



What is Hematology?

And why is it a wonderful challenge for System Engineers?

Presentation for
Santa Clara Chapter of INCOSE
Amy Sams, PhD – Oct 20007



Engineering Challenges of Physiological Systems

1. Broad Dynamic Ranges – (evolved, not designed)
 2. Temperature Dependent Systems
 3. Chemically Dependent Systems
 4. Time Dependent Systems – (they're alive, they're alive !!)
- *In vivo*
 - 37° C
 - Homeostatic forces
 - Functionality dominates
 - *In vitro*
 - 21° C
 - Dying or chemically altered
 - Morphology dominates



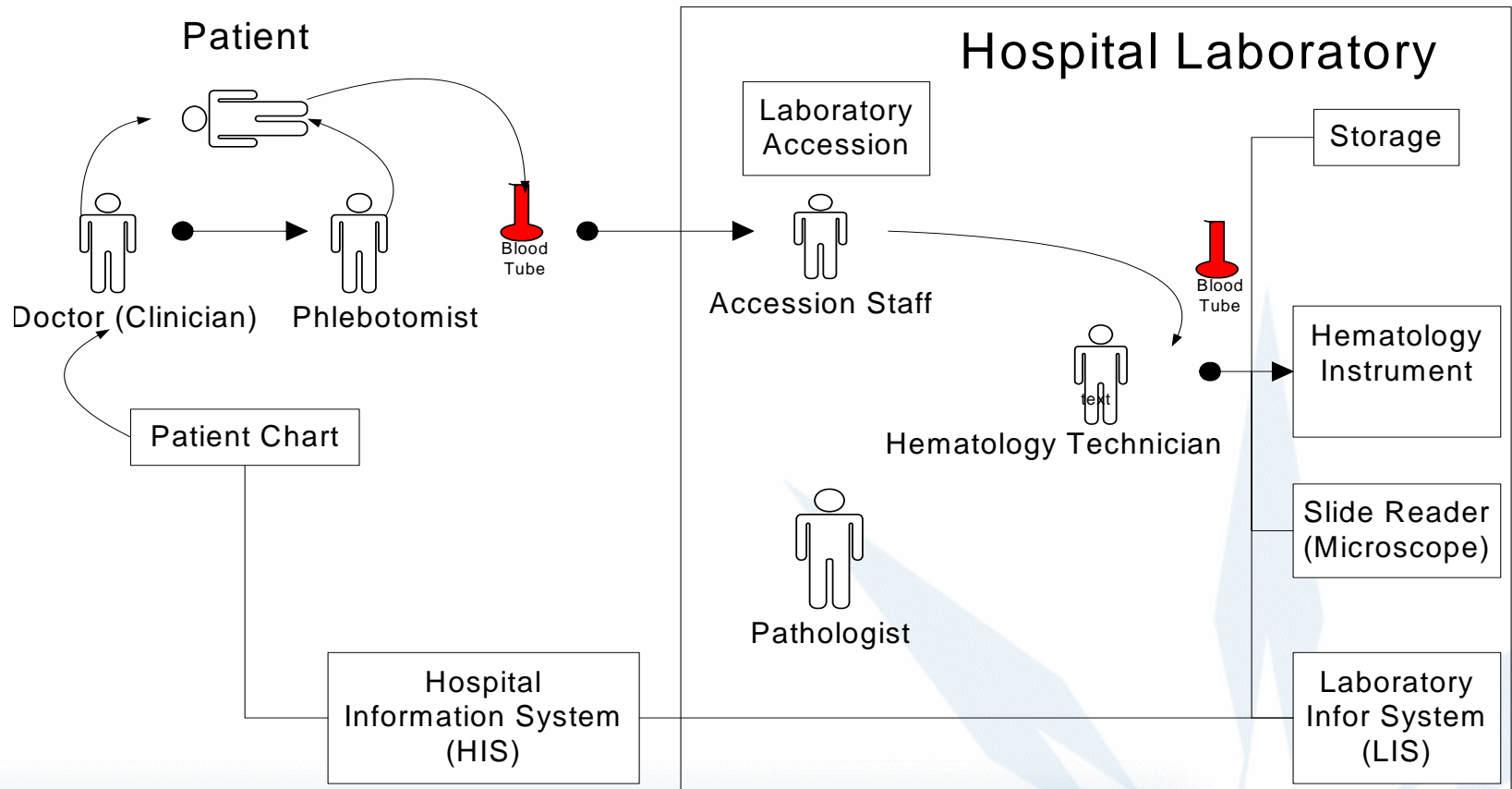
Hematology

The science of blood and blood-forming tissues, including its functions, diseases, and use in treatment ¹

- ¹Rothenberg, Mikel A. and Chapman, Charles F., Dictionary of Medical Terms, 2nd edition, Barron's Medical Guide, 1989.



