Cardiovascular Research

Presented by:

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What's up in cardiology at the University of Colorado and elsewhere

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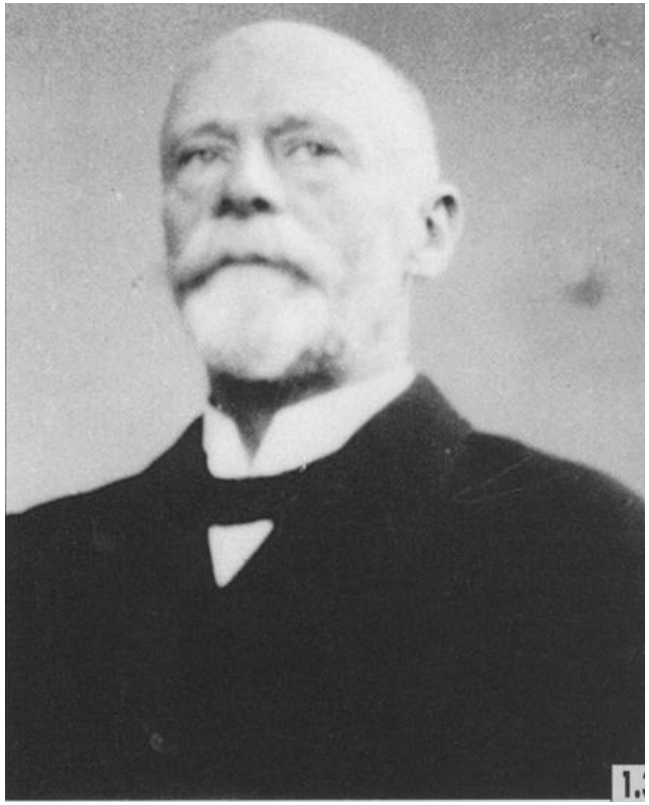
Overview

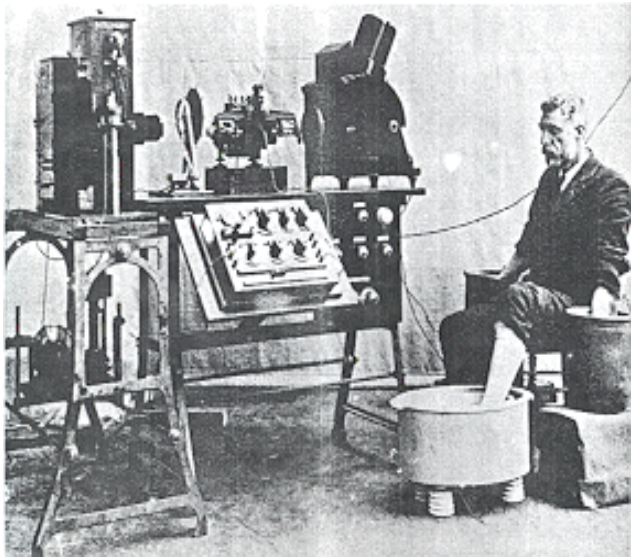
- Brief history of innovation in cardiology
- Current state of affairs at CU and elsewhere
  - Major challenges on the horizon
  - Failure of linear thinking
- Things that are on-going in the Buttrick lab and in the division that might be of interest

