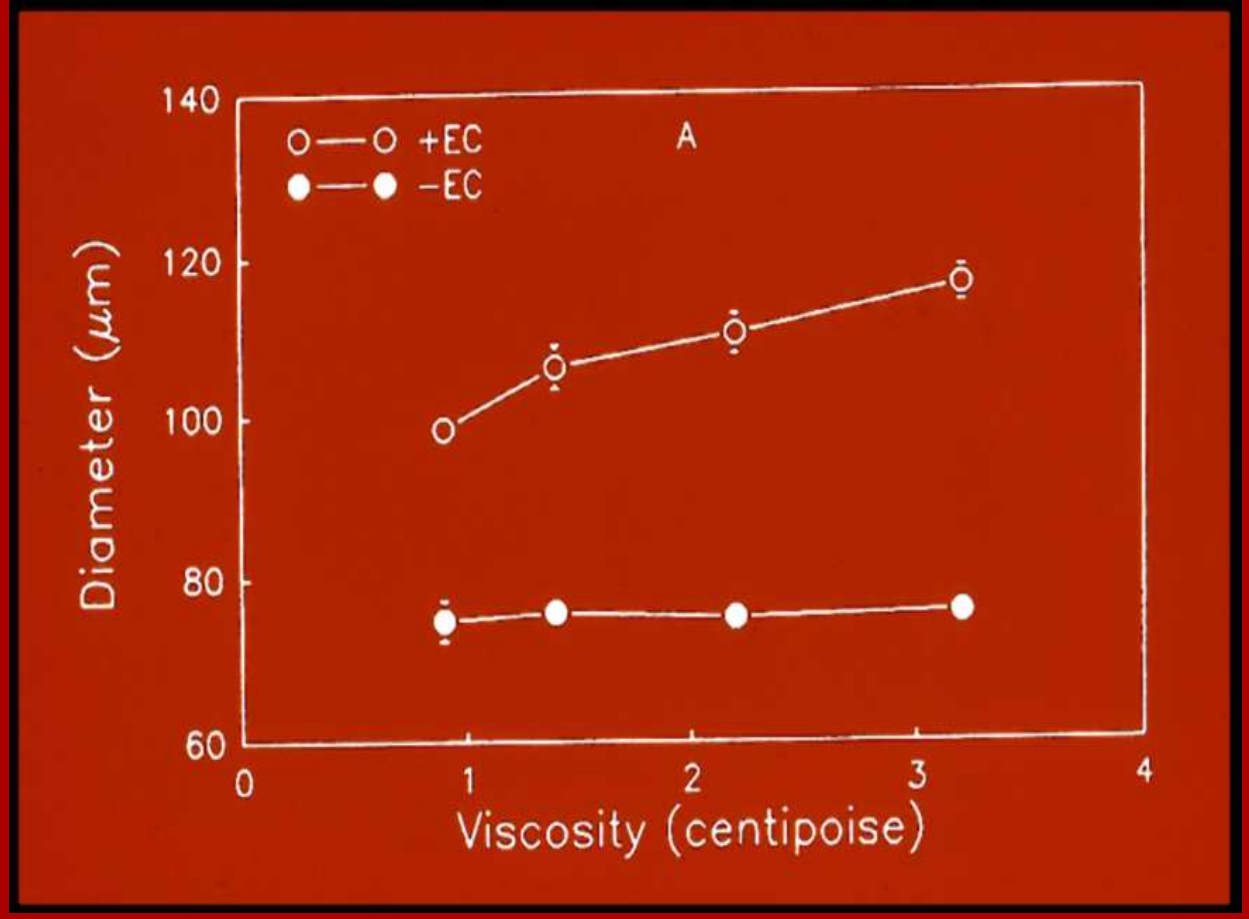
The efficacy of *anticoagulants* is nil, while the risk of reinforcing hemostatic defect(s) and provoking hemorrhage is considerable.

The efficacy of *thrombolytic agents*, including intrapulmonary administration, is nil.

Abnormal Hemostasis in Cyanotic Congenital Heart Disease

Increased tissue vascularity

Intrinsic hemostatic defects



Kohler et al Circulation Research 1993

The viscous erythrocytotic perfusate in CCHD is associated with an increase in endothelial shear stress, elaboration of NO, arterial dilatation, and *increased tissue vascularity.*

