Blood Disorders in the Elderly

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Some Statistics

- 2000 decennial census
  - 35 million adults 65 years and older
- 12.4% of the total U.S population
- Projected to grow to 40%
- One out of five will be elderly
- The oldest old (85 years and older) projected to grow 400% and will represent the fastest growing age group in the U.S.A

Anemia in Older Adults

- WHO definition
  - Hemoglobin concentration of 13 G/dl in men and12 G/dl in women
- Established Population Studies of the Elderly 15.2% and12.6% over 70 years
- CHIANTI study 11.1% and 11.5%
- NHANES study (1998-1994) 11% and 10.2%
- In institutionalized settings range between 30-48%

Anemia with Nutrient Deficiency

- Among 3 million adults with anemia
  - 34% had anemia related to iron, folate and/or vitamin B_{12} deficiency
- Impairs erythropoiesis
- Iron deficiency reduces the production of red cells (microcytic and normocytic)
- Deficiency in folate and B_{12}
  - Impairs deoxyribonucleic acid synthesis
  - Reduces production of hematopoietic precursors
  - Causes red cell apoptosis (macrocytic and normocytic)

Iron Deficiency

- One fifth of all anemia cases
- Over half of all cases associated with nutrient deficiency
- Most cases result from G.I blood loss although may also be associated with dietary behavior
- Diagnosing iron deficiency in older adults and distinguishing it from other causes often difficult

Iron Storage

- Serum Ferritin until now considered best lab test of iron storage
- Value less than 12 ug/L
- Increases with age and in chronic medical conditions
- Ferritin, serum iron and transferrin saturation reported to be insensitive in elderly hospitalized patients over 80 years
- Therefore deficiency likely underestimated

Iron Storage

- Serum transferrin receptor alternative measure of iron storage
- Expression or transferrin receptor regulated by the amount of iron reaching pro-erythroid cell surfaces
- When iron stores low
  - Transferrin receptors over expressed and appear in blood serum from proteolysis

Diagnosis of Iron Deficiency

- Ratio of serum transferrin receptor level to log ferritin is the transferrin receptor-ferritin index
- Sensitivity of 88% and specificity of 93% using a cut-off value of 1.5
- Bone marrow aspirate examination of normoblasts and iron stores more definite but more painful
- Recent South Korean study suggested a serum ferritin level less than or equal to 22 ug/L with a sensitivity and specificity of 89%
  - not been compared to bone marrow exam

Folate and Vitamin B_{12} Deficiency

- 14% of all anemia cases
- Folate deficiency
  - inadequate dietary intake
  - absorption problems
- B_{12} deficiency
  - releasing vitamin from food
    - decreased gastric acidity
    - decreased production of gastrin
    - food-cobalamin malabsorption syndrome
  - decreased absorption
    - inadequate levels of B_{12}
    - deficiency of intrinsic factor

Diagnosis of Folate and Vitamin B_{12} Deficiency

- Not by serum levels alone
- Other metabolites must be considered
- B_{12}
  - Associated with higher level of Methyl Malonic acid (MMA) and/or homocysteine
- Folate
  - Associated with higher homocysteine only and not MMA

Diagnosis

- Vitamin B_{12} concentration low and MMA high in B_{12} deficiency
- Folate level low and homocysteine high and MMA normal in Folate deficiency
- Specific cut off values for these parameters not well established
  - currently no gold standard tests for these vitamin deficiencies

Anemia of Chronic Disease or Chronic Inflammation (ACI)

- Characterized by
  - chronic inflammation
  - chronic immune activation
  - Above are associated with chronic medical conditions
- Generally severity of anemia correlates positively with the severity of underlying medical condition
- Chronic infections
  - TB
  - HIV
  - Cancer
  - Autoimmune disorders (RA,IBD)
  - Diabetes
  - CHF

Anemia of Chronic Inflammation or Chronic Disease

- Most common form of anemia in older adults
- Estimated prevalence of 19.7%
- Reflects low grade pro-inflammatory state with multiple morbidities
- Higher prevalence of C-reactive and rheumatoid factor positivity with anemic older adults more likely to have arthritis and diabetes
- Non-Hispanic Blacks with ACI
  - significantly higher proportion