TOP 10 INNOVATIVE EVENTS IN THE PAST ~100 YEARS

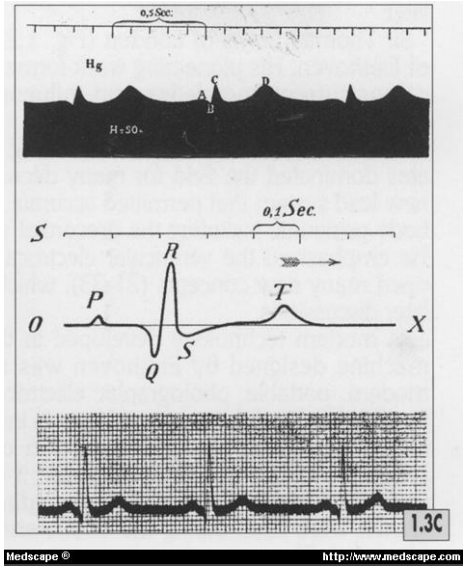
Willem Einthoven

First EKG -1903





String galvanometer

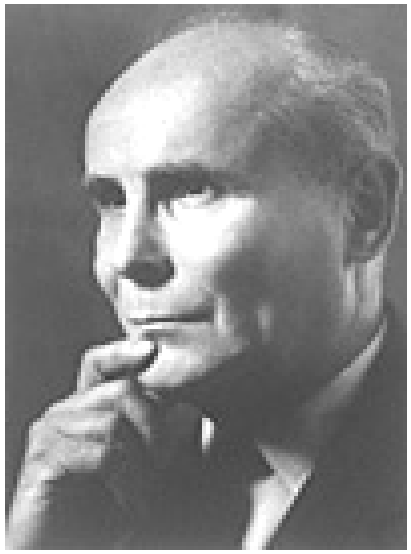


Initial record

Nobel prize 1924

Cardiac Catheterization and Invasive Hemodynamics

Cath 1929



Right heart hemodynamics, and gas exchange 1941

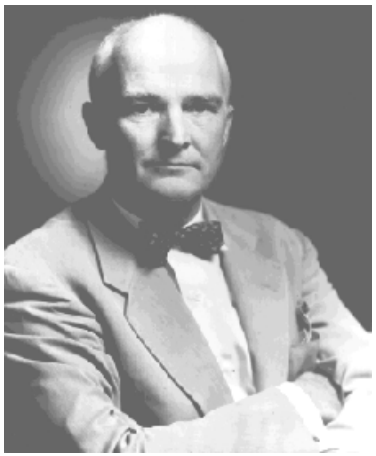
Forssmann, Cournand, Richards

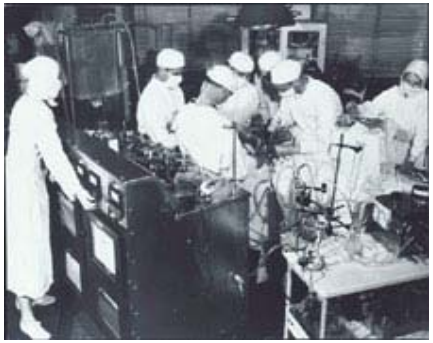
Nobel prize 1956

Origins of open heart surgery

Dwight Harkin – mitral stenosis
Closed commisurotomy 1948

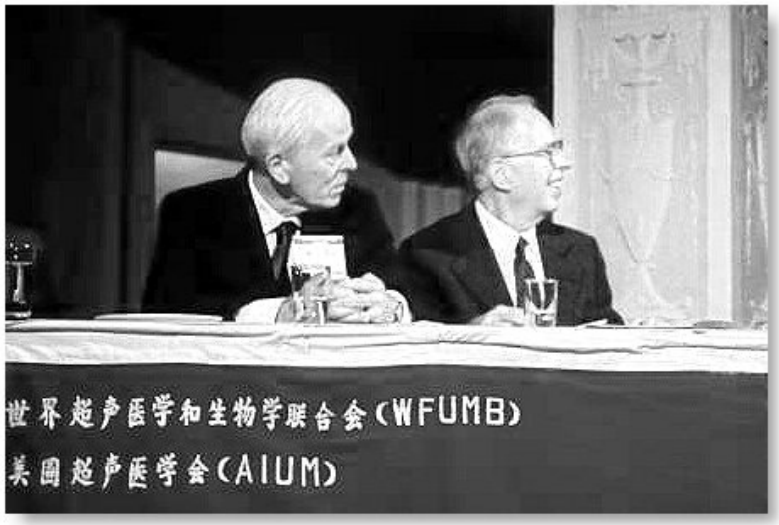
C. Walton Lillehei – First open Heart Surgery 1952



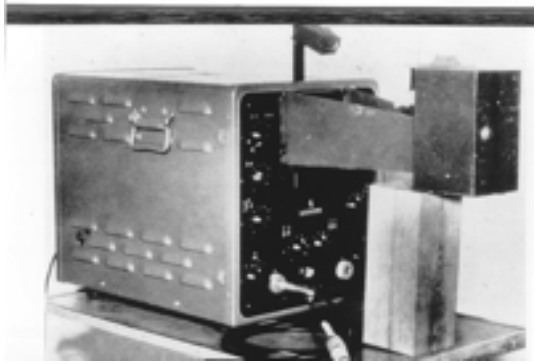


John Gibbon -- Heart-lung Machine 1953

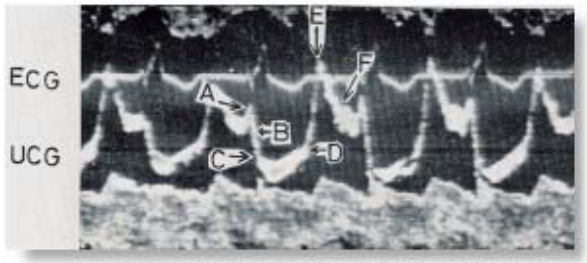
Echocardiographic imaging



Drs. Inge Edler and Carl Hellmuth Hertz at the History of Ultrasound Symposium in Washington D.C. in October 1988