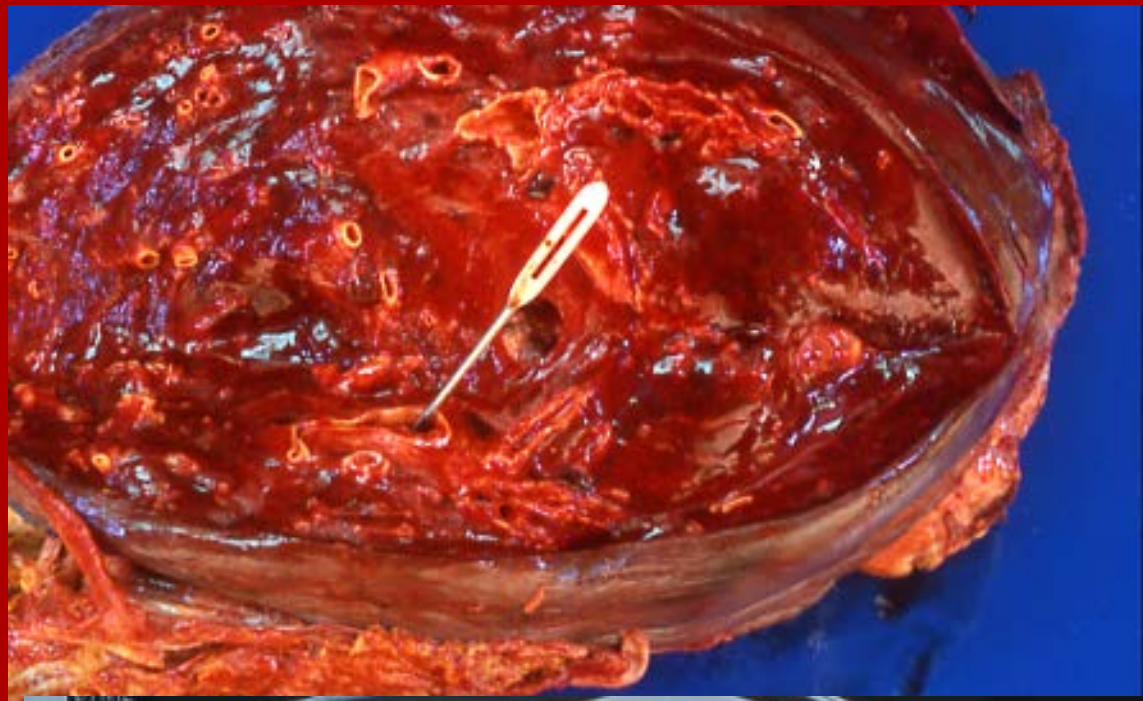
Intrinsic Hemostatic Defects

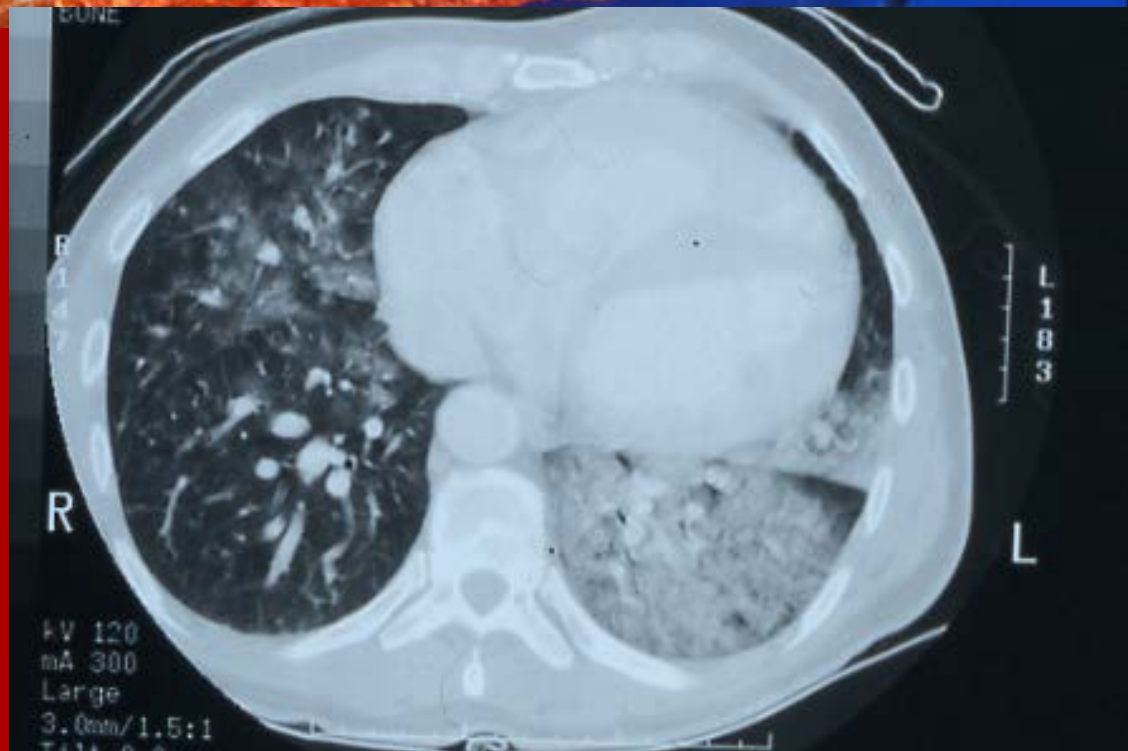
2) Decreased levels of fibrinogen and factors V, VII, VIII, IX.
3) Elevated levels of fibrin degradation products.
1) Prolongation of prothrombin time, activated partial thromboplastin time, and bleeding time.
4) Low platelet counts and thrombocytopenia.
5) Von Willebrand factor abnormalities.

Extra-Pulmonary Hemorrhage (Hemoptysis)

There's something ominous about blood coming from the mouth like the glow of a fire. *Anton Chekhov about himself*

Intrapulmonary Hemorrhage





Pulmonary Hemorrhage

Complications of pulmonary hemorrhage vary from mild and occasional to copious, recurrent, massive, and fatal. Eisenmenger's patient (1897) died suddenly following a large hemoptysis.

Massive intrapulmonary hemorrhage is the commonest cause of sudden death in Eisenmenger syndrome.

Management of *Hemoptysis*

1. ***Do not bronchoscope.***
2. **Antiplatelet or anti-inflamatory agents are questionable.**
3. **Chest x-ray for detection of intrapulmonary hemorrhage.**
4. **CT scan if x-ray detects infiltrates.**
5. **Hospitalize if intrapulmonary hemorrhage is moderate or greater.**

Management contd.

1. Thrombocytopenia – platelet transfusion.
2. Normal Platelet Count :
   a) Fresh frozen plasma.
   b) Cryoprecipitate.
3. Excessively low hematocrit--- red cell transfusion.

Eisenmenger Syndrome and Pregnancy

Hematologic Issues

Heparin During Pregnancy
Caveats

1. **Hypercoagulability does not occur in the first or second trimester, and is variable during the third trimester**
2. **Heparin is an antiplatelet agent. Platelet counts are low-normal or thrombocytopenic.**
3. **There are no reliable tests for measuring thrombin generation or antithrombin levels.**

Heparin Caveats, contd.

***In brief*: Heparin pharmacokinetics are complex, and the hemostatic substrate in gravidas with CCHD is variable. The risks of heparin far outweigh theoretical benefits.**

Conclusion: Proceed With Caution

LABOR

A hypercoagulable state is indicated by enhanced platelet activation and elevated fibrinogen and factor VII.

Postpartum

Hypercoagulability continues through the first postpartum day, but fibrin residues are cleared by enhanced fibrinolysis.

The Von Willebrand Factor (vWF)

vWF is a large, multimeric glycoprotein in plasma, in platelets, and in vascular endothelial cells. The vWF plays a central role in hemostasis, is a major adhesive link between vascular subendothelium and platelets, and is a carrier for factor VIII procoagulant.

Territo, Perloff et al. 1998

The von Willebrand Factor in Congenital Heart Disease

A relative decrease in or loss of the largest vWF multimetric forms occurs in 70% to 77% of patients with cyanosis, pulmonary vascular disease or tubulant blood flow.

Depletion normalizes after reparative surgery, indicating that the vWF abnormality is acquired and reversible.

