Blood Cells by Design

"If you plant it, it might grow"

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Blood Supply Issues

- Many developed countries have chronic blood supply shortages.
- Increasingly this is not just at holiday periods but is driven by increased demand throughout the year
- This is classic supply side economics.
- Why can’t we just increase the supply of blood products?

More Supply Issues

- Why can’t we recruit more donors ?
- Apathy, disinterest, poor message !!
- Somebody else will do it. (always do)
- The Rats Ass Syndrome

Even More Issues

- Even countries with previously "healthy" donor populations are now struggling to maintain their blood supply.
- Increased demand for components is not likely to decrease especially for platelets as more and "toxic" chemotherapy is used.

Some Answers ?

- If we can't recruit enough donors can we do anything else?
- Change donor criteria ?
- "Synthetic blood"
- Prolonged storage capability e.g frozen cells.
- Stem Cell sources

Artificial Blood !!

- What happened ?
- Perfluorocarbons have been around for 30 years.
- They do carry and deliver oxygen but have many limitations.
- Red cells have functions that are more than oxygen delivery.
- Not ever going to be viable alternative to RBC transfusions.

Blood Substitutes

- Lot of interest and development in last 20 years.
- Usually involved some kind of Hb compound in artificial membrane.
- Did deliver oxygen but many complications.
- “Biopure” was approved for dogs.
- FDA forced closure of largest lab.

More Blood Substitutes

- Some are available for compassionate use (Jehovah's witnesses).
- Huge IRB/regulatory issues even for compassionate use.
- Never going to be FDA approved.
- Not a viable long term alternative to the dwindling donor pool.

Alternatives

- If we can't cheat nature what are the options?
- What about frozen blood?
- RBCs can be frozen very successfully.
- They can only be thawed using chemical proservatives.
- It was used widely by the US Navy in Vietnam.

More Frozen Blood

- If you could freeze/thaw blood on a large scale would have little outdated blood and improve the blood supply.
- Very costly, very equipment driven, lose a significant amount by washing.
- Very short viability after washing.
- Expense and availability, short outdate make this non viable on large scale.

Damn ! What to do?

- Huge interest in stem cells in past 20 years.
- A ***stem cell*** is basic cellular building block in which a common single "cell of origin" can differentiate into a cell in the body
- Scientific description is "pluripotent."