Anemia of Chronic Inflammation or Chronic Disease

- Elevated levels of cytokines
  - IL-1
  - IL-6
  - TNF α
- R.E system impairs
  - delivery of iron
  - proliferation of erythroid progenitor cells
  - production of erythropoietin
  - reduces red cell survival
- IL-6 induces expression of hepcidin

Hepcidin

- Small hepatic polypeptide
  - iron regulatory hormone
    - induces degradation of iron exporting ferroportin in macrophages
    - decreases duodenal absorption of iron
- Leads to inhibition of erythropoiesis
- Hepcidin has limited assay availability
  - potential screening utility not investigated

Anemia of chronic inflammation or chronic disease

- Typically mild with Hemoglobin 10 to 12 G/dl
- Distinguishing ACI from iron deficiency difficult
  - Potentially coexisting blood loss
  - Effects of medication
  - Serum iron and transferrin saturation levels reduced in both
  - Evaluation of ferritin levels and transferrin receptor levels (down regulated) useful

ACI

- Serum ferritin levels normal or increased in ACI
- Expression of transferrin receptor down regulated by pro-inflammatory cytokines
- Transferrin receptor-ferritin index
  - Value < 1 suggests ACI
  - Value > 2 indicates iron deficiency

Patient with ACI and Iron Deficiency (Anemia)

- Transferrin receptor-ferritin index high (> 2)
  - Accompanied by clinical or bio-chemical evidence of inflammation
  - Suggested that the percentage of hypo chromic red cells or reticulocyte hemoglobin content also helps identify patients with both types of anemia

Anemia of Chronic Kidney Disease (CKD)

- Impairs production of erythropoietin
- 8.2% of older adults with anemia have CKD
- Additional 4.3% have both CKD and ACI
- Prevalence of anemia (Hb < 12 G/dl)
  - Declines as a function of creatinine clearance

Creatinine Clearance

- Adjusting for age and race/ethnicity, creatinine clearance threshold at which hemoglobin levels significantly reduced
  - Below 60 ml/min in men
  - Below 50 ml/min in women
- Later studies show no age variation in the prevalence of anemia among patients with CKD

Unexplained Anemia

- One third of anemia cases in older adults unexplained
- Condition accounting for largest portion of unexplained anemia in NHANESIII
  - Likely due to myelodysplastic syndrome (17.2%)
    - Macrocytosis, leukopenia, thrombocytopenia
- Swedish study 23% – 36% of unexplained anemia in 70 - 81 year olds
  - Even after bone marrow testing

Erythropoietin in Unexplained Anemia

- Speculation that production of erythropoietin in response to declining Hemoglobin (Hb) blunted
- Japanese study
  - Typical inverse relationship between erythropoietin and Hb concentration in iron deficiency
  - No relationship in unexplained anemia
- British study
  - Lower levels of erythropoietin in older patients compared to younger (< 70 years)

Erythropoietin in Unexplained Anemia

- Impairment of renal endocrine function, not undetected nephron dysfunction or CKD, contributes to unexplained anemia
  - Renal interstitial cells are responsible for erythropoietin production rather than renal glomeruli or tubules
- Alternatively, reduced erythropoietin may reflect incipient renal insufficiency which occurs with diabetic nephropathy

Summary of Anemia

- Anemia should not be viewed as a normal part of aging
- Potential negative impact on physical function and survival
- One third of anemia cases related to nutrient deficiency
  - Amenable to safe and inexpensive therapy
- Chronic kidney disease and other chronic conditions associated with inflammation account for another third
  - Potentially improved with erythropoietin therapy
- Remaining cases with no identifiable cause

Immunoglobulin Response and Aging

- Aging associated with increased incidence of infectious diseases
  - Influenza
  - Respiratory syncitial virus (RSV)
  - Herpes zoster
- Higher incidence of bacterial infections
  - Tuberculosis
  - Pneumococcal pneumonia
- Greater morbidity and mortality and hospitalization

Aging and Immunity

- Humoral immunity affected by aging
  - Natural serum antibodies decline with age
  - Age related decline in Ig production
    - Quantitative and qualitative
    - Mechanism poorly understood
    - Confined to IgG and IgG1 subtype
    - Determined by differences in immune priming
    - Age rather than immunosenescence – significantly lower avidity index
  - Health status also influences outcome of antibody response

Monoclonal Gammopathy

- Affects 2% of persons aged 50 years or older
- Affects 3% of those over 70 years
- Proliferation of a single clone of plasma cells
- Characterized by secretion of an immunologically homogenous monoclonal protein (M-protein, M-spike, M-component or paraprotein)

