

Joyce Niblack Memorial Conference

Early signs of migration to myelofibrosis

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Most of you already know but

Laboratory tests reflect a single moment in time

Includes that day's physical and emotional stress, diet, fatigue level, type and timing of medication, time of day, and so on.



Most of you already know this as well but



Good laboratory tests are accurate about 95-98% of the time.

Good laboratory tests have a small range of precision, that is, repeated tests on the same specimen will not always give the exact same result.

The tighter the range the more precise the result ~ but that does not increase accuracy and vice versa.

For most tests, you have to accept the ranges and compare the **CHANGE** over time.

Bone marrow disease progression

A general rule is that there are
10,000,000,000,000,000 cells in a liter
of bone marrow.

Most adults have 2 liters of bone
marrow space.

Bone marrow disease progression

All change starts with 1 cell going awry.

In the bone marrow, think that every cell undergoes mitosis every 24 hours.

So if you do the math –

A general assumption is that it takes about 5 years for that one odd cell to get to enough numbers to show up and cause trouble.

Bone marrow disease progression

Just a sense of work and time

Cells to fill marrow	1,000,000,000,000,000
Cells at diagnosis (S&S)	10,000,000,000,000
Cells at clinical remission	10,000,000,000
Cells at UMRD	1,000,000,000
Cells to go bad	1

This takes more time that people believe.

Bone marrow disease progression

❖ To make this math a little more interesting

- ❖ Malignant cells are damaged so not all of them will be able to achieve the same level of mitotic frequency or life span of the normal cell.
- ❖ It probably takes longer than what the math would support from the time of the 1 cell to full blown signs and symptoms.

Progression over time

❖ How do you know if progression is happening?

- ❖ Not easily
- ❖ Even daily bone marrow examinations will not be able to pick up the small daily changes
- ❖ Just as recovery from surgery or trauma shows you, comparison of progression over weeks or months is better.
- ❖ This is **NOT** a standard light switch (on/off) but much more like a dimmer switch.

Progression over time

❖ How do you know if progression is happening?

❖ Red cell changes

◆ RDW is one possibility

- ❖ It is the most sensitive of all CBC tests
- ❖ It starts to increase weeks before any other result changes beyond the usual daily changes.

◆ Shape changes

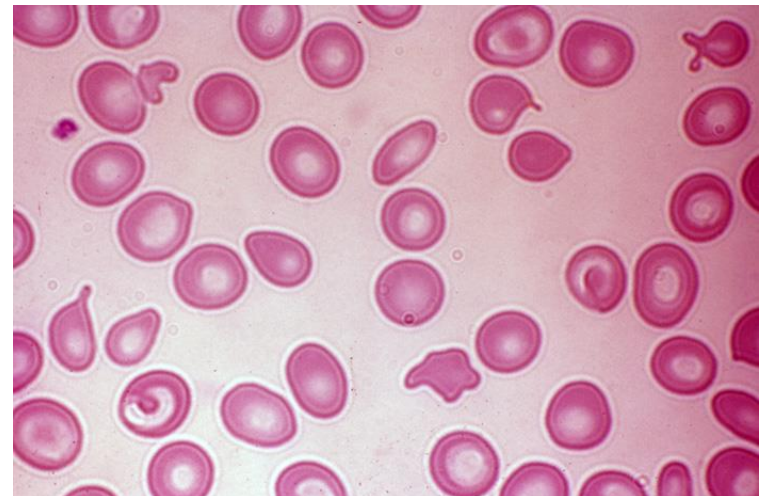
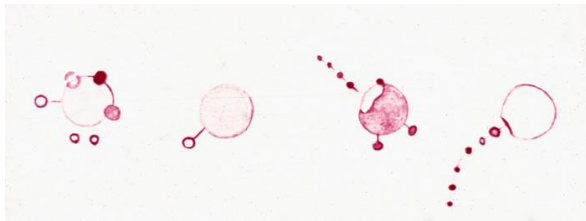
- ❖ From ET → MP
- ❖ As fibrotic material increases in the marrow, the red cells cannot just leave the marrow through the “correct door”. They have to slither out through smaller openings and they can get caught..