Scientific Agriculture

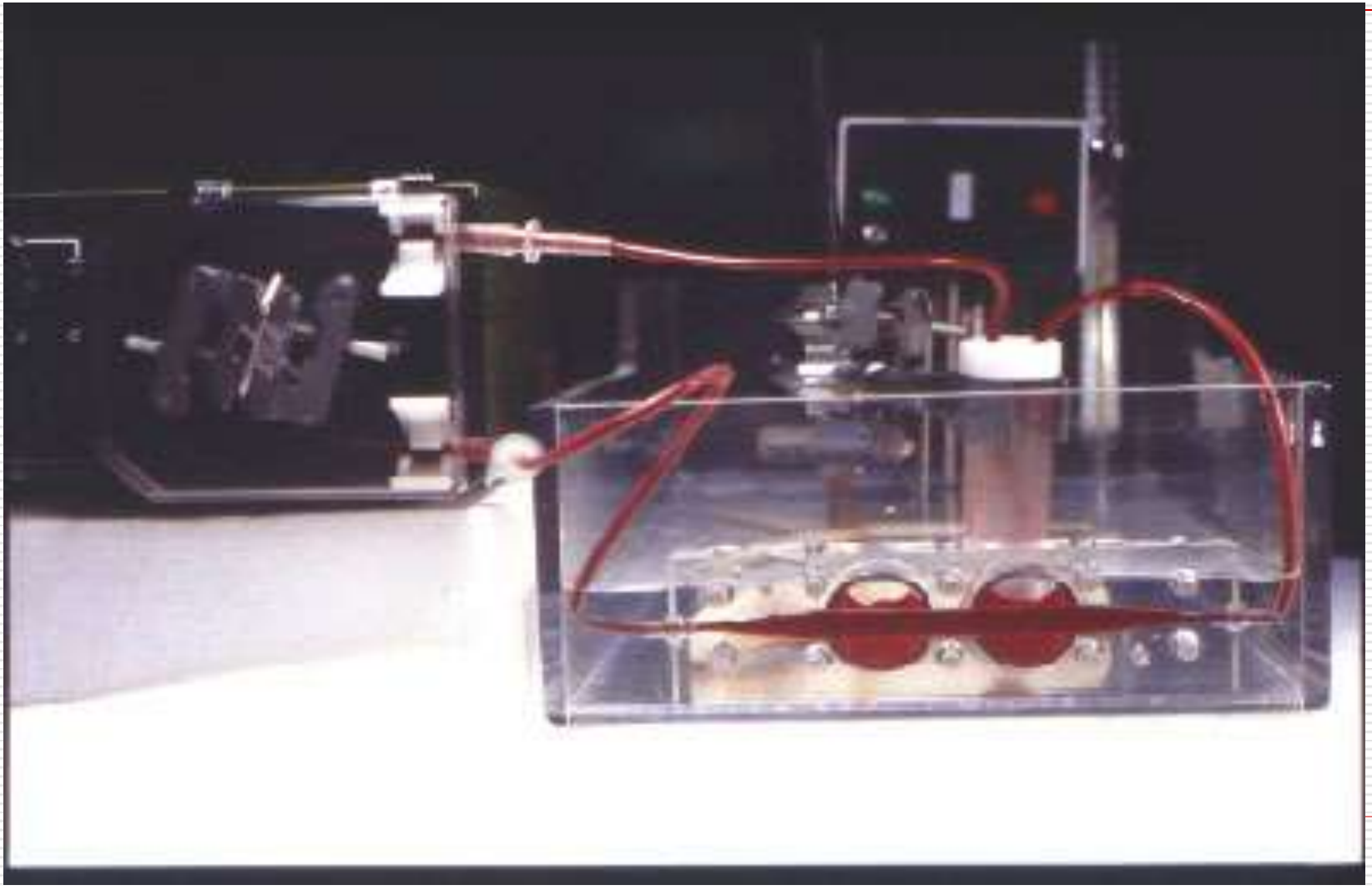
- Stem cells physiologically can be made to differentiate into specific and very different cell lines under the control of many factors.
- These include genes, growth factors, transcription factors, all of which send a message to support and produce specific cell lines from a common origin.