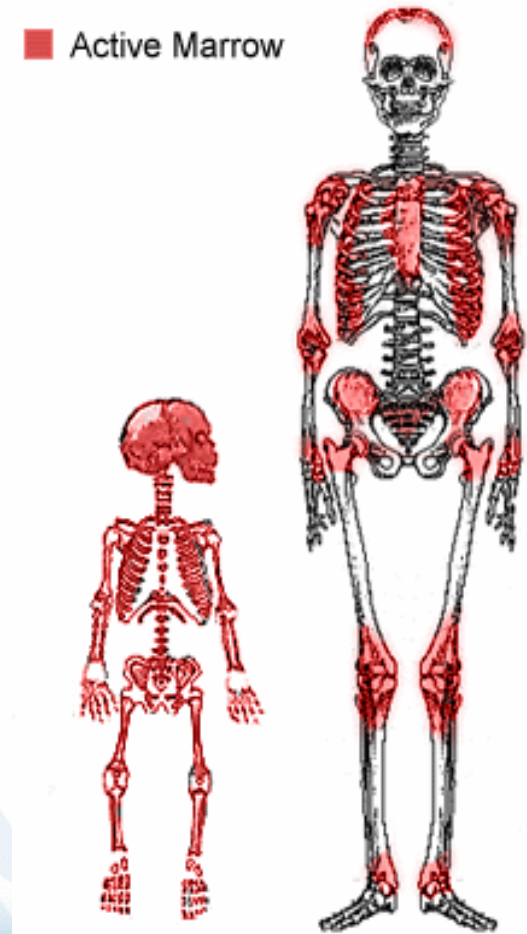
Hematology & Modern Medicine





BLOOD

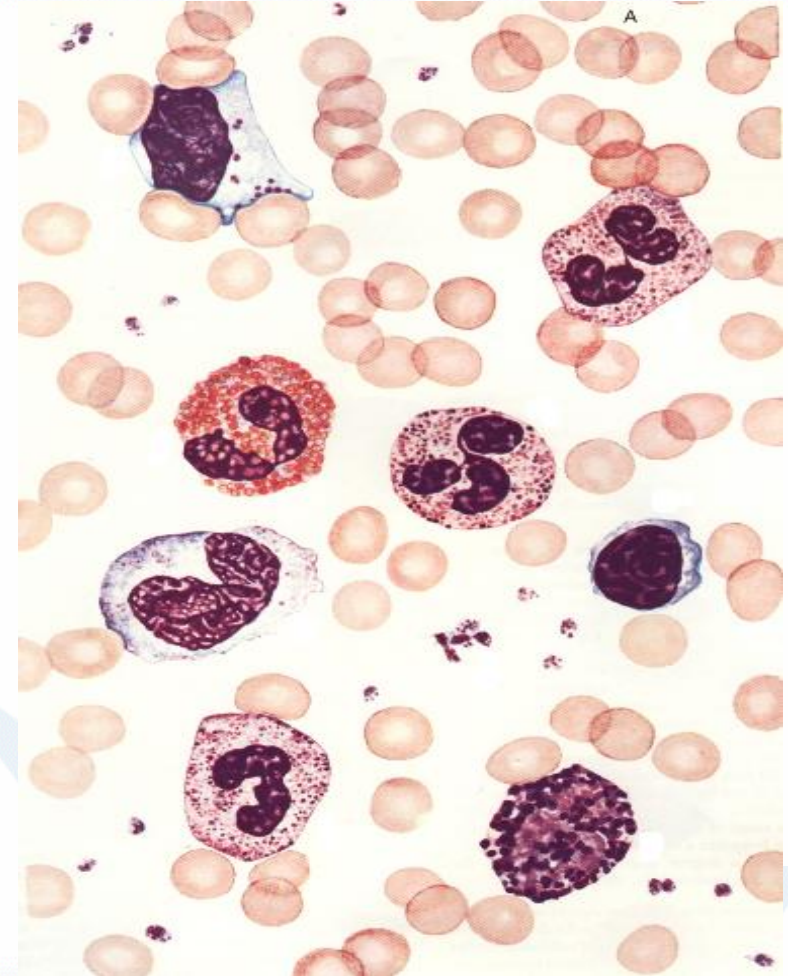
- Produced in the Bone Marrow
- Composed of:
 - Solid components
 - Red Blood Cells
 - Platelets
 - White Blood Cells
 - Liquid component
 - Plasma (Serum)
 - Contains nutrients, proteins, waste products
- Total volume, up to approximately 5-6 liters





Blood Cells

- Red Blood Cells
- Platelets
- White Blood Cells
 - Granulocytes
 - Neutrophils
 - Eosinophils
 - Basophils
 - Lymphocytes
 - Monocytes

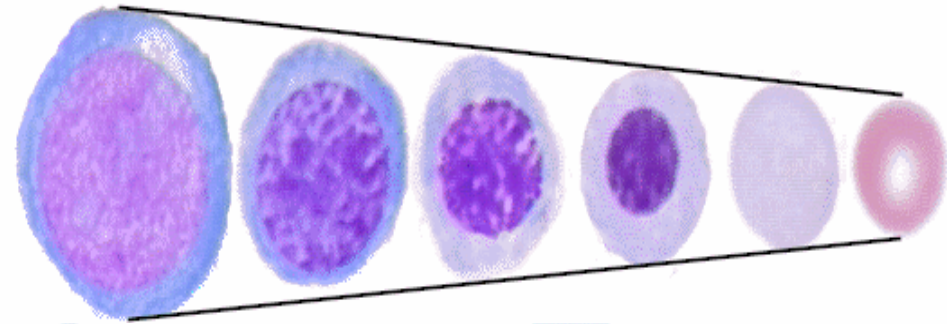




Red Blood Cells

Red Blood Corpuscle
(erythrocytes)

- Usually released in peripheral blood in mature form
- Sometimes released nucleated (NRBC)
- Reticulocyte is between the NRBC and the mature cell

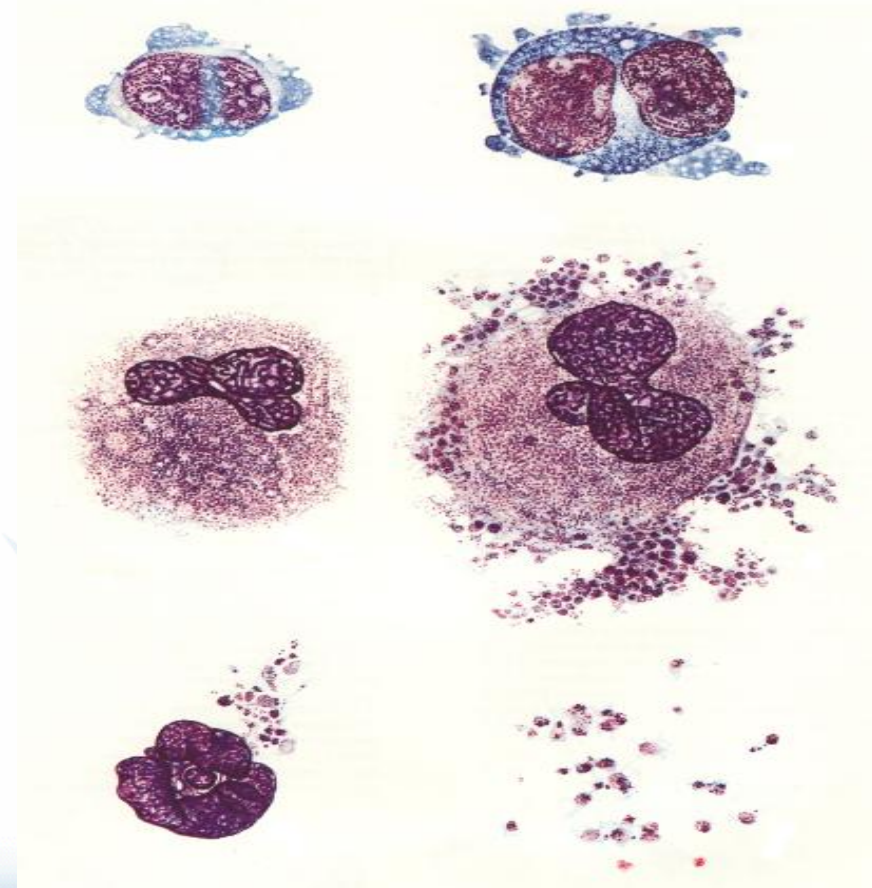




Platelets

(Thrombocytes)

- Produced in Bone Marrow
- Involved in Blood Clotting
- Can be normal in number but defective
- Very low numbers can cause spontaneous bleeding