Progression over time



Small and large = anisocytosis

Teardrop and spherocytes
= poikilocytosis



Progression over time

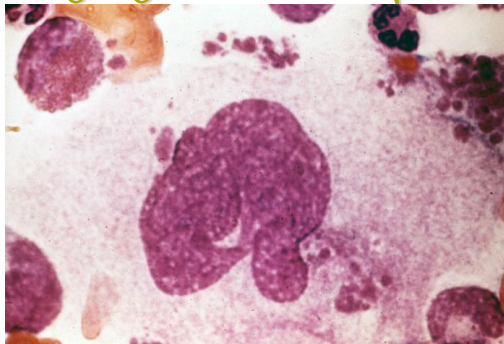
Liver Function tests that reflect RBC changes

- ✧ Decreased Haptoglobin ~measures increased red cell death well
- ✧ Increased bilirubin ~ measures a break down product of red cell metabolism
- ✧ Increased lactate dehydrogenase (LD)
 - ◆ Isoenzymes I and II
- ✧ Elevated Plasma Hemoglobin (usually not done anymore)

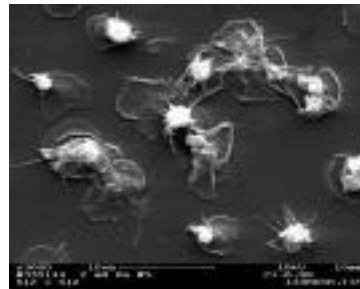
Progression over time

Platelets

- ✧ Megakaryocytes buds off platelets



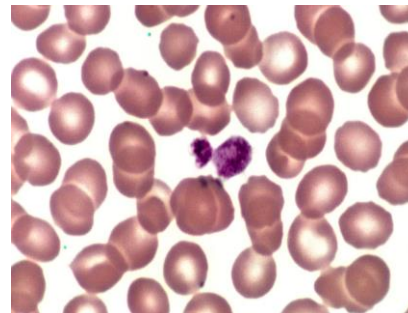
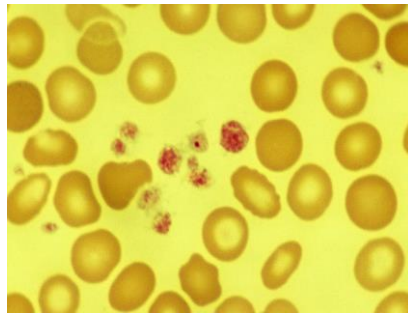
- ✧ Platelets typically have granules in the center with wispy cytoplasm



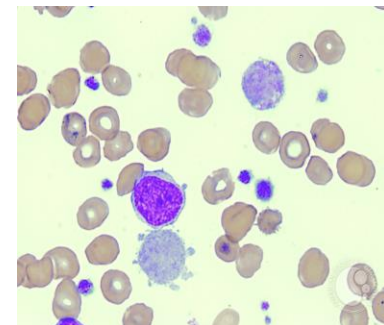
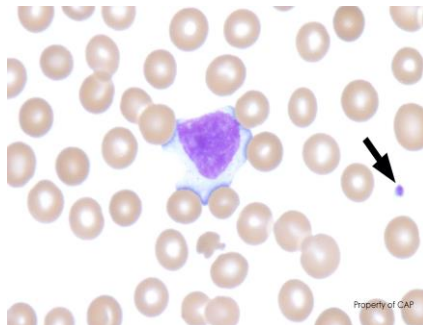
Progression over time

Platelets under bone marrow stress

- ✧ Are bigger and less well organized and have wonky function



- ✧ Overtime they get larger, less granular (and less functional)



Progression over time

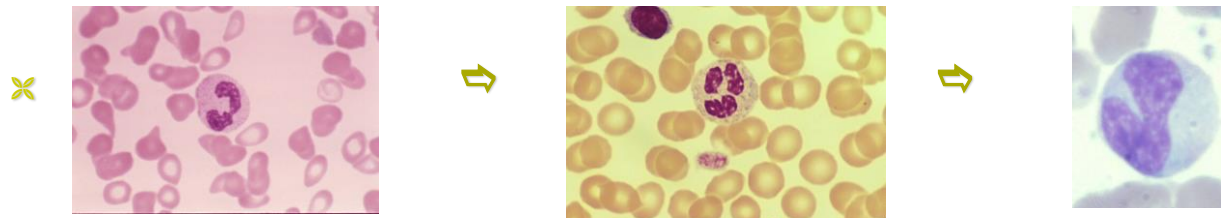
Granulocytes under bone marrow stress

- ✧ The faster a cell tries to become mature, the less functional it will be.
- ✧ Normal
 - ◆ During maturation, early granules contain a bleach-like substance. They start out dark blue/purple and “bleach” themselves to a lighter blue/lilac. These can kill living organisms.
 - ◆ Secondary and tertiary granules degrade, detoxify and make compounds ready for excretion.
- ✧ Stress (for any reason)
 - ◆ Granules are darker and bigger
 - ◆ Nucleus is less mature
 - ◆ function is lost

Progression over time

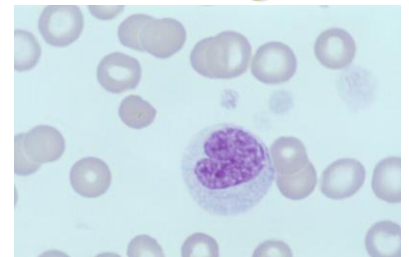
✧ Poly's, PMN, Neu, Seg's – fully functional

- ◆ Spend all of their time in the bloodstream or tissues.
- ◆ Can move to a specific site, phagocytize, kill and degrade what it eats
- ◆ Loses granules as it works
- ◆ When there are no more granules, it dies.