The "Seed Concept"

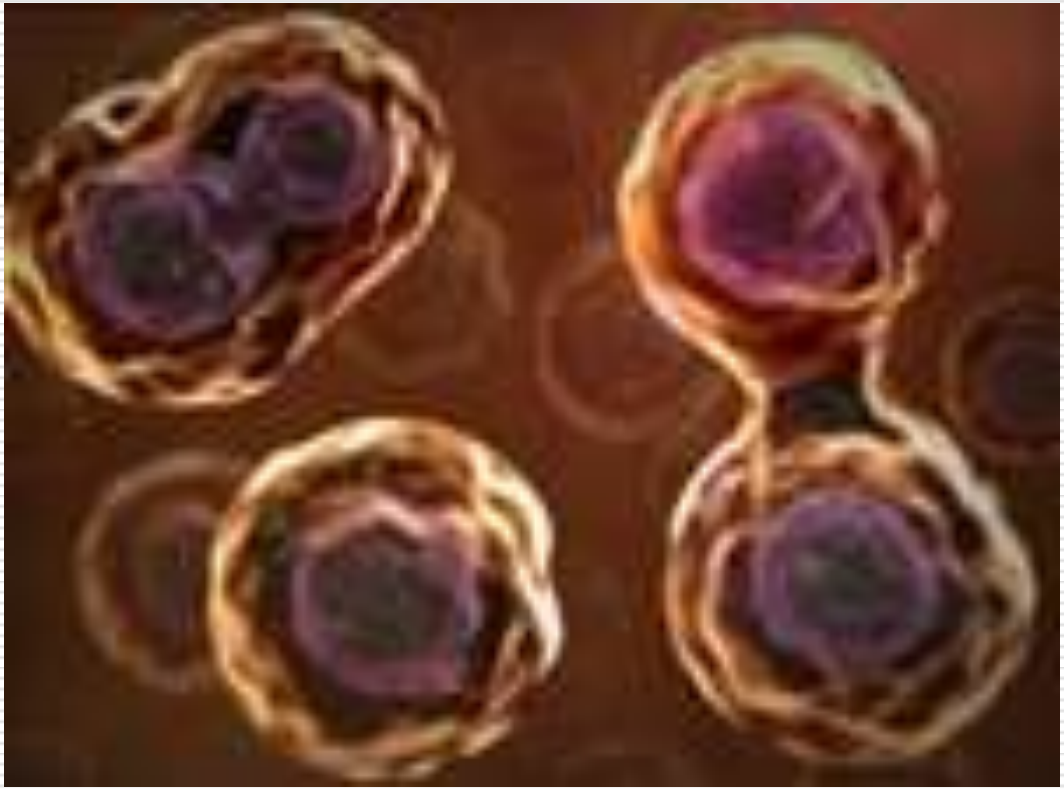
- If we consider the stem cell as a *"seed"* then can we find out how to make them into red cells, white cells and platelets.
- The "Bioagriculture" conditions are the challenge.
- Many kinds of body cells can be generated in the laboratory from stem cells by scientific manipulation.