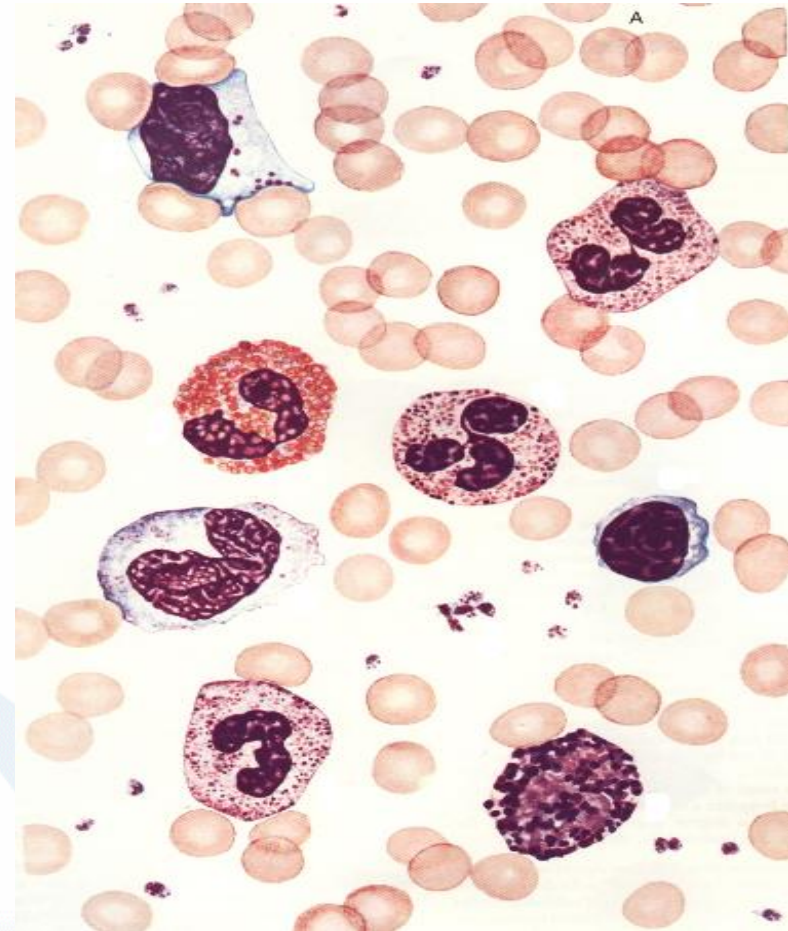




White Blood Cells

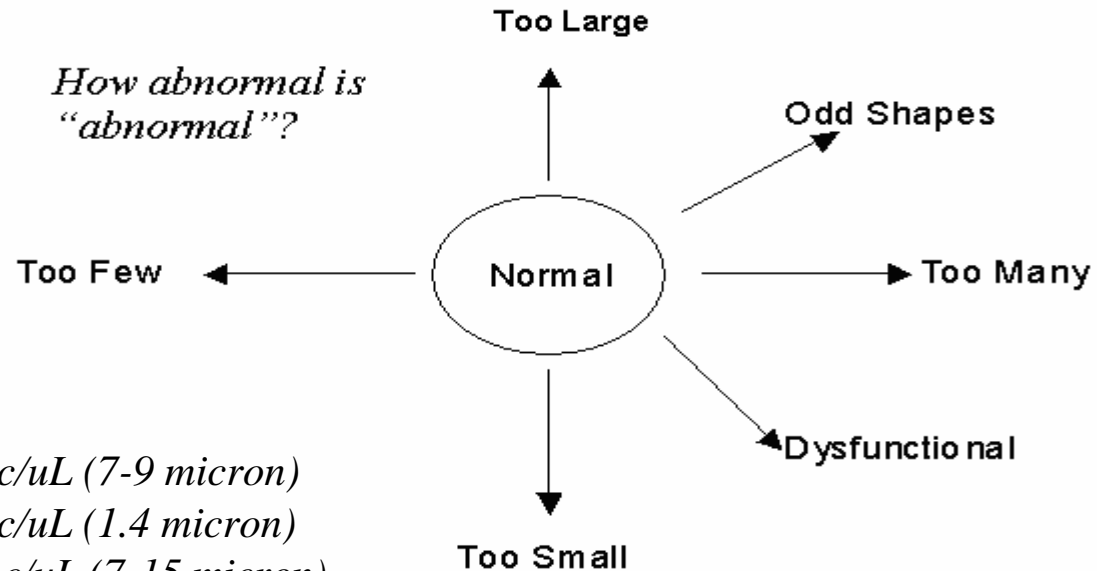
(Leukocytes)

- Granulocytes
 - Neutrophils
 - Eosinophils
 - Basophils
- Lymphocytes
- Monocytes





The challenges are the proportions and the pathologies



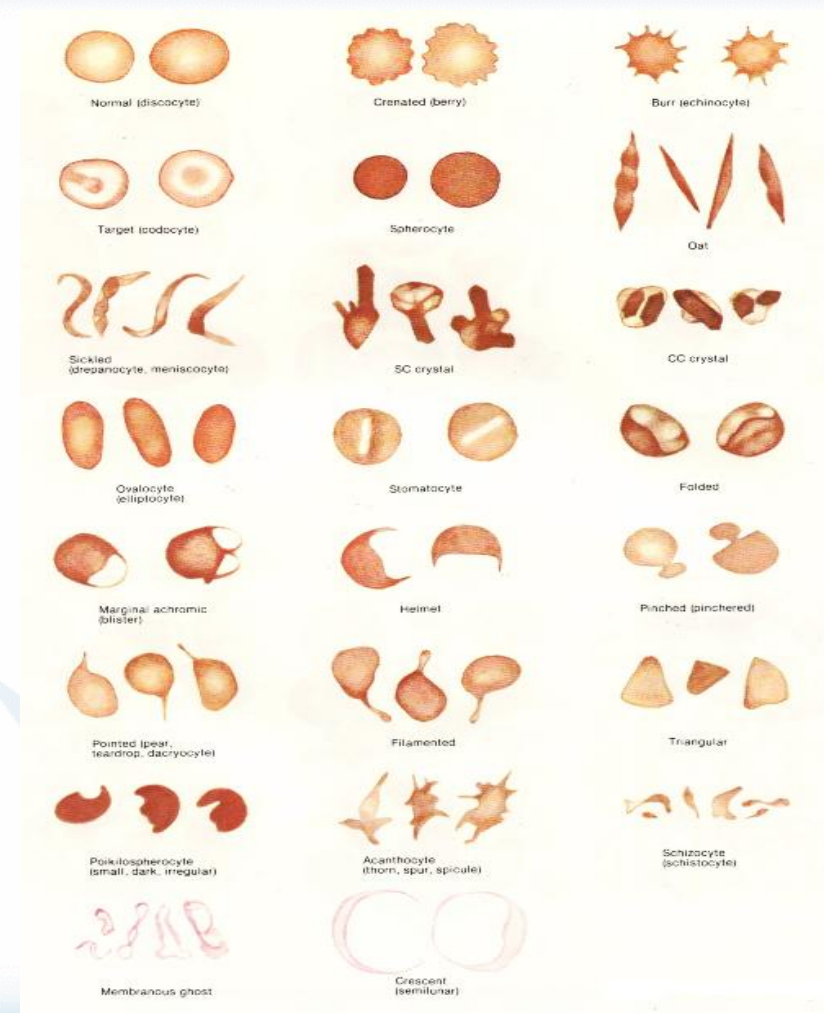
*Normal ~ 5,000,000 RBC c/uL (7-9 micron)
200,000 PLT c/uL (1.4 micron)
5,000 WBC c/uL (7-15 micron)*



Red Blood Cells

Red Blood Corpuscle (erythrocytes)

- Abnormal RBC's can be caused by:
 - Nutritional deficiencies
 - Iron deficiency
 - B12 or folate deficiency
 - Abnormal Hemoglobin
 - Hgb S (sickle) and C
 - Abnormal Production of Normal Hemoglobin
 - Thalassemias
 - Other Hereditary Defects
 - Spherocytosis
 - Elliptocytosis
 - Enzyme Deficiencies
 - Mechanical Damage
 - Burns
 - Heart Valves
 - Clotting