Agarose Gel Electrophorisis

Paucity of Coronary Atherosclerosis in CCHD

Hypocholesterolemia

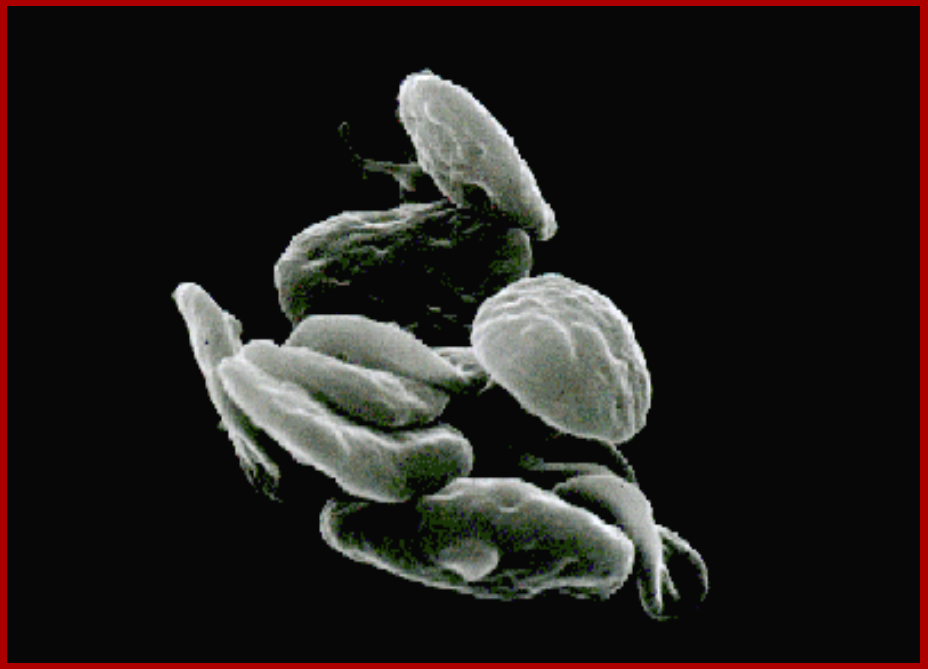
Hypoxemia

Low platelet counts

Up-regulated nitric oxide

Bilirubin

Platelets



Each cubic millimeter of blood contains about 250 million platelets that survive about 10 days after they are released into the circulation.

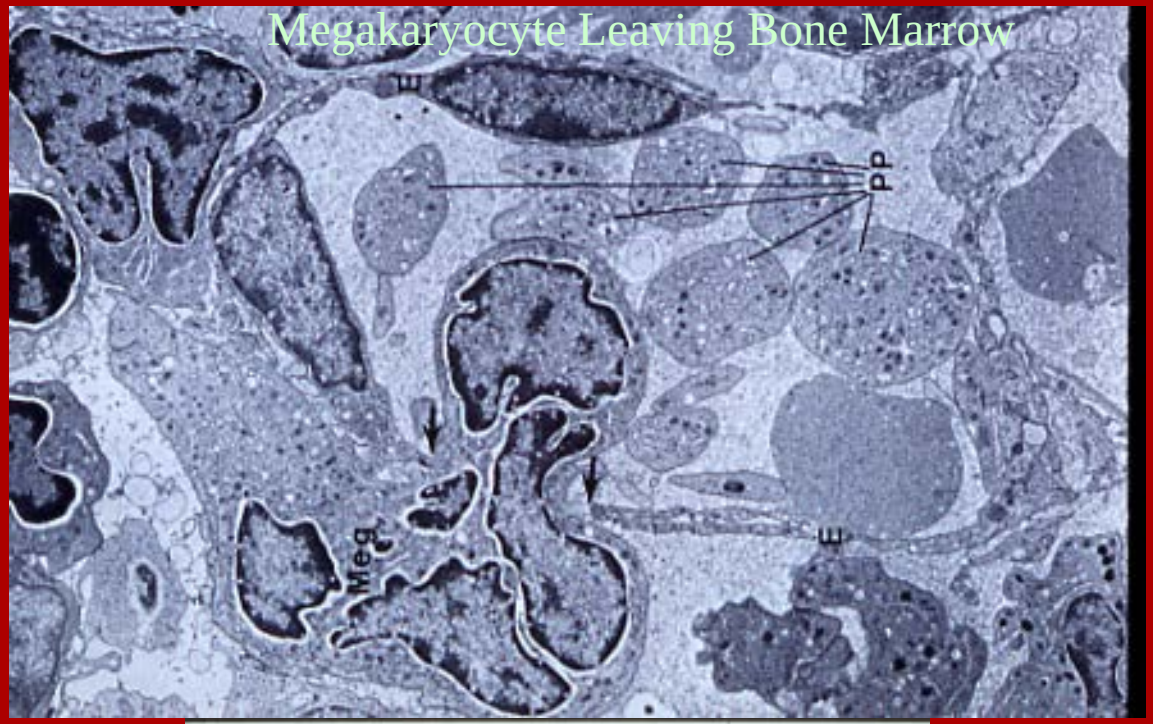
Platelet Counts

Low platelet counts and thrombocytopenia are common in CCHD. Platelet production is decreased because of ineffective thrombopoiesis, not because of increased platelet destruction or activation.

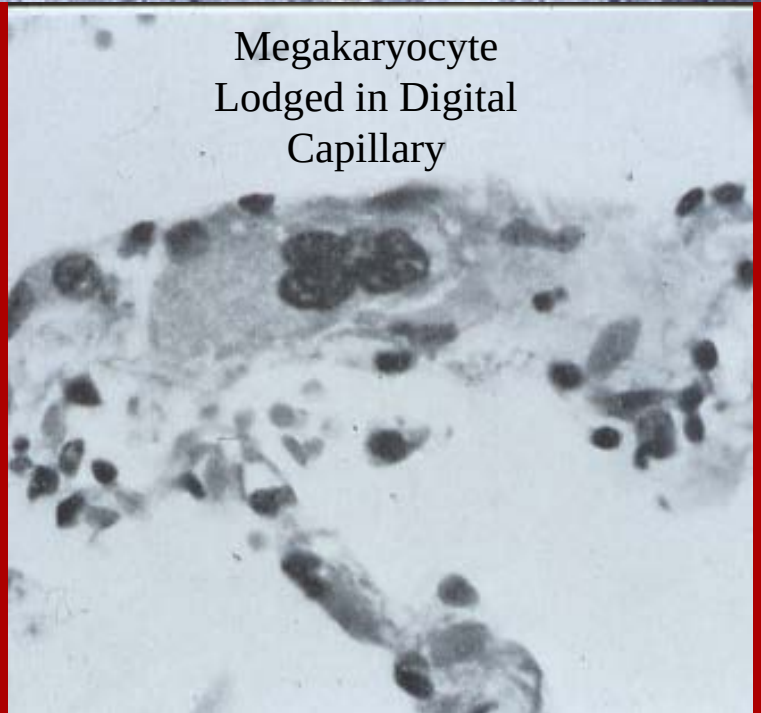
Platelet Production

1) **Whole megakaryocytes leave the bone marrow and enter the systemic venous circulation.**
2) **Platelets are produced by fragmentation of the cytoplasm of circulating megakaryocytes during their pulmonary transit.**