Immunoglobulin – M protein

- Consists of two heavy polypeptide chains of the same class and subclass (IgG, IgM, IgA, IgD, IgE)
- Two light chains of the same type (kappa or lambda)
- Polyclonal gammopathy characterized by
  - Increase in one or more heavy chains
  - Both types of light chains
  - Associated with inflammatory or reactive process

Monoclonal Gammopathy of Unknown Significance (MGUS)

- First coined by Kyle et al
- Replaced term benign monoclonal gammopathy
  - misleading not known if the disease process will remain stable and asymptomatic or evolve into symptomatic multiple myeloma

Monoclonal Gammopathy of Unknown Significance (MGUS)

- Identified by
  - M-spike of < 3 g/dl
  - Or trace
  - Or no light chains in a 24 hr urine collection
  - < 10% plasma cells in bone marrow
  - No related organ or tissue impairment
    - Absence of anemia, hypercalcemia, renal insufficiency
    - No lytic bone lesions
  - No evidence of
    - amyloidosis, Waldenstrom macroglobulinemia
    - B-cell lymphoproliferative disorder or multiple myeloma

MGUS

- More frequent in African-Americans than in whites
- Lower in elderly, Japanese patients
- Most commonly IgG 73%, followed by IgM 14% and IgA 11%
- Light chains most commonly involve kappa molecules

MGUS

- Frequently single abnormality
- May be associated with many other diseases
  - B-cell lymphoproliferative disorders
    - CLL, NHL, hairy-cell leukemia
    - 1.1% of patients with solid tumors
    - A third of patients with chronic neutrophilic leukomia
  - Gaucher's disease, myelofibrosis, hepatitis, HIV, rheumatoid arthritis
  - Post liver, renal, bone marrow transplants correlating with viral infection

MGUS

- 3% - 4% have a biclonal gammopathy
- Characterized by
  - Production of 2 different M-proteins
  - May be due to proliferation of 2 different clones of plasma cells (each producing an unrelated monoclonal protein)
  - Or from a single cell of plasma cells producing 2 M-proteins
- Triclonal gammopathy also reported

MGUS and Aging

- Hypothesized in mice
  - May be a dysregulated immune system
- Imbalance between a failing T-cell compartment with an otherwise intact B-cell compartment
  - Leads to restriction of the B-cell repertoire
  - Excessive B-cell clonal proliferation
  - Excessive immunoglobulin production
  - Development of a monoclonal myopathy
- Increased levels of IL-6 and other related cytokines (TNF α and β) with aging
  - Stimulates differentiation of mature B-cells in plasma cells
  - Allows proliferation of plasma blasts in bone marrow
  - Seems to inhibit plasma cell apoptosis in vitro

MGUS

- Complete history and physical examination
- Complete blood count, blood film, serum electrolytes, BUN, creatinine and calcium
- SPEP, immunofixation
- UPEP, immunofixation of 24 hr urine
- Bone marrow aspiration biopsy
- Radiological skeletal bone survey
- Serum free light chains

MGUS Diagnosis

- Asymptomatic
- No organ or tissue damage
- 30% have decrease in polyclonal immunoglobulins
- $Beta_2$ microglobulin not useful
- < 10% plasma cells in BN
  - Phenotypically normal plasma cells higher in patients with MGUS
  - Clonal plasma cells similar to MM
    - CD 38+, CD 56+, CD 19-
  - Cytogenetics not useful but FISH helpful

MGUS

- Need regular follow-up to detect development of malignant form
  - <1.5 g/dl and no other features need annual SPEP
  - Between 1.5 and 2.5 g/dl and asymptomatic features need quantitative immunoglobulins and 24 hr UPEP with SPEP every 3 to 6 months for a year
  - >2.5 g/dl needs complete workup and follow-up
    - Average risk of development of malignant process is 1% per year
    - Serum free light chains useful as follow-up

Aging and stem cell exhaustion

- Hematopoietic stem cell produces over $4x10^{15}$ erythrocytes, lymphocytes and myeloid cells over a lifetime
- A single HSC can repopulate the entire hematopoietic system in irradiated mice
- Pluripotent stem cells proliferate, differentiate and self renew
- In a widely used mouse strain the absolute number of HSCs increase during the lifetime and does not decrease
- HSCs show aging-associated changes