Edler and Hertz 1954



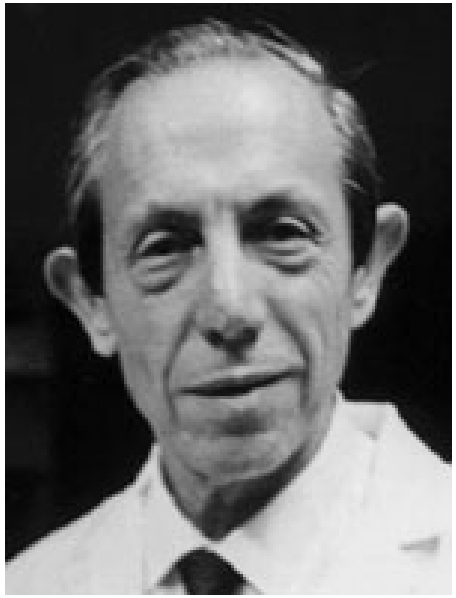
Edler and Hertz's echocardiographic trace of the anterior mitral valve leaflet in the late 1950s

Coronary angiography

Mason Sones 1958

While conducting an imaging procedure in which dye was to be injected into the aortic root of a patient with valvular disease, Dr. Mason Sones a pediatric cardiologist at The Cleveland Clinic discovered that the catheter had accidentally entered the patient's right coronary artery and, before it could be removed, 30cc's of contrast dye had been released. “I thought for certain that the patient would fibrillate….”