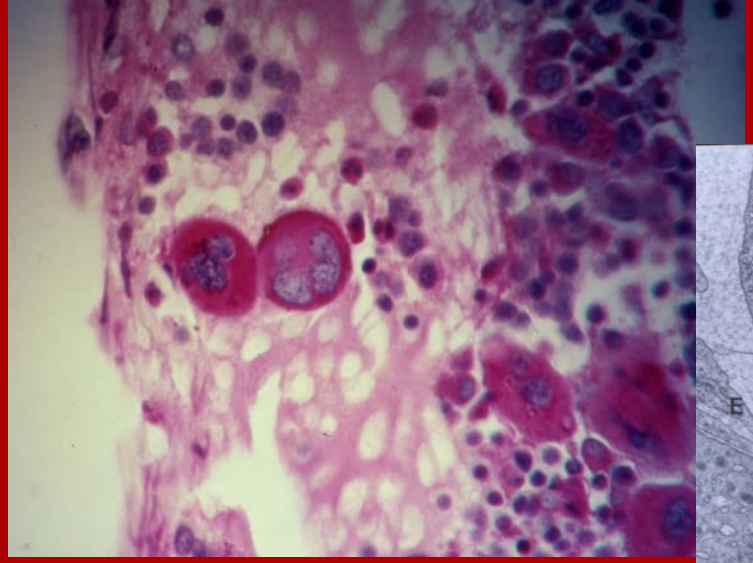
Megakaryocyte Leaving Bone Marrow



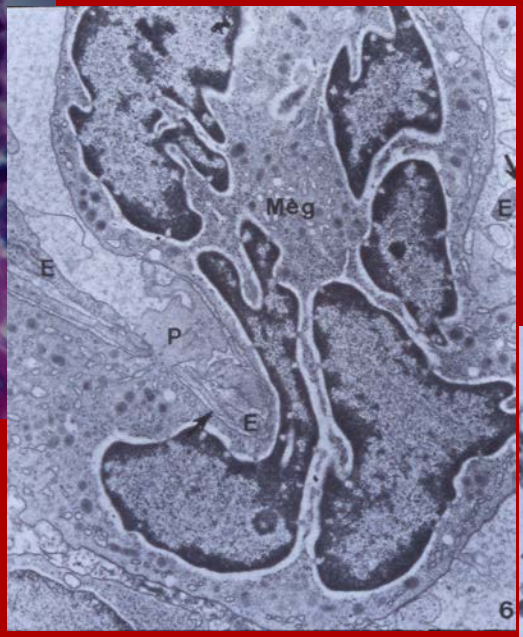
Megakaryocyte
Lodged in Digital
Capillary