Hematopoietic stem cell (HSC)

- HSCs show aging-associated changes
  - Impairment of functional capacity
  - Subsequent exhaustion
  - Exhaustion refers to
    - Decreased hematopoietic capacity of HSCs
    - Decline in the number to a level that impairs steady state or stress hematopoiesis

Two systems of aging

- Systemic - hormonal control where changes in humoral factors with age can cause system wide changes in the homeostatic condition
- Cell-autonomous – individual cells are the target of the aging process via a time-dependent increase in homeostatic dysfunction
  - Increase in the production of reactive oxygen species
  - Telomere shortening
  - Genomic instability

HSC

- One or more of a highly quiescent population divide to produce highly proliferative progenitors with restricted development potential in response to both intrinsic and extrinsic cues
- Proliferative nature of HSCs change during aging - consistent with the observation that the incidence of myeloproliferative disorders markedly increases with age in both mice and humans.
- Self renewal ability undergoes progressive decline with alterations in the frequency of cycling HSCs

Myelodyspastic Syndrome (MDS)

- A heterogeneous group of closely related clonal hematopoietic disorders characterized by
  - Hypercellular or hypocellular marrow with impaired morphology and maturation (dysmyelopoiesis)
  - Peripheral blood cytopenias resulting from ineffective blood cell production
- All 3 cell lineages in myeloid hematopoiesis can be involved
  - Erythrocytic
  - Granulocytic
  - Megakaryocytic

MDS Classification

- Primary – No known exposure
- Secondary – As a complication of aggressive treatment of other cancers with exposure to
  - Radiation
  - Alkylating Agents
  - Topoisomerase II Inhibitors
  - Heavily pretreated patients with autologous bone marrow transplants

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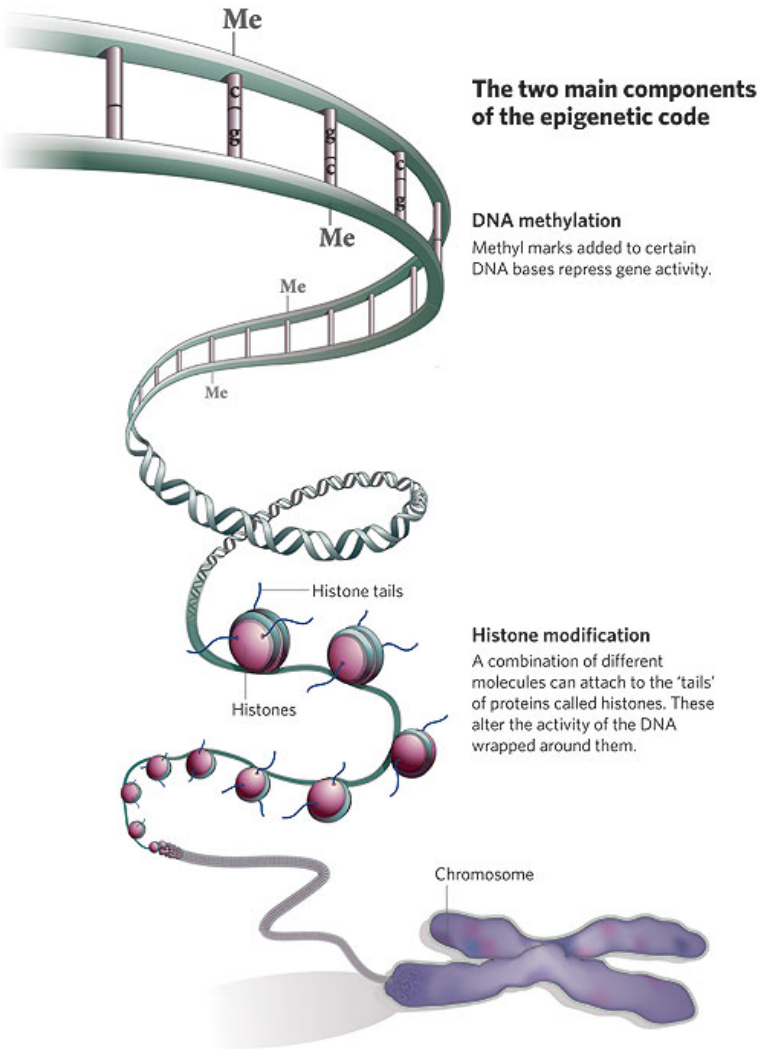
Stem cell injuries