Pacemakers and Electrical Devices



Paul Zoll

External pacemaker 1952
Defibrillator 1956

Sy Furman

Earl Bakken

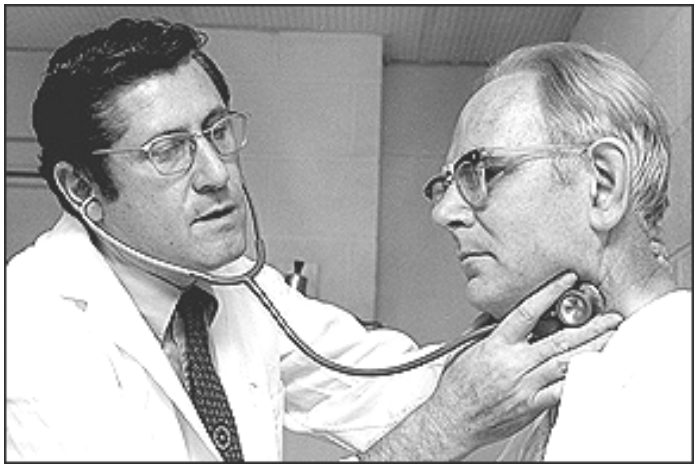
Transvenous pacemaker
1958 - 1960

Michel Mirowski

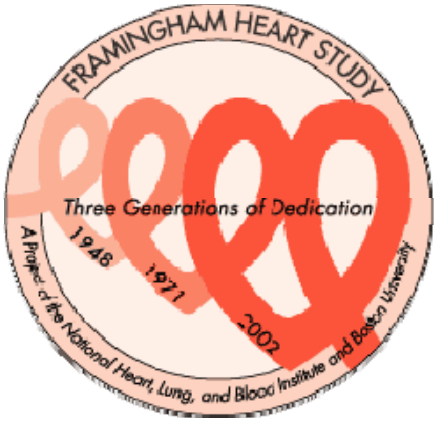
AICD 1970

Cardiac Prevention

1938



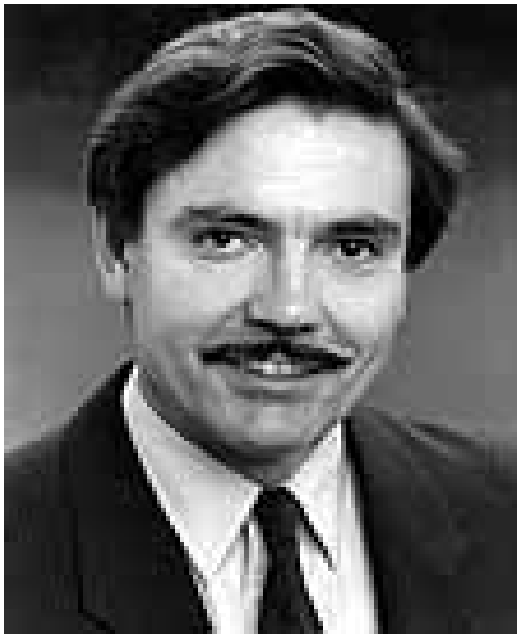
William Kannel



1948

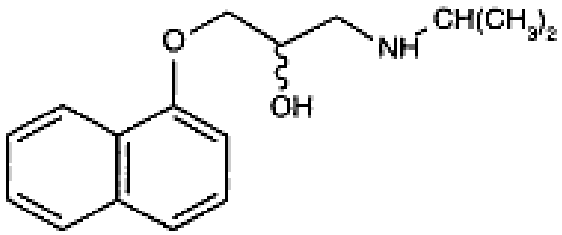
William Castelli

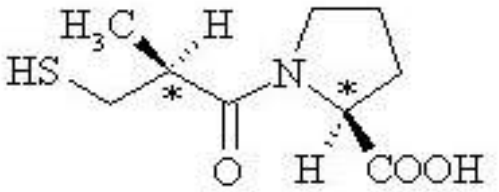
Coronary angioplasty

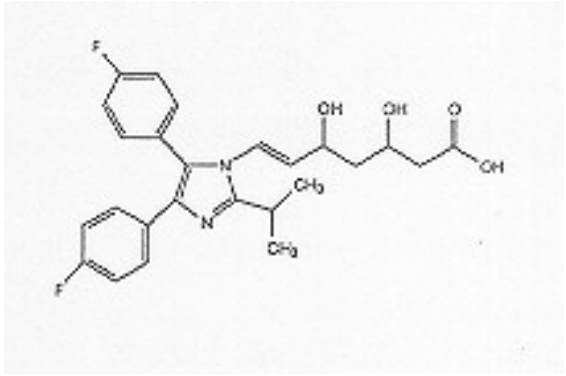


Andreas Gruentzig : 1976

Drugs







James Black 1962

Nobel prize 1988

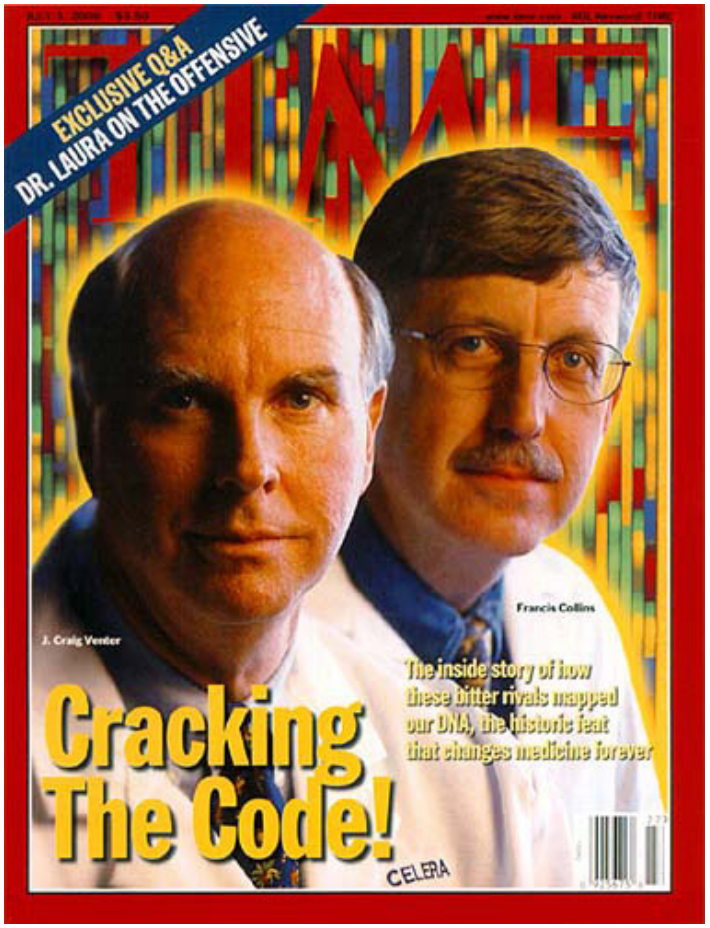
Cushman and Ondetti 1975

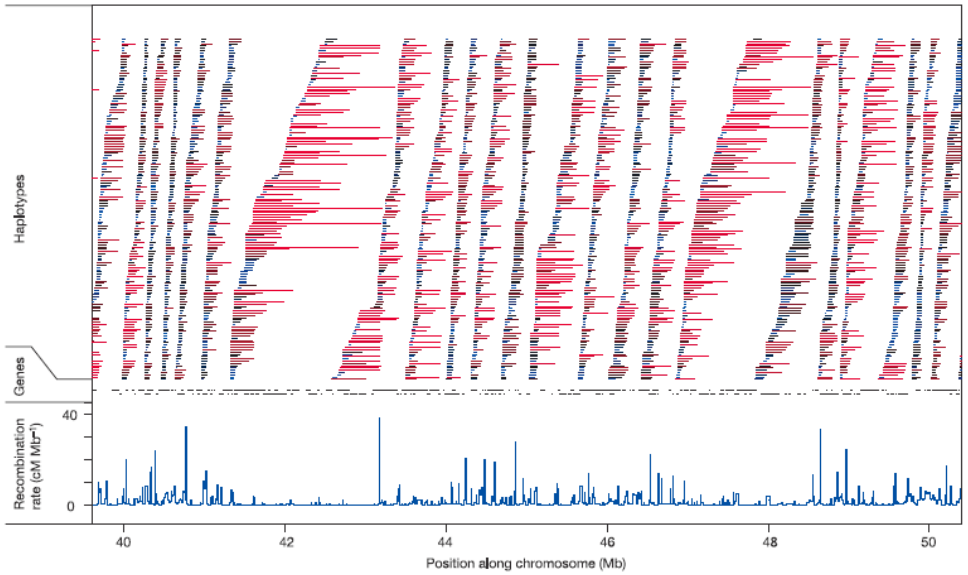
Brown and Goldstein

Akira Endo 1976

Nobel prize 1985