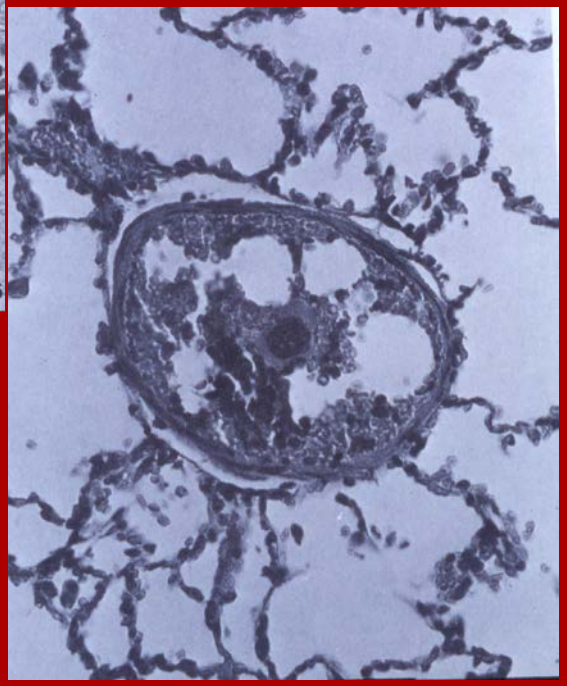
Megakaryocytes



In Bone Marrow



Leaving the Marrow



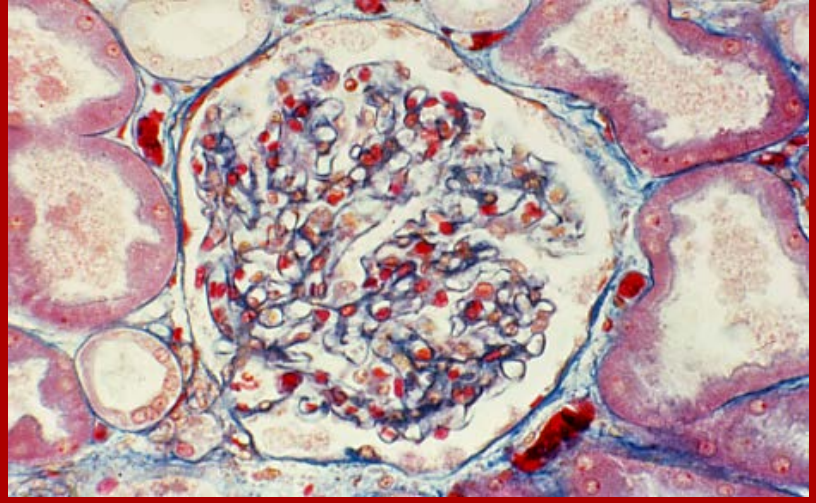
Lodged in a Pulmonary Capillary

Perloff, Latta, Barsatti. Am J Cardiol 2000

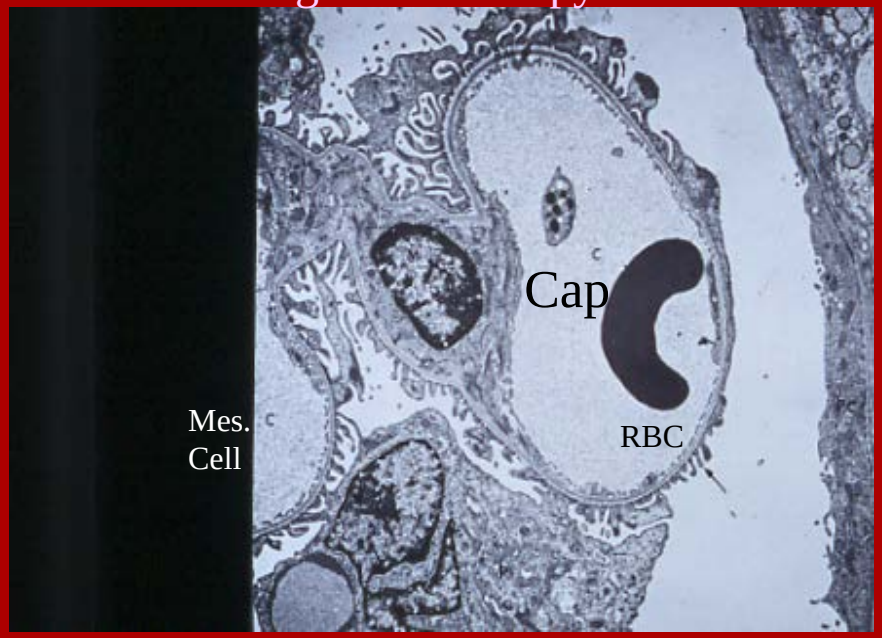
Nitric Oxide and the Kidney in CCHD

NO is synthesized in the cytosol of mesangeal cells and glomerular capillary endothelial cells. The molecule functions as an autocrine hormone that modulates the glomerular response to the increased perfusion resistance of erythrocytosis. Arterioles and capillaries dilate. Glomerular vascularity, blood flow, and size increase.

Normal Glomeruli



Light Microscopy

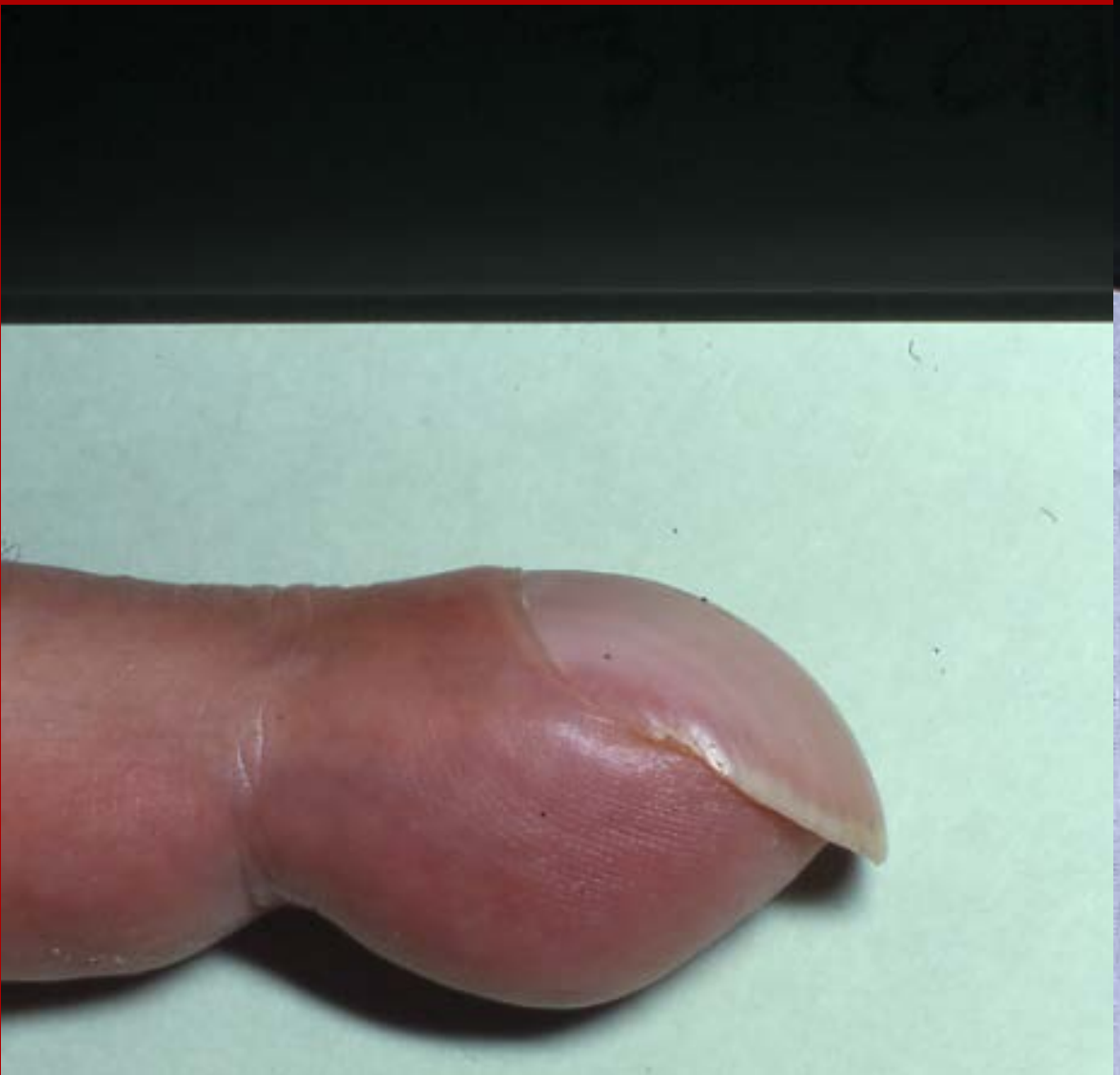


Electron Microscopy

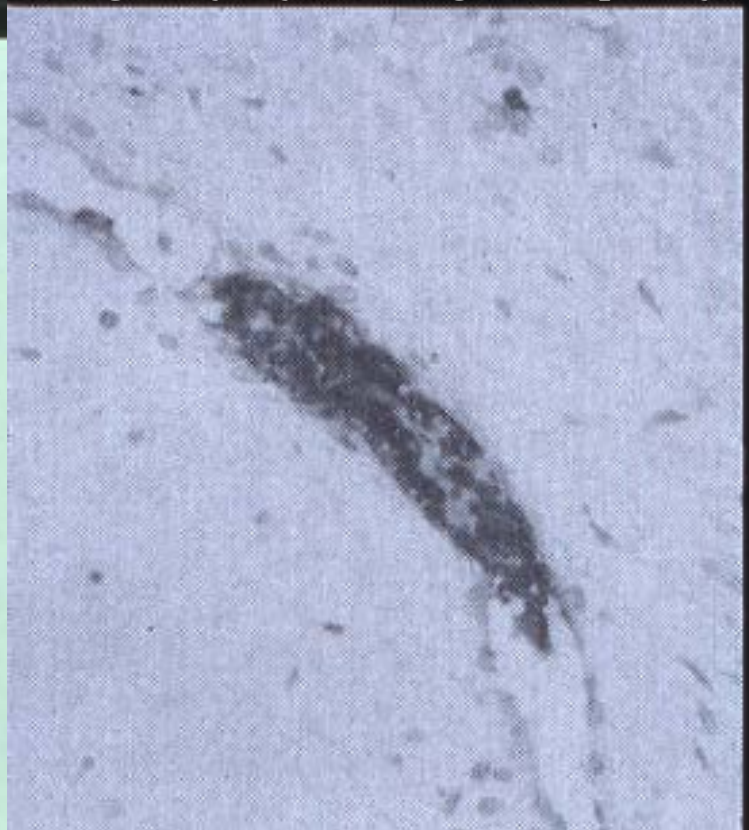
The Pathogenesis of Clubbing, Hypertrophic Osteoarthropathy, and the Non-vascular Glomerular Abnormality

