

La production des plaquettes sanguines

Jeudis de Fleurus 2016

Prof. Christian CHATELAIN

NTHC

Université de Namur

CHRONOLOGIE

1881: Identification des plaquettes (Bizzozero)

1910: Mégacaryocyte (Wright)

1958: Thrombopoïétine (Kelemen)

1967: Mesure de la production plaquettaire (Odell)

1968: Morphométrie des mégakaryocytes (Harker)

1975: CFU-MK (Metcalf)

1984: Cytokines (IL-3,...) (Ihle, Quesenberry)

1994: *mpl* et Thrombopoïétine

2016: rupture mégacaryocytaire (IL-1 α)

L'OSSERVATORE

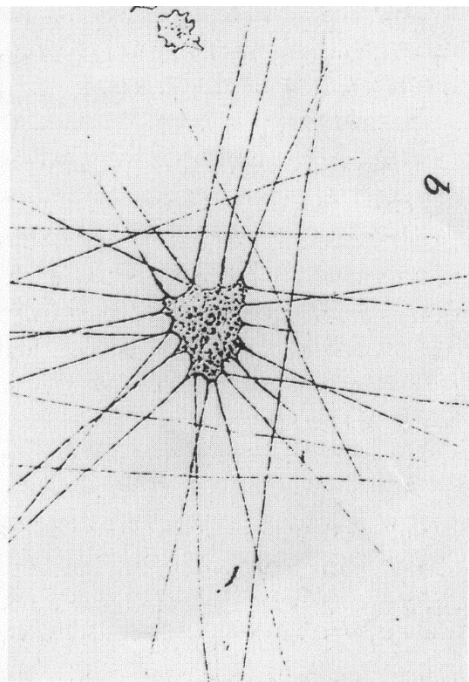
GAZZETTA DELLE CLINICHE

Giornale Ufficiale della Società di Medicina e Chirurgia di Torino

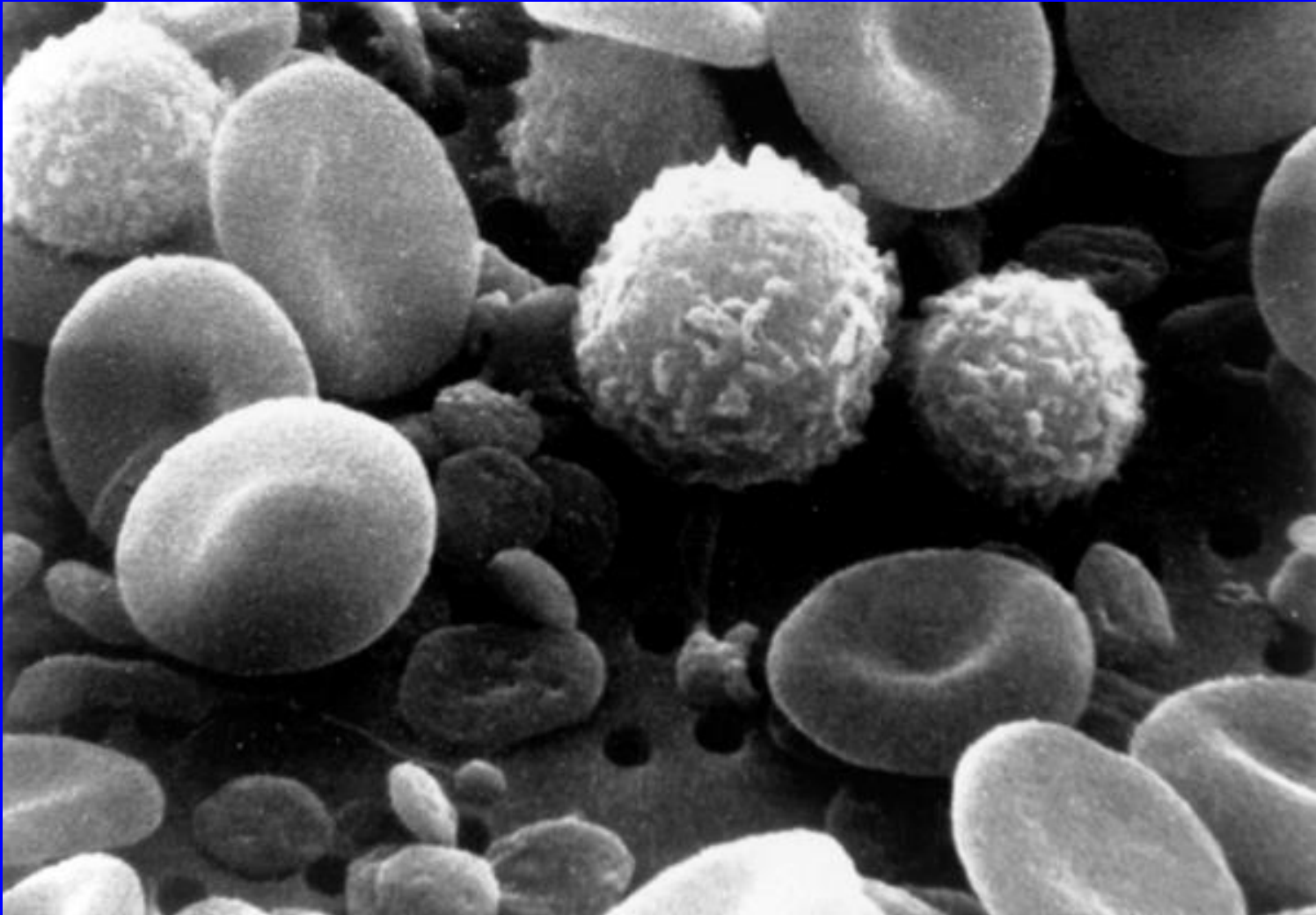
SOMMARIO. — Su di un nuovo elemento morfologico del sangue dei mammiferi e della sua importanza nella trombosì e nella coagulazione, pel dott. G. Bizzozzo. — Casistica delle lesioni traumatiche occorse nella clinica del prof. Bruno nell'anno scolastico 1880-81, pel dott. Gerolamo Mo. — Rivista giornalistica. Malattie della pelle: del loro trattamento presso la Scuola di Vienna. — Sul trattamento della febbre nei bambini. — Formulario. — Effemeridi mediche.