Let’s Just Make It.

Cell Manufacture



Basic Stem Cells



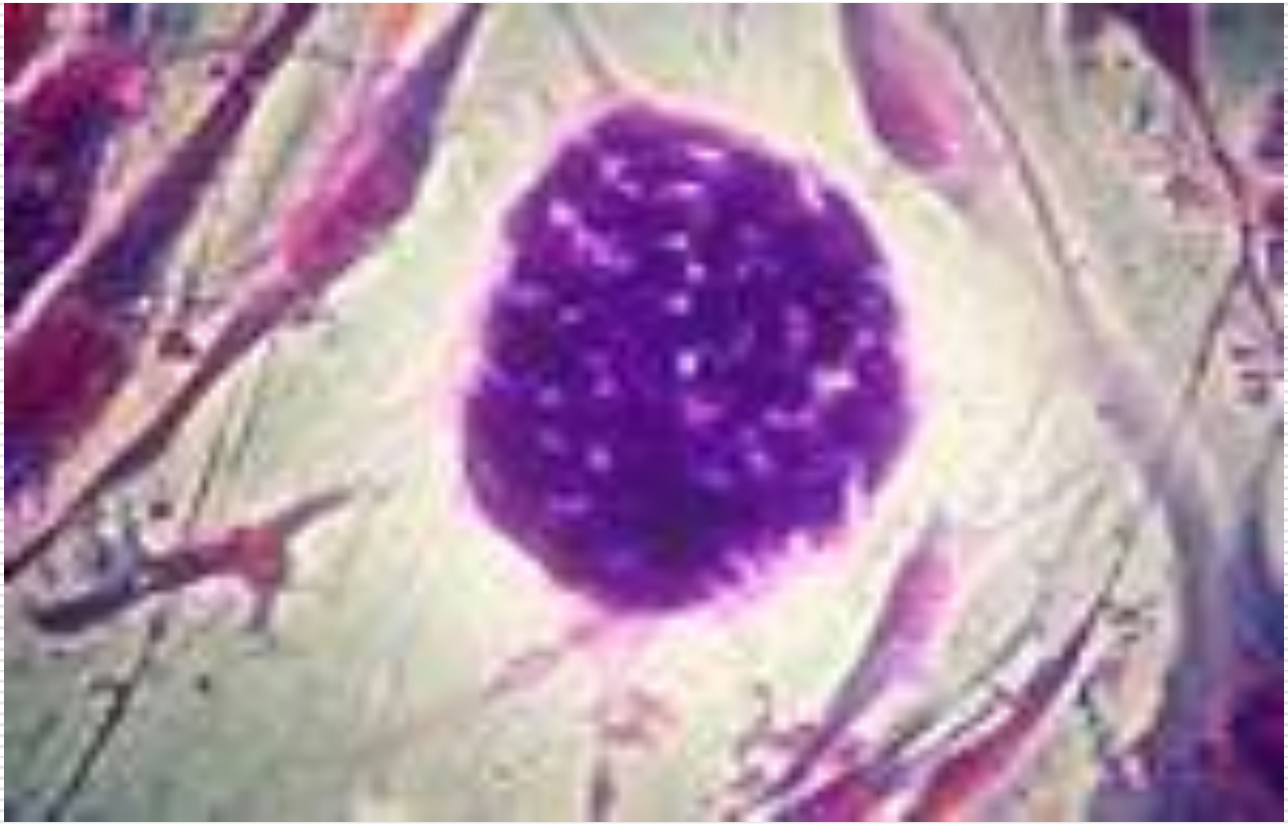
More Basic Stem Cells

- How do we identify basic Stem cells.
- Can we identify and purify Hematopoetic stem cells. (CD34+)
- How many do we need to seed the production process.
- What scale can this be done on?
- How expensive will this be?

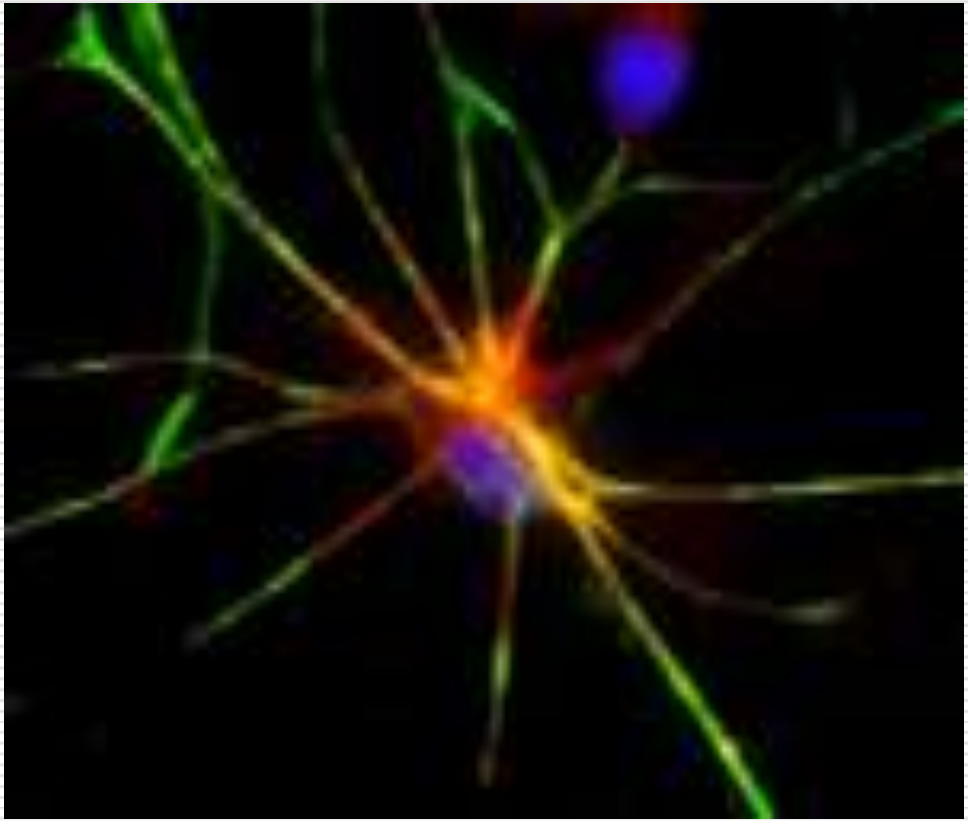
Even More Basic Stem Cells

- In theory we can customise this process for each patient.
- We can produce RBCs, Platelets& WBC for each patient.
- No X-matching, No alloimunisation
- No thrombocytopenia !!!!
- Less antibiotics more WBCs.
- **WOW!**

Stem Cell Nodule



Neural Stem Cell



Embryonic Stem Cells

Blood Cell Bioagriculture-1

- It has been shown that you can differentiate stem cells into RBCs.
- You can also generate white cells.
- Uncertain about platelets.
- If feasible could be the answer to the blood supply issues.