- Initial hematopoietic stem cell injury can stem from
  - Cytotoxic chemotherapy
  - Radiation exposure
  - Viral infection
  - Chemical exposure to toxins (occupational)
    - Benzene
    - Ammonia
  - genetic predisposition
- A clonal mutation predominates over bone marrow, suppressing healthy stem cells

DNA Methylation

- DNA Methylation is a
  important regulator o
  gene transcription
- Appears to play a key
  role in pathogenesis o
  hematologic
  malignancies



FAB Classification

- Five MDS are described
  1) Refractory Anaemia (RA)
  2) RA with ring sideroblasts
  3) RA with excess of blasts (RAEB)
  4) Chronic myelomonocytic leukaemia (CMML)
  5) RAEB "in transformation"

WHO Classification of MDS

WHO
RA Refractory cytopenia with multilineage dysplasia MDS– unclassified MDS with isolated del (5q)
RARS Refractory cytopenias with multilineage dysplasia and ringed sideroblasts
RAEB-1 (5-9% blasts) RAEB-2 (10-19% blasts)
Acute myeloid leukemia (>20% blasts)

Clinical Symptoms

- Common manifestations of a low platelet count or bleeding under the skin
  - Petechiae
  - Ecchymoses
  - Epistaxis and gum bleeding
  - Hemoptysis
  - Hematuria
  - Blood in still
- Poor platelet function is another cause of increased risk of hemorrhage

Prognosis

Prognostic Variable	0 Points	0.5 Points	1 Point	1.5 Points	2 Points
Bone marrow blasts, %	<5	5-10	–	11-20	21-30
Karyotype*	Good	Intermediate	Poor	–	–
Cytopenias	0/1	2/3	–	–	–

Rating

- Good
  - No abnormality (46, XX or 46, XY)
  - – Y
  - del(5q) and del (20q)
- Intermediate
  - Other abnormalities
    - Trisomy 8 (+8)
- Poor
  - Complex
  - 33 abnormalities or chromosome 7 abnormality
    - 7q – or – 7

Treatment Options for low and intermediate risk MDS

- Standard care for patients with MDS and decreased blood counts constantly changing
- Supportive therapy and treatment of infections are main treatments
  - Transfusions of missing cells (RBCs or platelets)
    - Goal is to replace cells prematurely undergoing apoptosis in patient's bone marrow
    - A response rate of 60% in low-risk IPSS score MDS patients with Refractory Anemia and in patients with serum EPO levels below 500 µL and a transfusion requirement of less than 2 units per month

New Drugs for high risk MDS

- Approved by the USFDA for MDS – goal is to maintain Hemoglobin and to prevent transformation to acute leukemia
- 5-azacytidine
  - Azacytidine [Vidaza]
- 5-aza-2-deoxycytidine
  - Decitabine [Dacogen]
  - Lenalidomide [Revlimid]
- Hematopoietic growth factor for anemia shown to improve anemia in 20-25% of unselected patients with MDS
  - Erythropoietin (EPO [Procrit])

Acute Myeloid Leukemia in the Elderly

- May occur de novo
- Arise secondarily from pre-existing myelodysplastic syndrome or myeloproliferative syndromes
- Consequence of exposure to previously administered chemotherapeutic agents like alkylators or epipodophyllotoxins

Acute Myeloid Leukemia in the Elderly

- Therapies targeting new oncogenes and molecular targets
- Advances in supportive care through antibiotics and blood support
- Still, AML remains incurable in the majority and outcomes dismal in the elderly
- Under represented in Clinical Trials
  - Severity of clinical comorbidities

Acute Myeloid Leukemia (AML)

- Incidence 20-25 per 100,000 in people over age 75 years while < 2.5 per 100,000 in younger individuals (<55 years)
- Few known environmental exposures
  - Chronic benzene
  - External radiation
  - Exposure to alkylators, epipodophyllotoxins, topoisomerase II inhibitors – characterized by anomalies in chromosome 5,7 and 11
  - High dose therapy and auto transplantation for multiple myeloma and NHL
  - Cigarette smoking

Diagnosis and classification of AML - WHO

- Morphologic and Cytogenetic criteria
- Lowering of threshold from 30 to 20% blasts in the bone marrow aspirate or peripheral blood
- Eliminated MDS with RAEB-T
- Specifies AML with multilineage dysplasia – significant proportion of cases in the elderly arise from MDS