The cytoplasm of intact shunted systemic venous megakaryocytes carries PDGF and TGF beta to the digits, the periostium, and to the glomerular capillaries. These mitogens and cytokines act locally because of their short half life, stimulating mesenchymally derived cells, enhancing connective tissue formation, promoting protein synthesis, extracellular matrix, fibrosis and cell proliferation, and causing *clubbing, hypertrophic osteoarthropathy,* and the *non-vascular glomerular abnormality.*

Digits and Long Bones

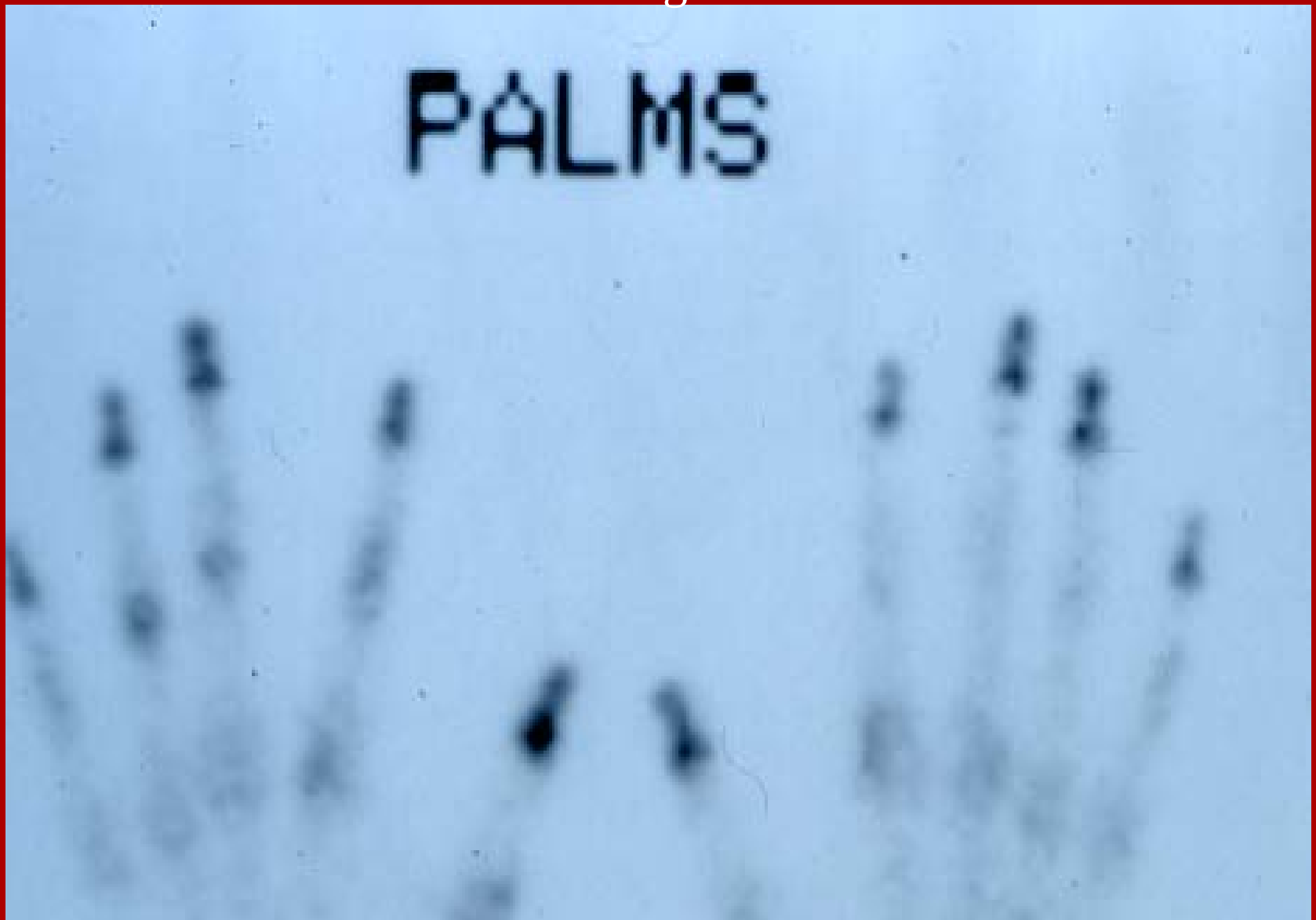


Megakaryocyte in Digital Capillary

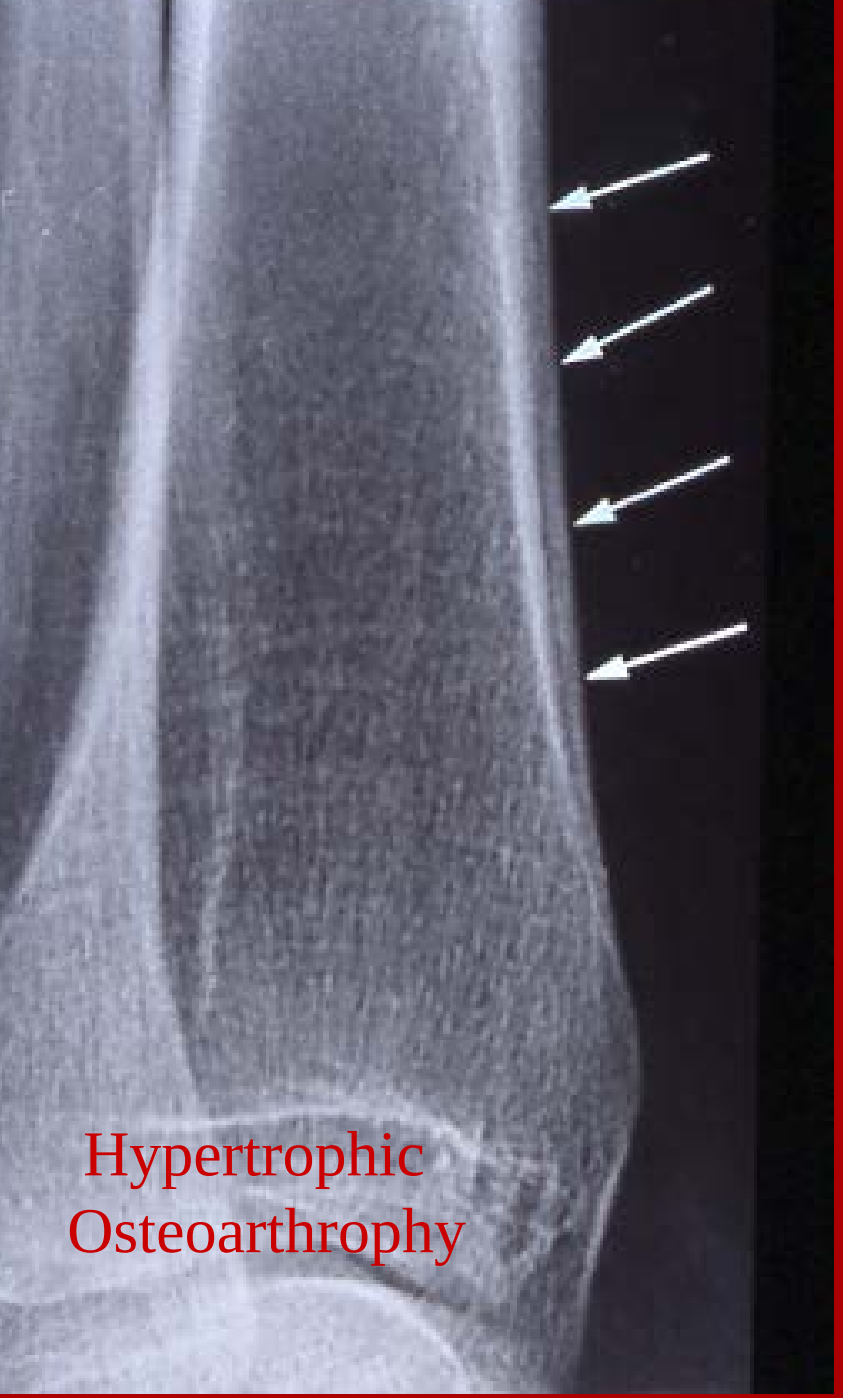


Technetium 99m Bone Scan

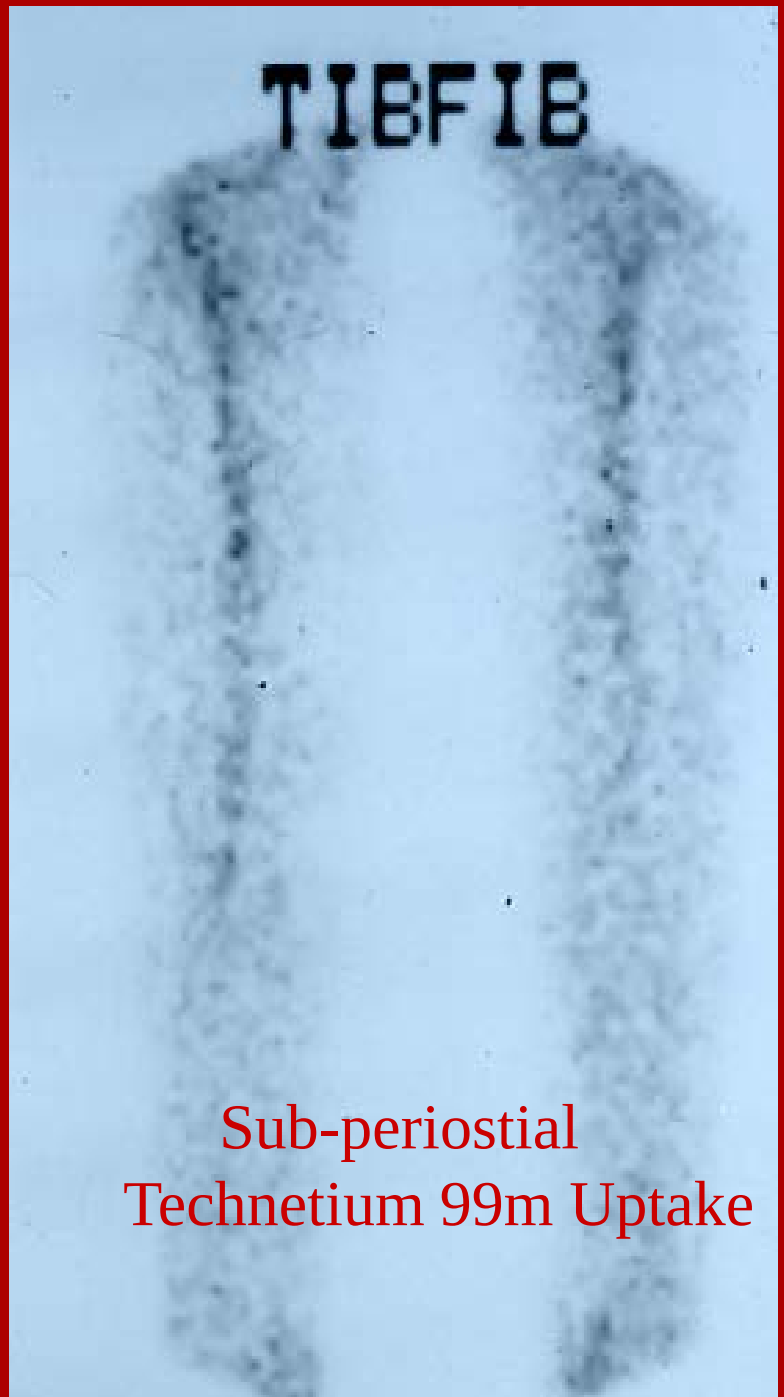
Increased Tracer in Clubbed
Distal Phalanges