Platelets

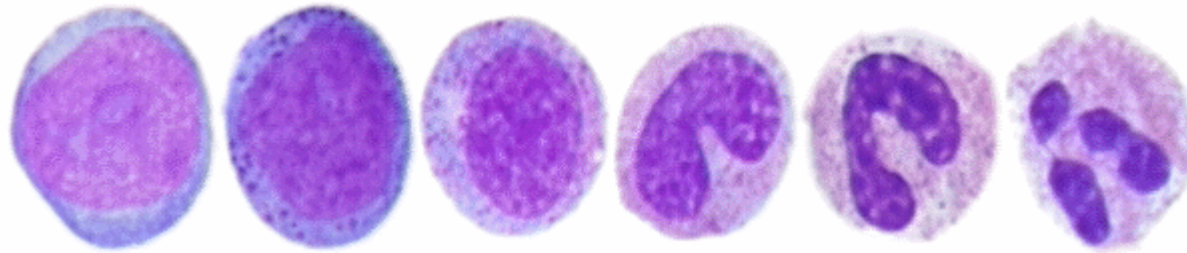
(Thrombocytes)

- Size = Tiny! – roughly 1.4 micron diameter
- Function = They fill in gaps and get sticky
 - The good:
 - Prevent you from bleeding to death when cut
 - The bad:
 - Stroke, deep vein thrombosis
 - The ugly:
 - Think of trying to move a cat on velcro
- And when they're insufficient or can't activate you risk spontaneously bleeding into tissue



White Blood Cells

(Leukocytes)

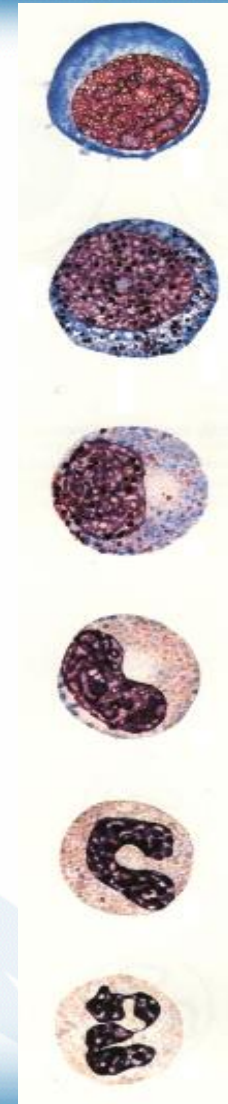


- Immature forms of any WBC may be present under certain conditions
- Blasts and very early forms are very abnormal except in disorders such as leukemia.



Neutrophils

- Increased in bacterial infections
- Immature forms may be present





Eosinophils

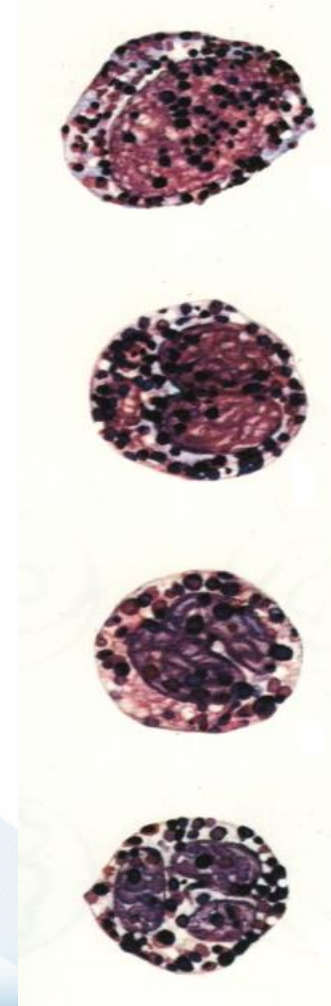
- Increased in allergic reactions and parasitic infections





Basophils

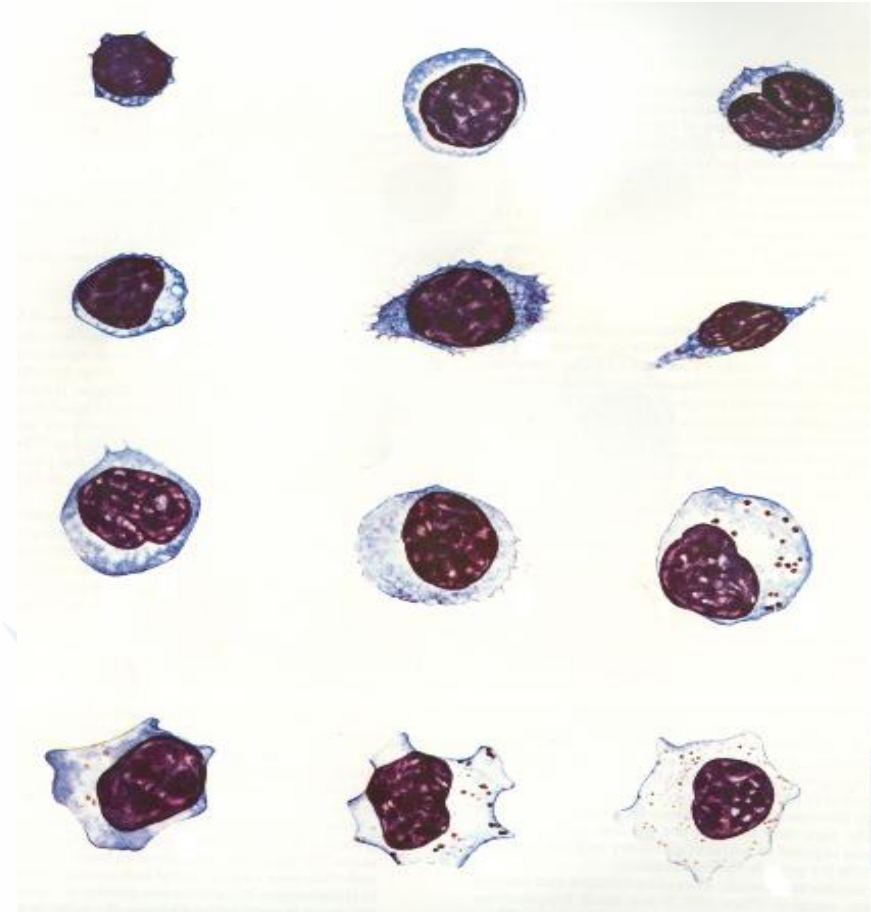
- An increase may be indicative of leukemia or other bone marrow disorders





Lymphocytes

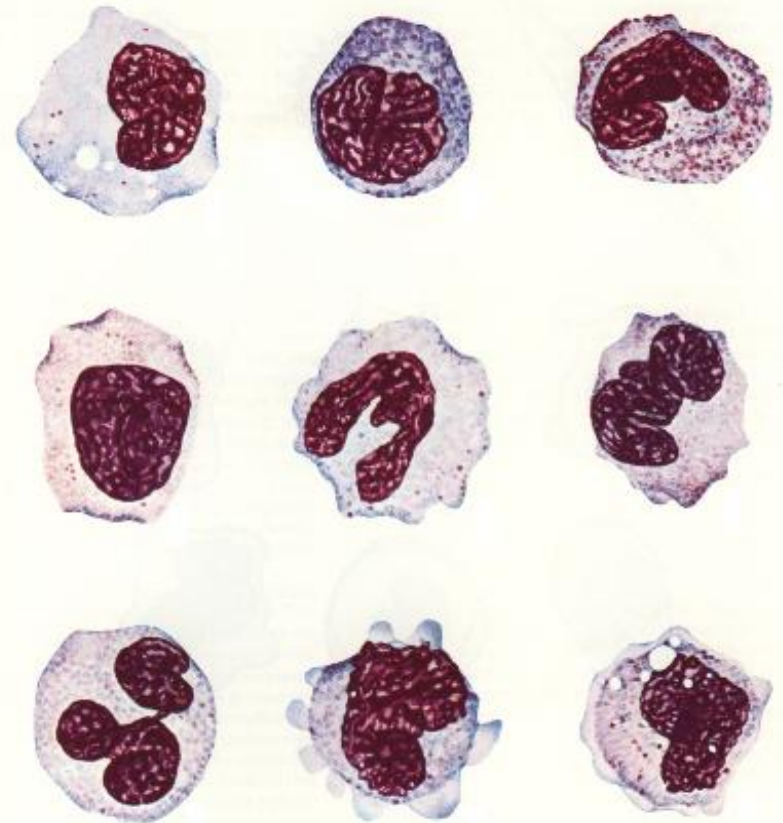
- Increased in viral infections
- Function is important aspect: T-cells, B-cells