SU DI UN NUOVO ELEMENTO MORFOLOGICO DEL SANGUE DEI MAMMIFERI

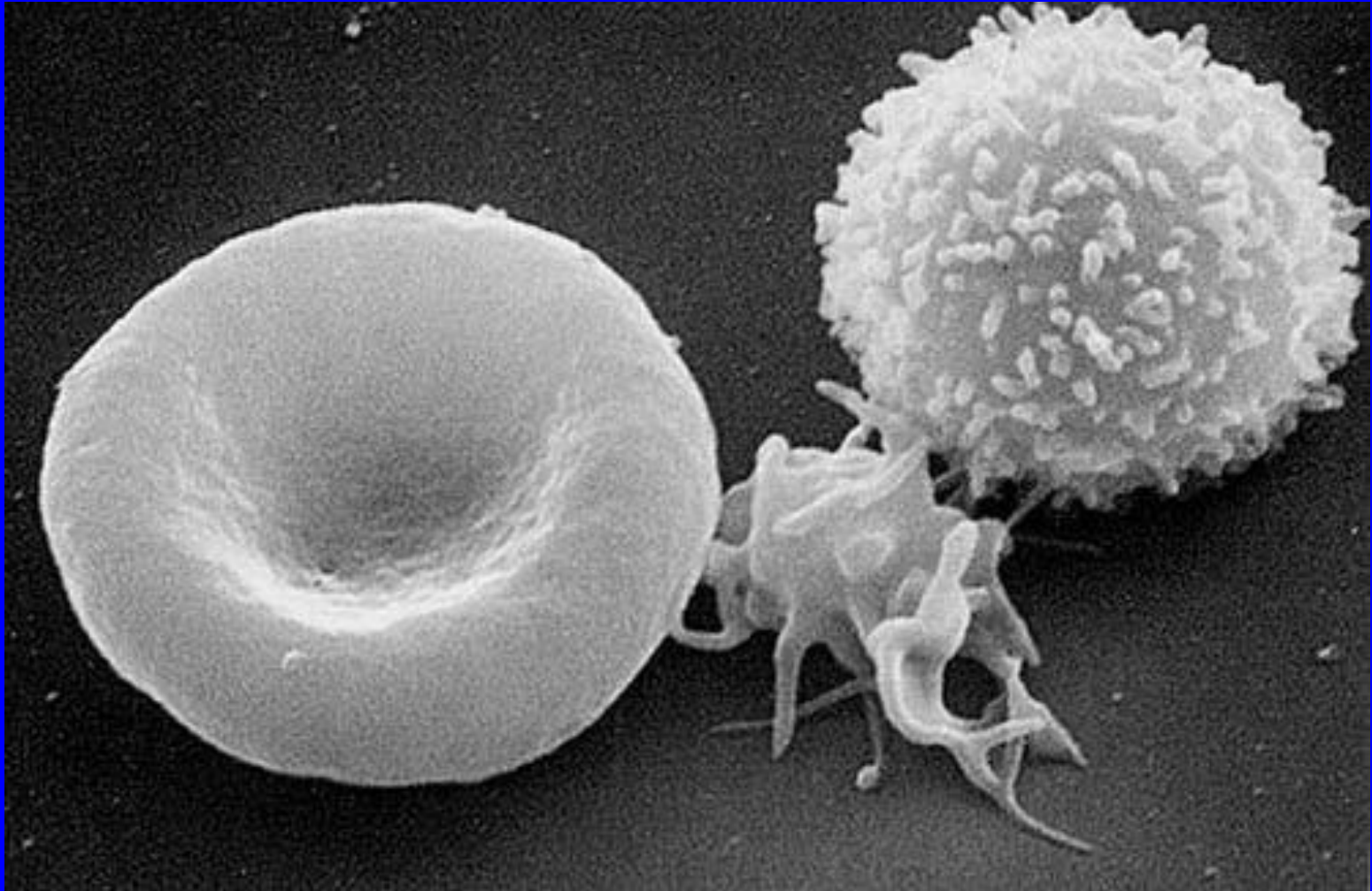
e della sua importanza nella trombosì e nella coagulazione.