Human genome project and the haplotype map





Francis Collins and Craig Ventner

Nature 2002,2005,2007

Top 10 Moments in Cardiology History: Last ~100 years

1. Electrocardiography 1903
2. Intravascular catheterization and hemodynamics 1929,1941
3. Origins of cardiac surgery 1948, 1953
4. Echocardiography 1954
5. Coronary angiography 1958
6. Preventative cardiology 1961
7. Cardiac pharmacotherapy 1962-1976
8. Electrical stimulation and defibrillation 1956, 1970
9. Percutaneous coronary angioplasty 1977
10. Sequence of human genome and “hapmap” 2002, 2007

WHAT TO ANTICIPATE GOING FORWARD

Major clinical challenges/opportunities

- Heart failure (5M cases in the US; highest medicare costs)
  - Systolic versus diastolic (how real is this distinction)
  - Pharmacotherapy versus device driven therapy
  - Cell based (or paracrine factor driven) myoplasty
- Arrhythmias (in particular AF: 2.2M cases, 10% >80)
  - Need to focus on cellular substrate versus overt manifestation
  - Smarter devices and more effective techniques for ablation
  - Need for comparative effectiveness analyses
- Structural and valvular heart disease (AoSt alone 4% >75)
  - Percutaneous interventional strategies (device driven)
  - To date, almost no analyses of cellular / genetic mechanisms

Pharmacogenomics and personalized medicine

12 years to sequence the human genome (1990-2002)

Affymetrics chip with cDNA tags commercialized in 2003

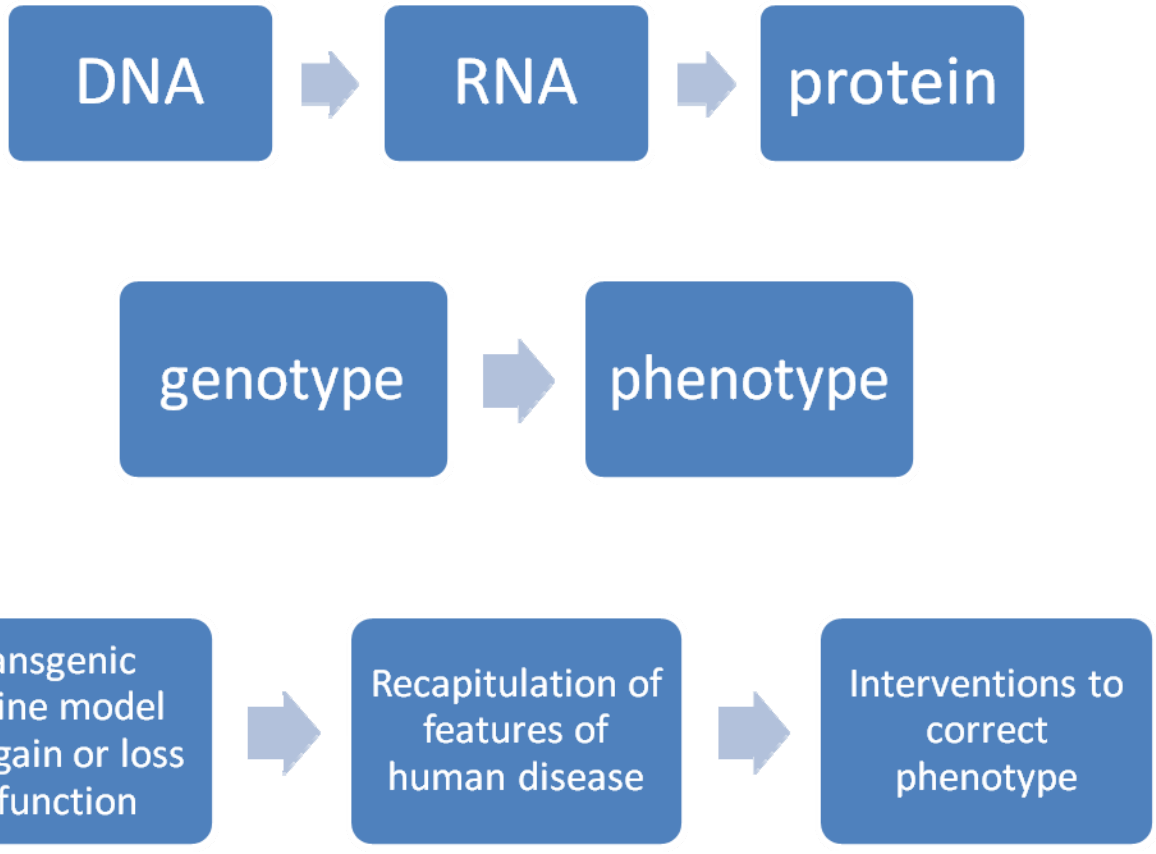
Haplotype map of the human genome completed in two years (2004-6)