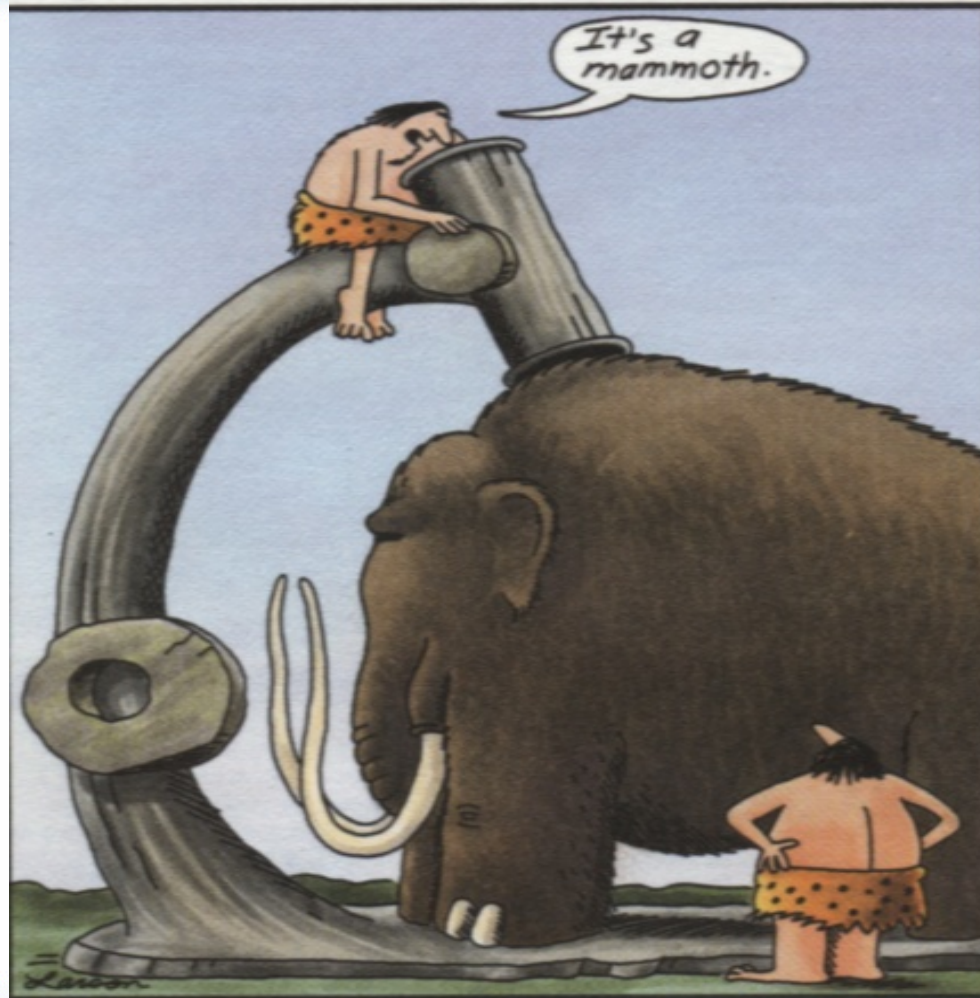




Monocytes

- Increased in bacterial infections

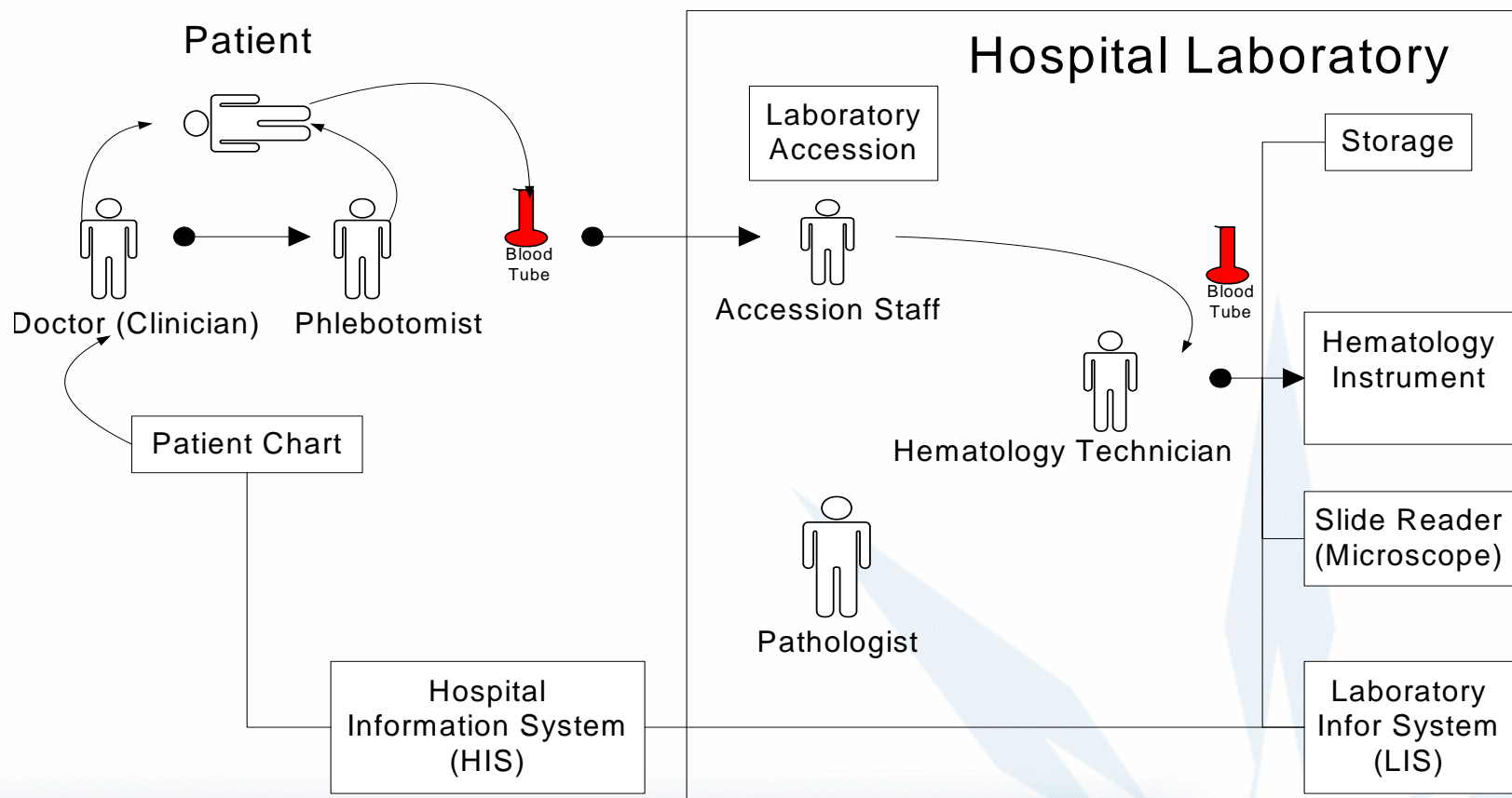




Early microscopes



Hematology & Modern Medicine





CBC

Complete Blood Count

- Measured Parameters

- WBC (WOC,NOC,WIC)
 - Differential (%)
- RBC
- Hemoglobin
- MCV
- Platelets
- MPV