Long Bones

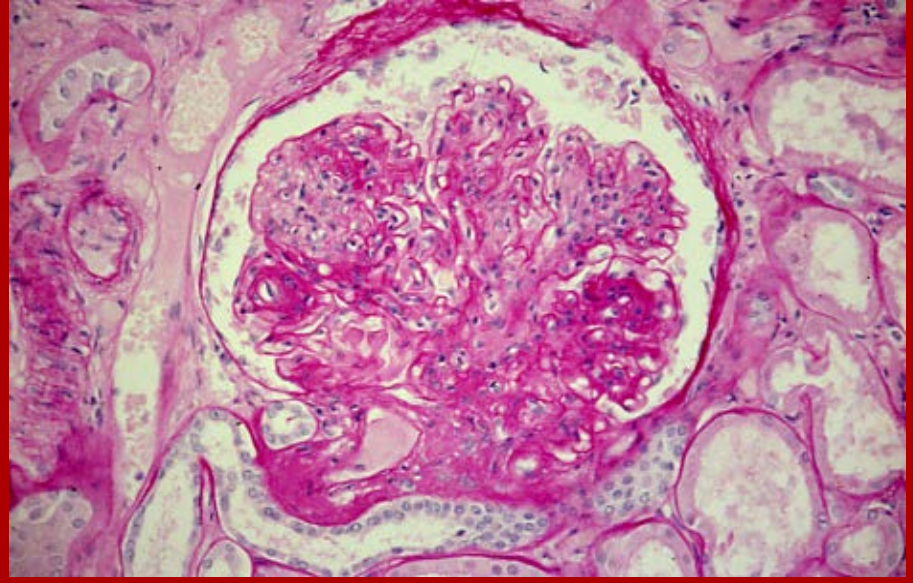


Hypertrophic Osteoarthrophy

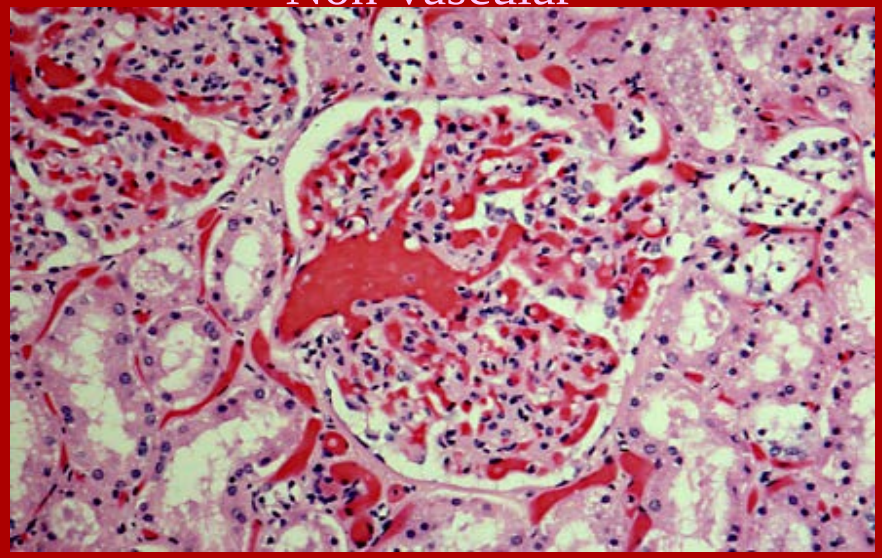


Sub-periostial Technetium 99m Uptake

Glomerular Abnormalities

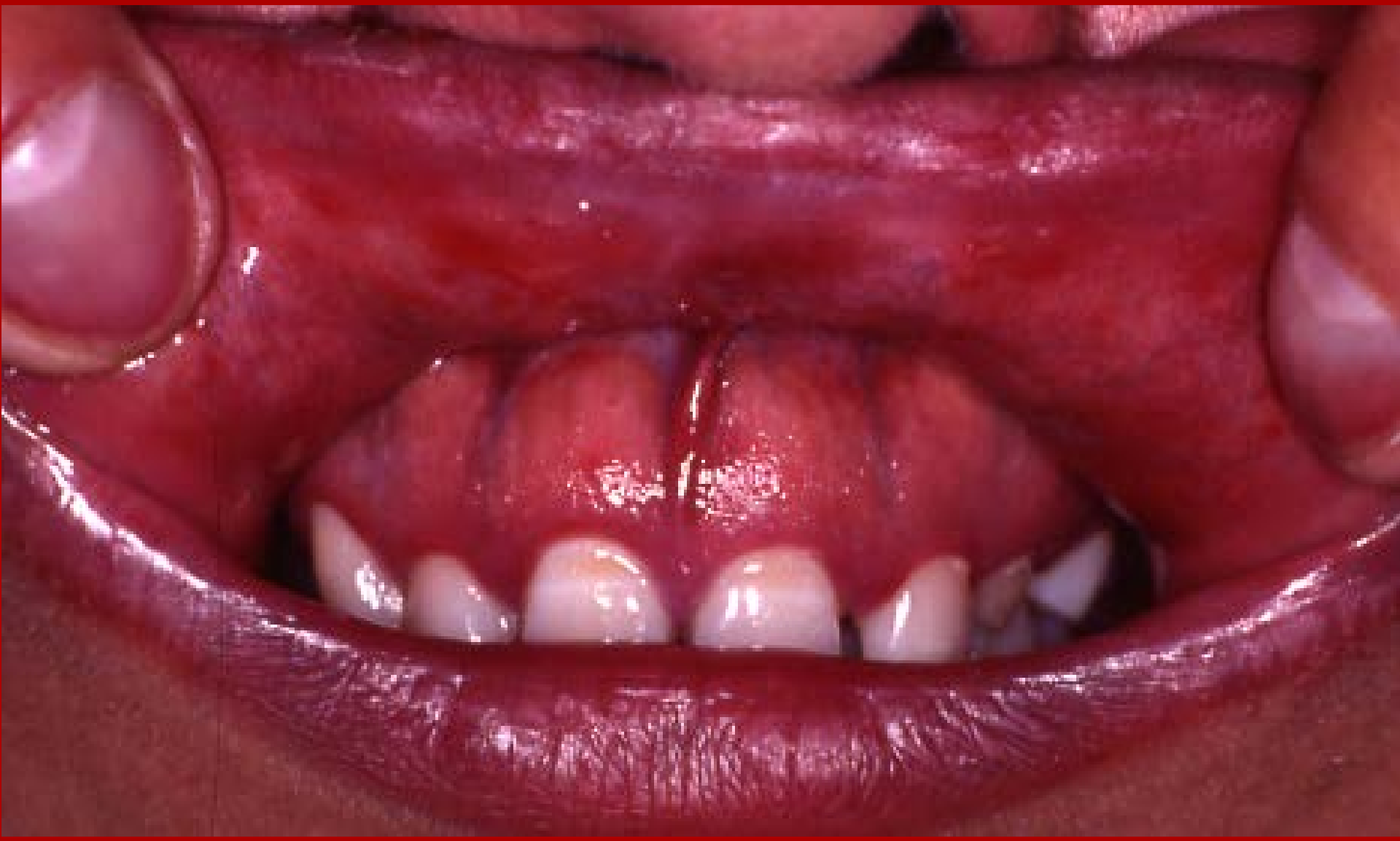


Non-vascular



Vascular

Spongy Fragile Gums



CCHD - A Multi-System Systemic Disorder