Blood Cell Bioagriculture-2

- Several groups in the last 4 years have generated functioning RBCs from embryonic human stem cells.
- Used mouse fetal liver cells cultured with human stem cells and by 20 days had "grown" RBCs with adult Hb without remaining nuclei indicating cell maturity.

Blood Cell Bioagriculture-3

- More recently a group headed by the U of Minnesota generated 100 billion RBCs equivalent to 3 tubes in blood.
- They were able to generate all the ABO blood types with 65% of cells being mature RBCs
- Still had some residual fetal Hb but was considered major progress.

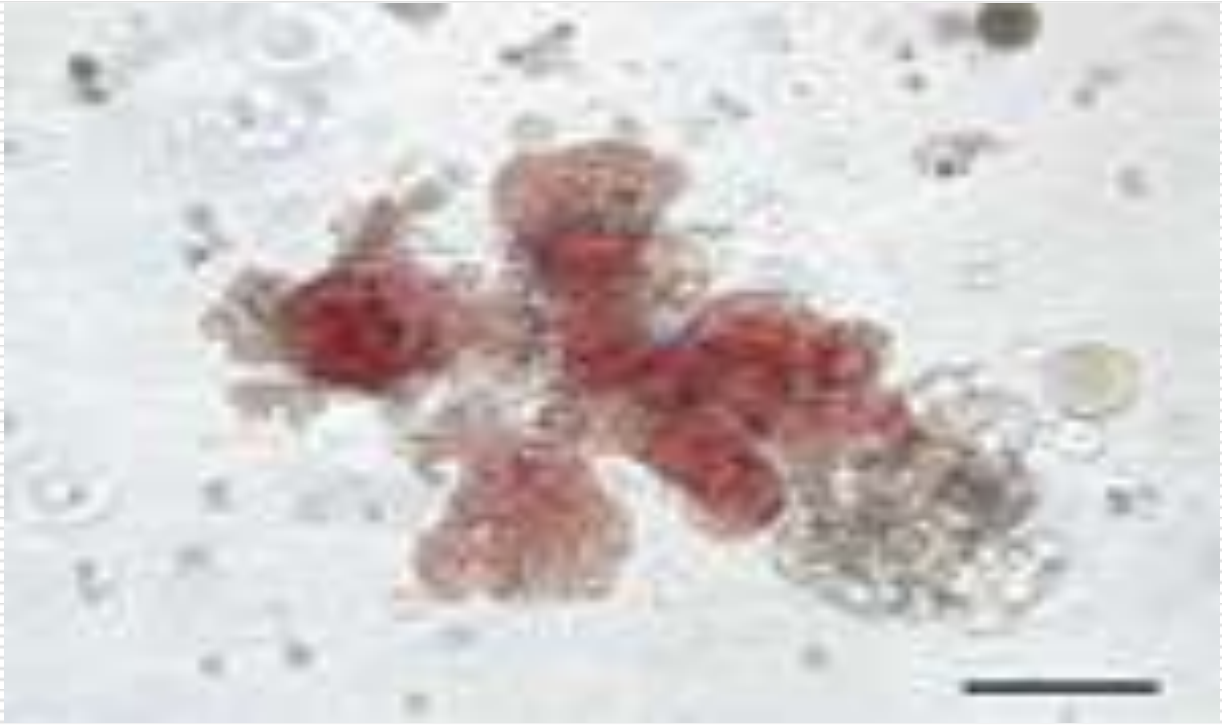
Blood Cell Bioagriculture-4

- In December 2011 a group in Paris published a study where they took donor hematopoetic stem cells and grew them in a lab to generate 10 billion RBCs. (2 ml of blood)
- These were then labelled and injected back into the donors.
- At day 5, 94% of cells remained & at day 26, 41-63% remained.