- Derived Parameters

- Hematocrit
- MCH
- MCHC
- RDW
- White Cell Differential
 - Absolute Counts
 - Flags



The economics of it

- **Basic “test order” - on 1 tube of patient blood**
 - CBC = 9 results ~ \$15.00
 - WBC, RBC, HGB, PLT, MCV, RDW, HCT, MCH, MCHC
 - Or “CBC+DIFF” = 19 results ~ \$17.00
 - RETIC = 3 results ~ \$ 5.60
- **Instrument – one time purchase (5-7 yrs)**
 - List price: \$40K – \$250K (never pay list \$\$)
- **Reagents, Calibrators, Controls - ongoing expense**
 - Reagent costs per test: \$1;
 - Cal/Ctrls (per month): \$120-\$185



Basic steps in the (3-in-1) “assay”

- Mix the blood in specimen tube
- Vent the tube and Aspirate a slug of blood
- Shear the slug into measured aliquots (HGB, WBC, RBC/PLT)
- Deposit aliquots into fixed reaction vessels
- Add “chemistry” (reagents = salt water buffers; lytic agents, stains)
 - To dilute; to improve signal/noise ratio (blow away RBC’s, tag cell of interest)
- Mix with the “chemistry” (equilibrate/incubate)
- Stage to the measurement chamber (line cells up single file! – optics/imped)
- Measure (HGB by bulk; all others: 1-5 dimensions per cell)
- Send to waste
- (and while doing these things clean up used equipment; go again)



CBC Start to Finish – in less than 60 seconds

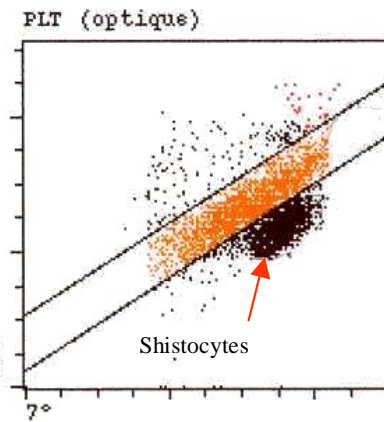
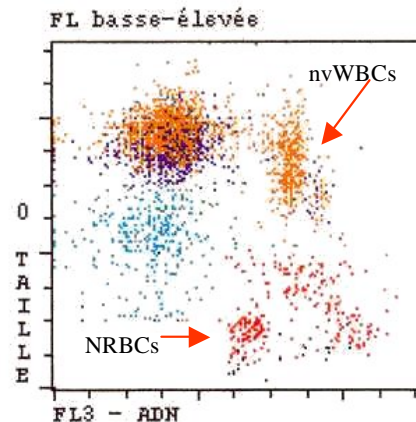
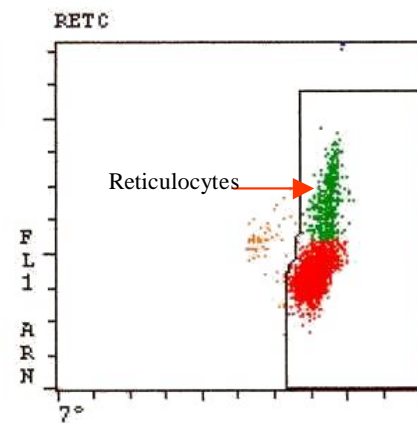
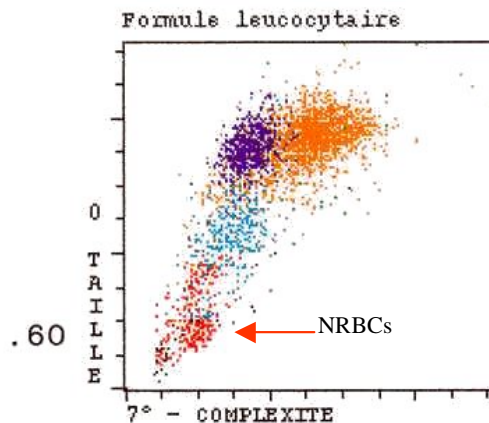
FOCUS
on what counts

WBC	5.15	10e3/u1	WVF	.837	WBCnv
NEU	3.28s		%N	63.7s	
LYM	.544		%L	10.6	
MONO	1.31		%M	25.4	
EOS	.020		%E	.389	
BASO	0.00		%B	0.00	

IG

RBC	3.06s	10e6/u1	RBCco	2.82	
HGB	10.9	g/dl			
HCT	29.3s	%			ASYM
MCV	95.8s	fl			
MCH	35.5s	pg			
MCHC	37.0s	g/dl			
RDW	22.7s	%			
RETc	319.s	10e3/u1	%R	10.4s	IR
IRF	.412				
NRBC	.422	10e3/u1	NR/W	8.19	

PLTo	23.3*	10e3/u1	PLTi	49.6*	
MPV	12.0*	fl	CD61	----	





The Engineering Challenges – User *vs* Designer

- Samples

- Well mixed, venous, peripheral whole blood
- Collected in anticoagulant (which particular anticoagulant *does* matter)
- Other samples presented (outside label claims): bone marrow aspirates, body fluids, platelet-rich-plasmas, etc

- Critical design aspects

- Mixing !! – (can be pathological)
- Sample tubes vary in length, width, diameter, material, base geometry, cap geometry
- Piercing (multiple times!!) a variety of tube caps without coring



The Engineering Challenges – User *vs* Designer (2)

- **Customer Workflow**

- First Pass Reportable (with babies, you may only have 1 shot)
- Workload varies – “every now and then” to 1200 a day
- STAT samples (< 30 min; reserve 20+ min for the blood to adjust)
- Microscope Review < 10%

- **Critical design aspects**

- First Pass Acceptance – must work thru common interferences
- Aspirate small volumes (< 125 uL open, <300 uL closed)
- Throughput (25 CBC/hr at low end; want 120 CBC/hr for high end)
- Flagging & Reflex testing



The Engineering Challenges – User *vs* Designer(3)

