COLUMBIA’S CONTRIBUTIONS TO HEMOGLOBIN DISORDERS

• Vernon Ingram - Predicted gene mutations in thalassemia.
• Ruth and Reinhold Benesch - Cooperativity & 2,3 DPG; Hemoglobin S gelation.
• Arthur Bank & Paul Marks - Gene defects in thalassemia.
• Sergio Piomelli - Transfusion in hemoglobinopathies; iron overload management
Hemoglobinopathies and Thalassemia

- Hemoglobinopathies: Qualitative change:
  Mutation in nucleotide sequence of globin chain

- Thalassemias: Quantitative change:
  Decreased or absent globin chain
GLOBIN SYNTHESIS IN β-THALASSEmia
( % OF NORMAL )

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>THAL</td>
<td>10-30%</td>
<td>100%</td>
</tr>
<tr>
<td>THAL</td>
<td>0</td>
<td>100%</td>
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1. Anemia due to decreased δ globin and HbA.
2. γ globin increased but insufficient.

<table>
<thead>
<tr>
<th>Blood Count in β-thalassaemia Trait</th>
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<tbody>
<tr>
<td>Hb</td>
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<tr>
<td>RBC</td>
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<tr>
<td>PCV</td>
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<td>MCV</td>
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<td>MCH</td>
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<td>reticulocytes</td>
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<tr>
<td>WBC</td>
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<td>platelets</td>
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NORMAL

β-THAL. MINOR

A A₂
Clinical Features of Homozygous β Thalassemia (Cooley's anemia)

- Severe anemia
- Hepatosplenomegaly
- Bone abnormalities
- Blood transfusion requirement
  - Hemochromatosis
  - Cardiac failure

Therapy for Homozygous β Thalassemia

- Current:
  - Blood transfusions
  - Parenteral iron chelators
  - Allogeneic bone marrow transplant
- Experimental/Future:
  - Oral iron chelators
  - Agents to increase fetal hemoglobin
  - Globin gene therapy with autotransplantation
Hemoglobinopathies and Thalassemia

- Hemoglobinopathies: Qualitative change: Mutation in nucleotide sequence of globin chain
- Thalassemias: Quantitative change: Decreased or absent globin chain
Complications of Sickle Cell (SS) Disease

- Painful crisis
- Hemolytic anemia
- Chest syndrome: Pulmonary thromboses or infections
- Stroke
- Bone and bone marrow infarct
Complications of Sickle Cell (SS) Disease

- Folate deficiency
- Aplastic crisis
- Renal papillary necrosis
- Infection (pneumococcal, other)
- Leg ulcer
- Priapism

Current Therapy for Sickle Cell (SS) Disease-2003

- Symptomatic for painful crises
- Hydroxyurea for painful crises
- Transfusions for severe anemia
- Exchange transfusion for CNS events, chest syndrome
- Folate prophylaxis
- Allogeneic marrow transplantation

Experimental/Future Therapy for Sickle Cell (SS) Disease-2003

- Other agents increasing fetal hemoglobin
- Anti-sickling drugs
- Globin gene therapy with autotransplantation

Prevention of Sickle Cell Disease and β Thalassemia

- Prenatal Screening
- Genetic counseling
- Antenatal diagnosis:
  - Chorionic villus biopsy
  - Amniocentesis

Direct Analysis: Mst I in Sickle Cell Anaemia

- Pro - val - glu -
- 1.3 kb CCT GAG GAG
- Mst II
- 1.1 kb CCT GAG GAG
-.glu -
- $\beta^+$
OTHER HEMOGLOBIN DISORDERS

- Unstable Hemoglobins
- High Affinity Hemoglobins
- Hemoglobin M
- Methemoglobin
- Carboxyhemoglobin