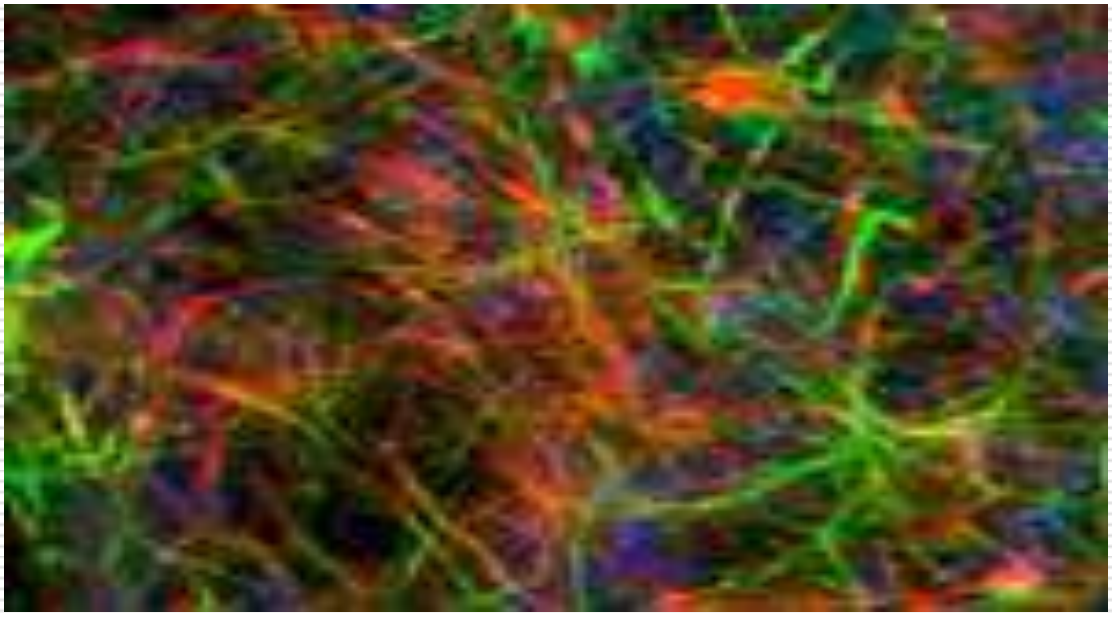
What does this tell us ?

- "Bioagriculture" of blood cellular elements is both feasible and practical on small scale.
- Industrial scale up will be challenging and probably very expensive.
- However countries are committing resources to this very end.
- It could solve the blood shortage

Cultured Red Cells



Growth of Neural Stem Cells



Where is the Big Picture ?

- In Scotland, the government is supporting a consortium of the National BTS, University of Glasgow engineering school and the Biopharmaceutical group at University of Strathclyde with $25 million to develop industrial production of blood cell components.
- Expect some results in 5 years.

More Big Picture

- If we can do this for RBcs even on a small scale consider the possibilities for Platelets and even Granulocytes?
- Maybe for the first time in history we could give enough granuloctyes by transfusion to actually work in ingfections.
- They do work ,we can never get enough to get an optimum response.

Even Bigger Picture

- The possibility of having enough platelets to treat all our cancer chemotherapy patients is like winning the lottery for a blood banker!
- We might be able to generate huge platelet numbers to make a single donor unit look " feable"

The Other Georgia

Ultimate Picture

- While still in it's infancy, many of the "proof of principal" issues for generating blood cell components from stem cells have been identified and validated.
- Huge issues still exists before this technological ability will generate functional volumes of product.

More Ultimate Picture

- It is unlikely that we will ever return to the situation where human blood donors will satisfy the need for cellular components.
- Biotechnology is expanding at a logarithmic pace.
- **Buckets of blood** are on the horizon!

Tbilisi