Cytogenetic abnormalities

- Clonal disorder – molecular lesions recognized as chromosomal aneuploidy or translocations
- Specific leukemic karyotype can be prognostically categorized
- Differs between older adults and younger ones

Cytogenetic abnormalities

- t(15;17), t(8;21), inv 16 rarely encountered in older adults – favorable cytogenetics
- Full or partial deletions of chromosomes 5 and 7, trisomy 8, 11q23 – higher in elderly, unfavorable
- Chromosome 5 and 7 associated with previous exposure to chemotherapy or environmental carcinogens
- Mixed lineage leukemia gene at 11q23 associated with topoisomerase II inhibitors (etoposide, mitoxantrone, doxorubicin)
- Complex karyotype more frequent in older adults – inferior complete remission and long time survival

Treatment of AML

- Response to standard chemotherapy is historically poor with lower response rates and increased treatment related mortality

  Tolerability to induction treatment is suboptimal - mortality 20-40%

  CR 30-50%,
- Decision to offer standard induction or post remission chemotherapies should be based on patient preferences, karyotype, performance status, and other prognostic factors.

Coagulation and Aging

- Thrombotic complications increase with age
  - Arterial disease in which thrombotic occlusion is a complication of an unstable atherosclerotic plaque
  - Venous thromboembolism
    - Increases from 1 per 1000 people per year before age 40 to 1 in 100 per year over age 70

Coagulation and Aging

- Number of clotting factors change with aging in the direction facilitating thrombosis
- Multifactorial:
  - Aging process per se
  - Low grade chronic inflammation
  - Decreased mobility

Centenarian study by Mari et al

- Older controls(51 to 69 yrs) slightly higher values of several coagulation and fibrinolysis measurements
- Centenarians had heightened activity
  - As measured by factor VIIa in plasma
  - By measuring peptides released following activation of prothrombin
  - Measuring factor IX or factor X
  - Increased circulating complexes of thrombin with antithrombin
  - High circulating levels of fibrinopeptide A
  - Elevated levels of D-dimer and plasmin complexed to alpha2 antiplasmin
  - Higher plasma fibrinogen and factor VIII

Fibrinogen in the Elderly

- Plasma fibrinogen concentration
  - Increases with age, obesity or smoking
  - Alcohol decreases level
  - Increased level a strong and independent predictor of risk of coronary death and M.I
  - Associated with risk of venous thrombosis
    - Increases size of thrombus
    - Increases resistance to fibrinolysis
    - Factor XIII rises with age and increases resistance to fibrinolysis

Factor VIII

- Factor VIII increases with age
- Clearly associated with thrombosis
- Associated with cardiovascular disease and mortality, risk of ischemic stroke
- Physical activity was significantly and inversely dose-response-related to plasma fibrinogen level, factors VIII and IX, D-dimer levels (less fibrin formation), tissue type plasminogen activator antigen(reduced endothelial irritation)

Factor VII

- Factor VII also rises with age
- associated with risk of increased ischemic heart disease
- increases resistance to fibrinolysis
- Level modulated by
  - dietary fat
    - Total fat intake positively related in elderly women
    - Unsaturated fat intake positively related in both elderly men and women
  - blood lipids
  - Fiber intake inversely related in both sexes
  - Polymorphisms in gene
    - 353R
      - In women positive correlation with R/Q353 polymorphism and serum triglycerides

Factor IX and Protein C

- factor IX increases with age
- Increases risk for venous thrombosis
- Protein C remains unchanged
- Age-dependent increase of factor IX and the age independence of the Protein C level
- Molecular mechanisms of the age-related regulation of genes
  - In mice two genetic elements
    - ASE (age stable expression)
    - AIE (age increased expression)

PAI-1

- Plasminogen activator inhibitor 1
  - Increased level
    - delays fibrin removal
    - promotes thrombosis
    - Centenarians have
      - significantly higher frequency of
        - the 4G/4G allele
        - The 4G allele
        - Compatible with successful aging if blood flow and vessels are healthy

Summary

- Old age is a hypercoagulable state
- May contribute to arterial and venous thrombosis in areas of vessel wall disease and of stasis
- Light exercise and a healthy diet have a beneficial effect on hyper coagulability and should be encouraged