Multiple genes sequences (genetic diversity codified) in 2007

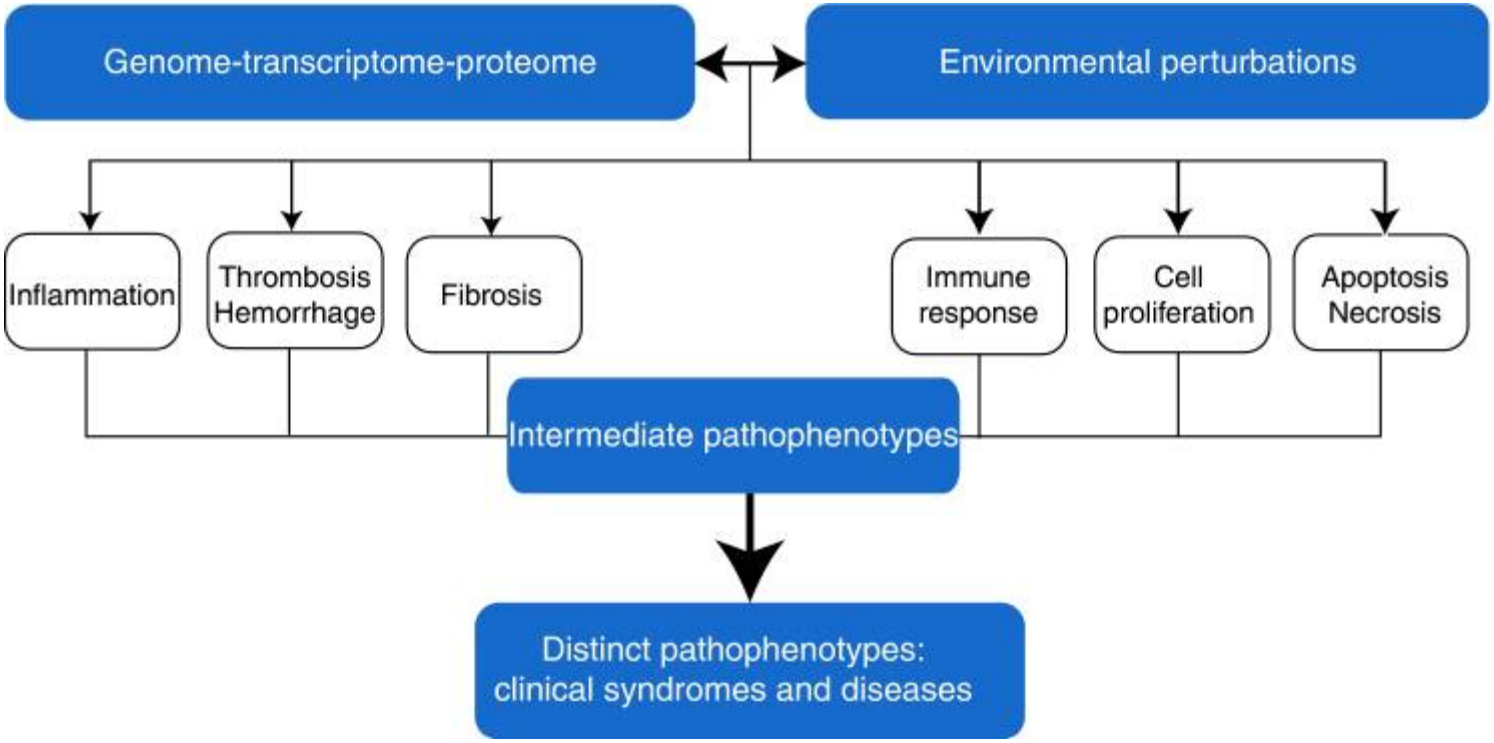
Current pace of DNA sequencing has accelerated so that individual gene profiles available for <$10,000