- **Intended Use**

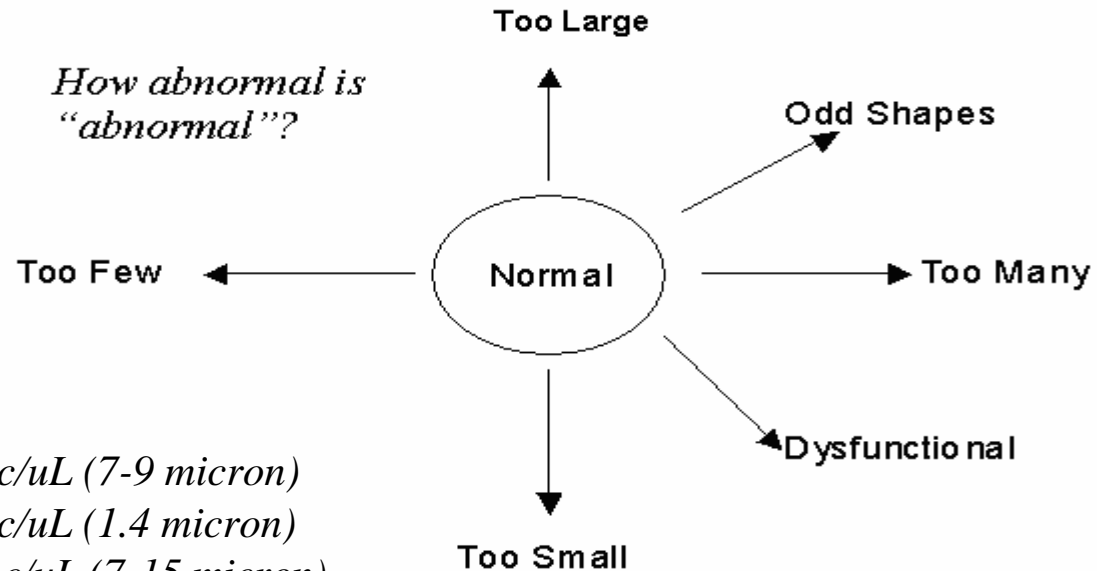
- Patient treatment (life & death decisions, some quite immediate - PLT)
- Patient monitoring (oncology, autologous transplants, HIV progression)

- **Critical design aspects**

- Accurate results (homogenous aliquots, near native state, calibration)
- Wide Dynamic Range (particle concentrations, particle size)
 - Bubbles – are they good, or bad ?
 - Precise dilution volumes, reagent-aliquot mixing
 - Fluid transport, tubing choices, rinsing & carryover concerns
 - Data Acquisition - count LOTS of events: 2,000 – 50,000



The challenges are the proportions and the pathologies



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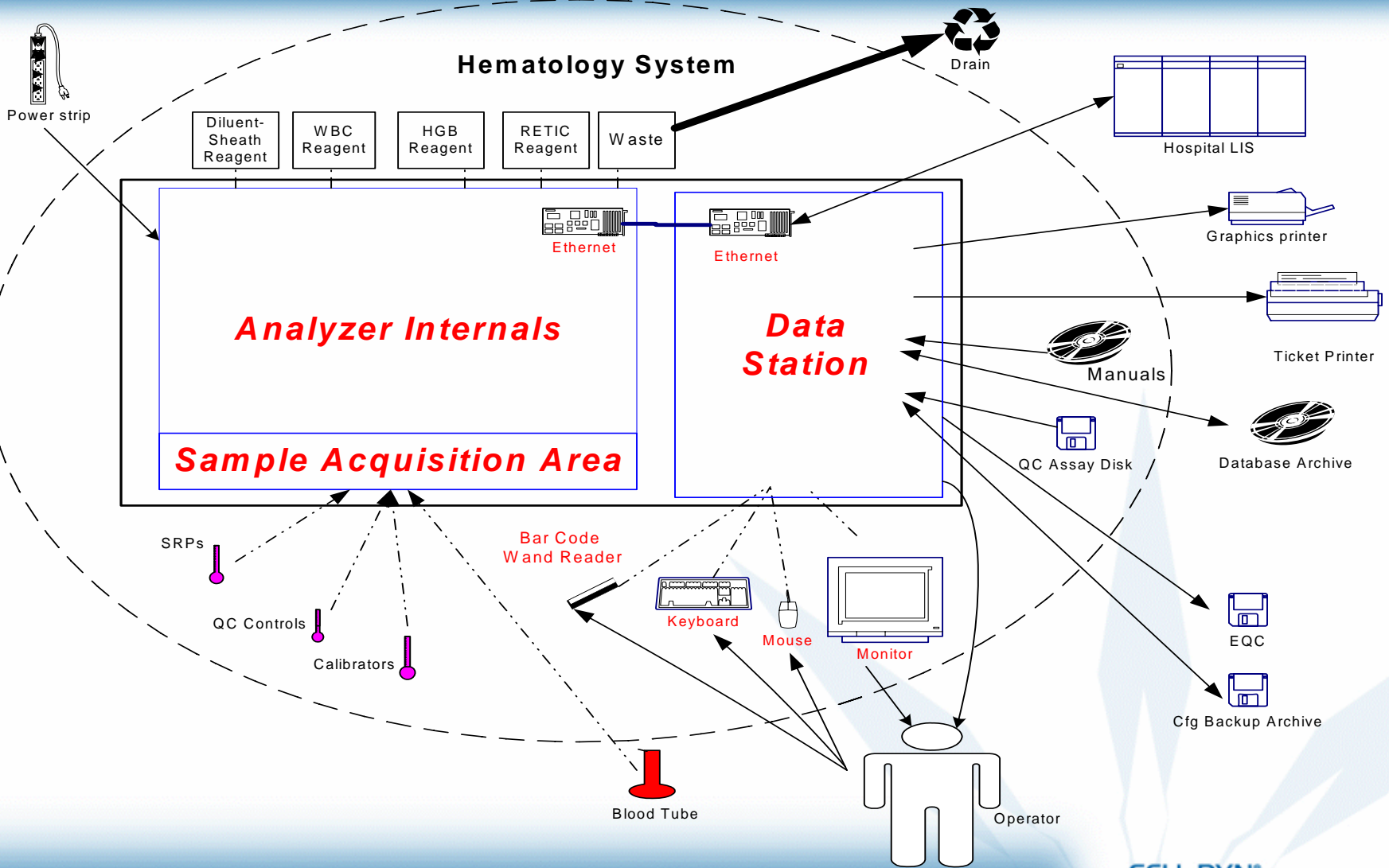


System Trade-offs

- To Lyse or Not to Lyse, that is a question....
 - Biological variation, normal and pathological
 - Interference: chemical resistance, overlapping size, debris
 - Time-variant characteristics: living and dying cells
- S & N (signal to noise ratios)
 - Proportions (normal or pathological)
 - Rare event detection
 - Precision and accuracy
 - Small sample volumes (neo-nates, geriatric)
- Speed of analysis
 - Precision, -cytotic vs -cytopenic samples