✧ Bands, Non seg's - approximately 80% functional (think teenagers - they can drive)

- ◆ Spend 50% of their time marginating
- ◆ the blood vessel walls (think male teenagers at their dance)
- ◆ They are clumsy and a little slow but they are functional.

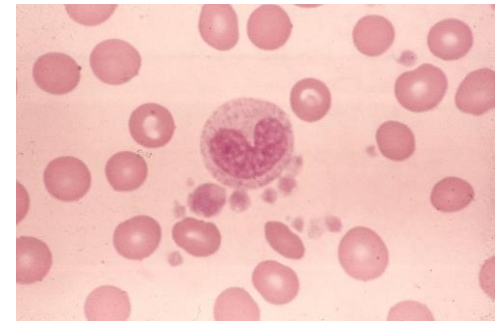


Progression over time

❖ Granulocytes under bone marrow stress

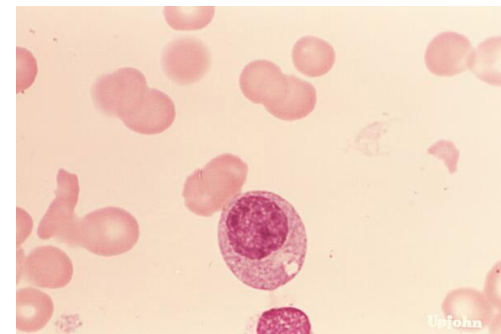
- ❖ Metamyelocyte ~ really shouldn't be in the peripheral blood

- ◆ Not fully functional
- ◆ They can travel but can not phagocytize.



- ❖ Myelocytes

- ◆ Can't eat, kill or degrade
- ◆ Can't move
- ◆ The bone marrow is just desperate to put out something.

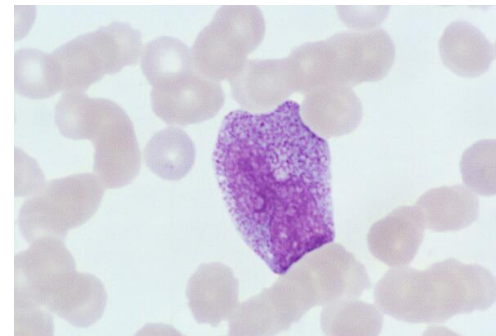


Progression over time

☒ Granulocytes under bone marrow stress

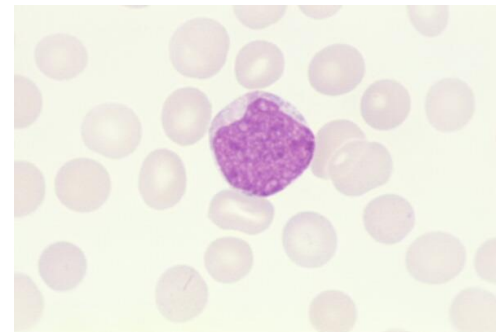
✧ Promyelocyte

- ◆ Can't move, recognize, eat,
- ◆ No good reason for it to be in the peripheral blood ever



Myeloblast (blast)

- ◆ Has no function other than mitosis
- ◆ And making granules



Progression over time

Granulocytes under bone marrow stress

- ✧ Every now and again a metamyelocyte can get out of the marrow.
 - ◆ Not consistently
 - ◆ Not in increasing numbers

- ✧ Every now and again a myelocyte can get out of the marrow
 - ◆ Not consistently
 - ◆ Not in increasing numbers

Progression over time

Granulocytes under bone marrow stress

- ✧ Every now and again, a granulocyte can have darker granules but still be functional
 - ◆ Not consistently
 - ◆ Not in increasing numbers

- ✧ Every now and again a granulocyte can be agranular
 - ◆ Not consistently
 - ◆ Not in increasing numbers

What does all this Jibber Jabber mean

❖ Change occurs slowly.

✕ It will be reflected by

- ◆ The consistent presence of something unusual
 - ✕ It doesn't have to have the same cell type or the same cell line.
- ◆ The increasing presence of something unusual
 - ✕ More often than not, more than one anomaly will be seen at the same time.
- ◆ None of these require intervention until and unless there is enough to interfere with quality of life

❖ Newer medications can / will / do alter this paradigm.