Given this pace of technological advancement, why has there been such limited clinical return? [Failure of linear thinking]

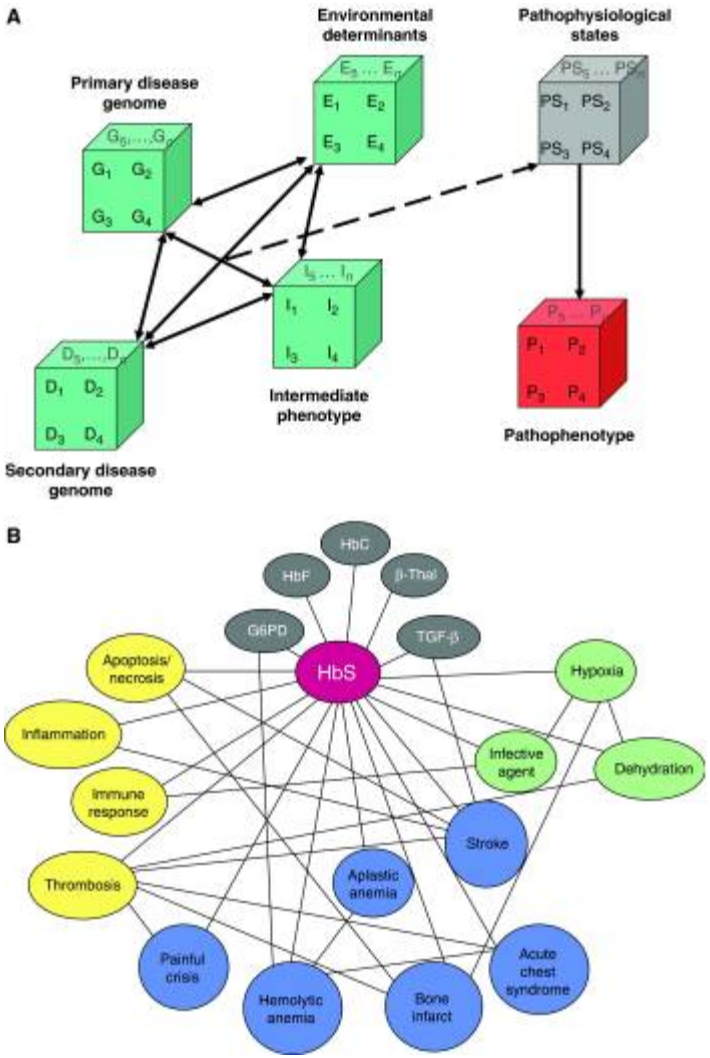
Linear Thinking



Disease processes are not linear

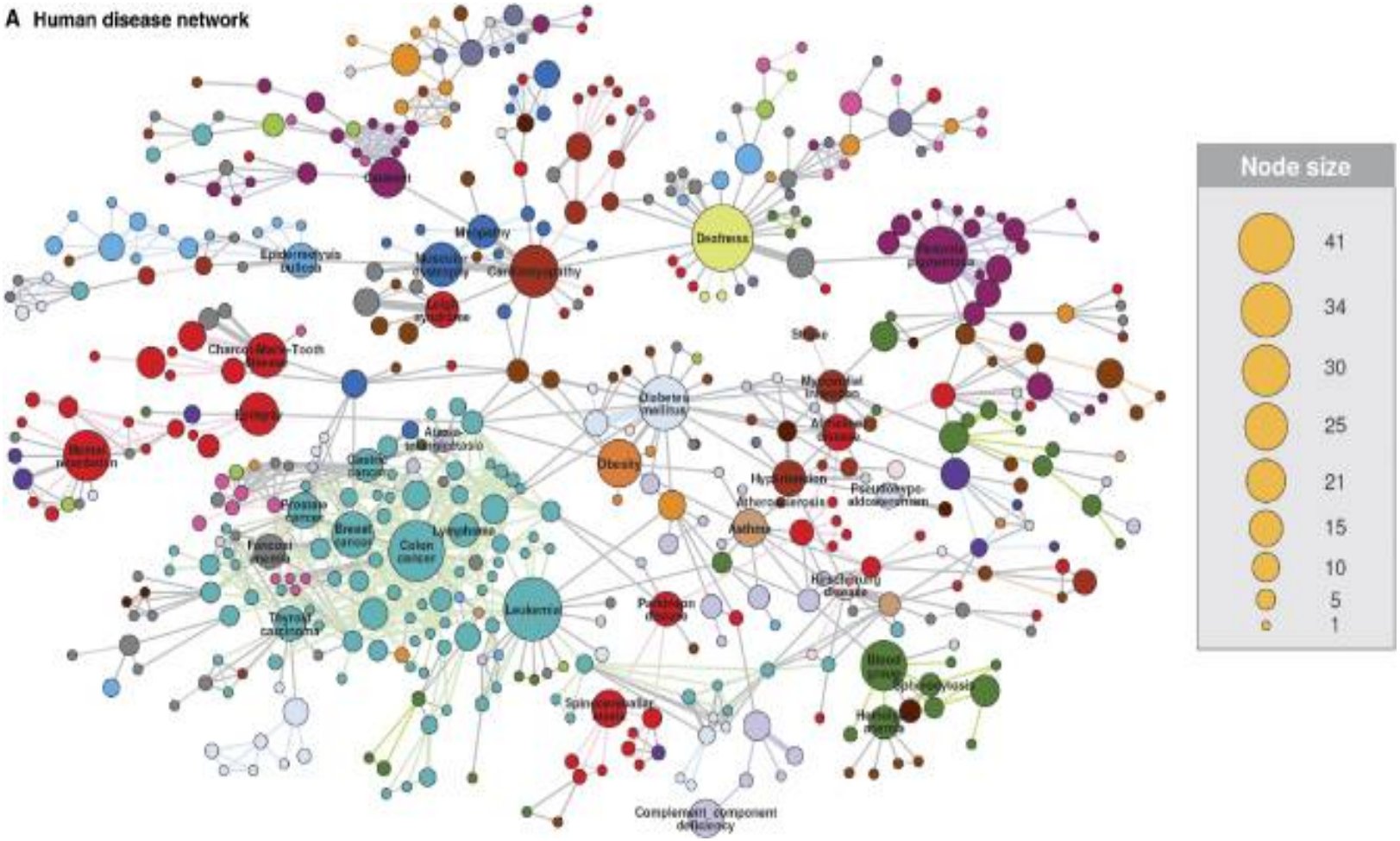


Non-linear thinking



(**A**) Theoretical human disease network Key: G, primary disease genome or proteome; D, secondary disease genome or proteome; I, intermediate phenotype; E, environmental determinants; PS, pathophysiological states leading to P, pathophenotype. (**B**) Example of this theoretical construct applied to sickle cell disease. Key: red, primary molecular abnormality; gray, disease-modifying genes; yellow, intermediate phenotypes; green, environmental determinants; blue, pathophenotypes.

Need for a complex systems approach



Speculative conclusions

- Progressive heart failure represents a summation of altered myocyte signaling pathways which may be integrated at the level of the sarcomere
- Shifting patterns of contractile protein phosphorylation (in particular of TnI) may be causally linked to LV dysfunction and ventricular dilation
- Increasing PKA dependent phosphorylation and decreasing PKC phosphorylation may be beneficial in DCM
- There are several plausible strategies, including isoform specific PKC blockade and targeted phosphatase activation, to effect this shift.

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  - Simon Shakar; JoAnn Lindenfeld; Andreas Brieke (clinical research)
- Pharmacogenomics
  - Mike Bristow; Matt Taylor; Luisa Mestroni
- Arrhythmias
  - Will Sauer, Ryan Aleong (clinical and devices)
  - Duey Nguyen (translational)
- Structural heart disease
  - John Carroll
- Small molecule drug discovery
  - Tim McKinsey (HDACs)

Clinical cardiology in 2011

- Sub sub-specialization
  - More complex interventional devices: coronary interventions, closure devices, valve implants
  - Invasive electrophysiology: ablation; smarter anti-tachycardia devices
  - Device driven CHF therapy – BiV pacing, LVAD
  - Diminished role for conventional OHS
- Emerging imaging technologies
  - 3-D echo; PET/CT; MRI + spectroscopy
- Identification of patients at risk
  - CRP; EBCT, CT angiography, other biomarkers
  - Phenotypic prevention