Hematology System

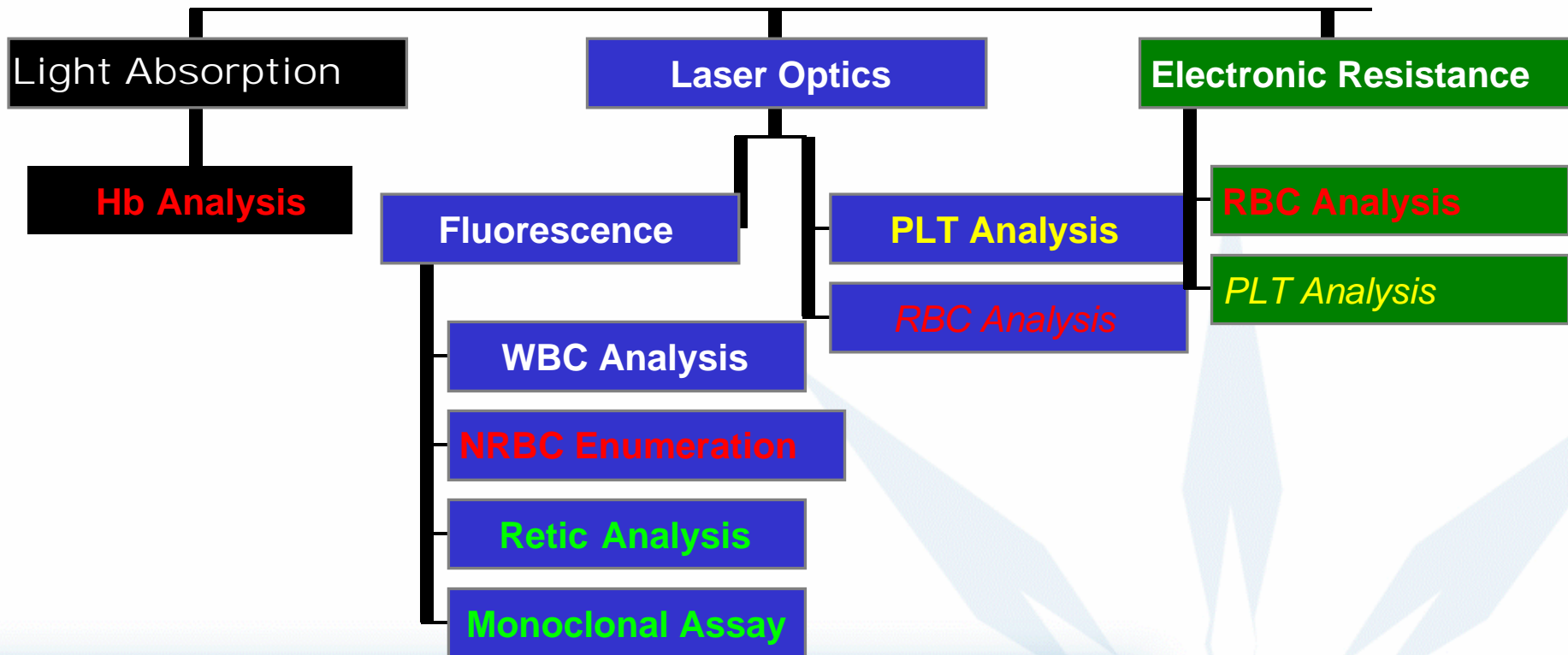




CELL-DYN 4000 Analytical Approach

FOCUS
on what counts

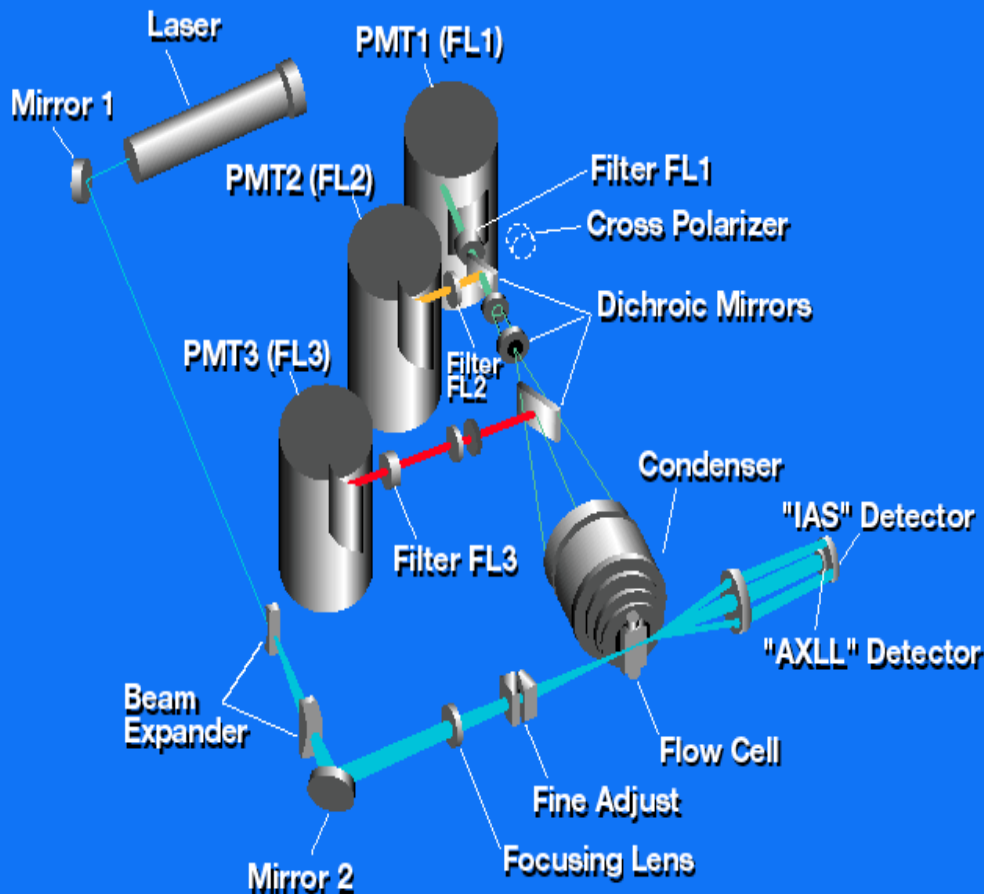
Detection Technologies





CELL-DYN 4000 Optical Bench

FOCUS
on what counts



Morphometric features :

ALL - Cell size

IAS - Complexity

PSS - Lobularity.

DSS - Separates Eosinophils from Neutrophils)

Fluorescence characteristics :

FL1 - Reticulocyte Analysis

FL2 - Monoclonal applications

FL3 - NRBC counting and white cell viability



Primary Subsystems

- Data Station
- Analyzer
 - Sample Loader
 - Mixer Assembly
 - Sample Processor
 - Aspiration, Aliquoting)
 - Flow Panels
 - Sample Cups
 - Dilution
 - Chemistry reaction vessels
 - Transducers (optics, imped, absorp)
 - Syringe Drives (dilution, delivery)
 - Pneumatic Module
 - (vacuum, pressure)
 - PCB's
 - Control and actuation
 - Sensing
 - Signal Processing
 - Communications, etc



Primary Engineering & Science Disciplines

- Software
 - Embedded systems
 - Motion control, sensors
 - Fluidics, data acquisition
 - Desktop systems
 - Communications, data analysis, data management
- Mechanical Engineering
- Fluid Mechanics
- Optics
- Industrial Engineering
- Electrical Engineering
 - Analog
 - Digital signal processing
 - Power
- Materials Science
- Biological Sciences
 - Reagent chemistry
 - Cell physiology
 - Cell membrane physics
 - Hematology
- Systems Engineering



Physiology is Fun !

Biological systems

- are more than the sum of their chemistry and physics
- are evolutionary products, not engineered products
- are interdisciplinary challenges

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