Nota preventiva del Prof. G. Bizzozzo.

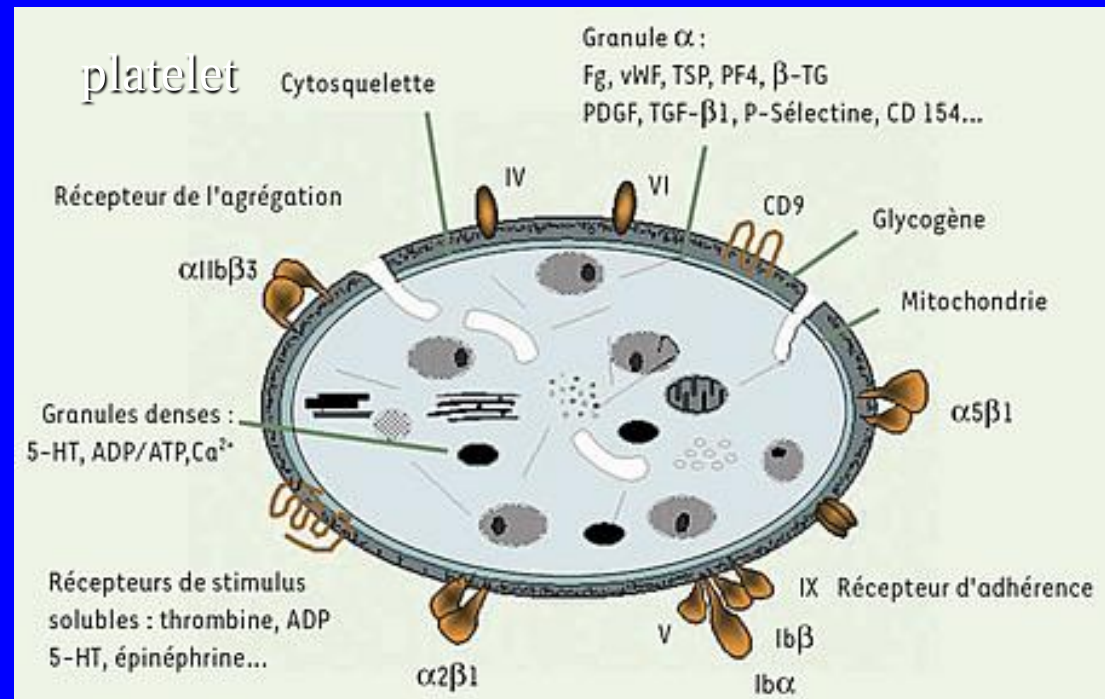
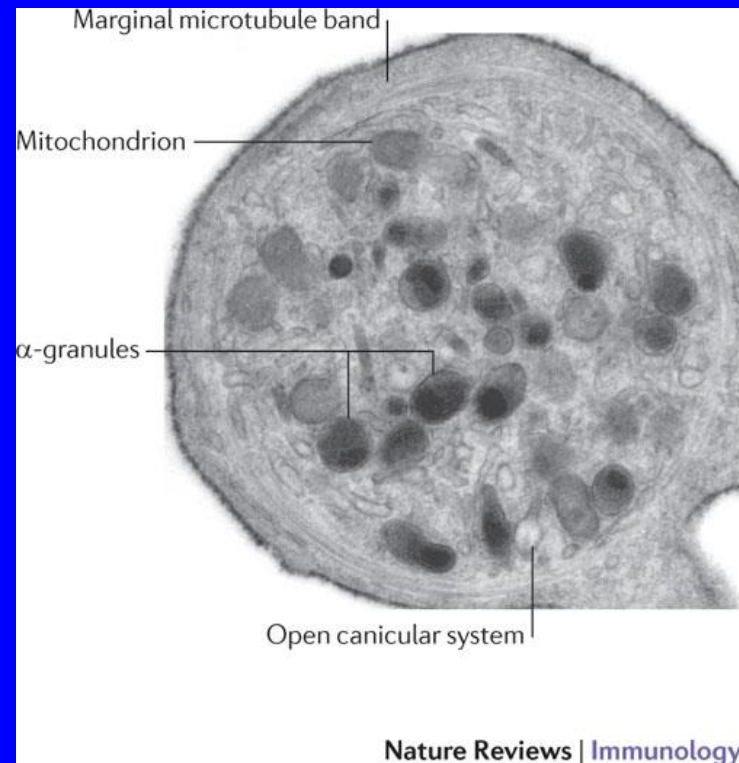
Plaquette sanguine



Plaquette sanguine



Plaquette sanguine



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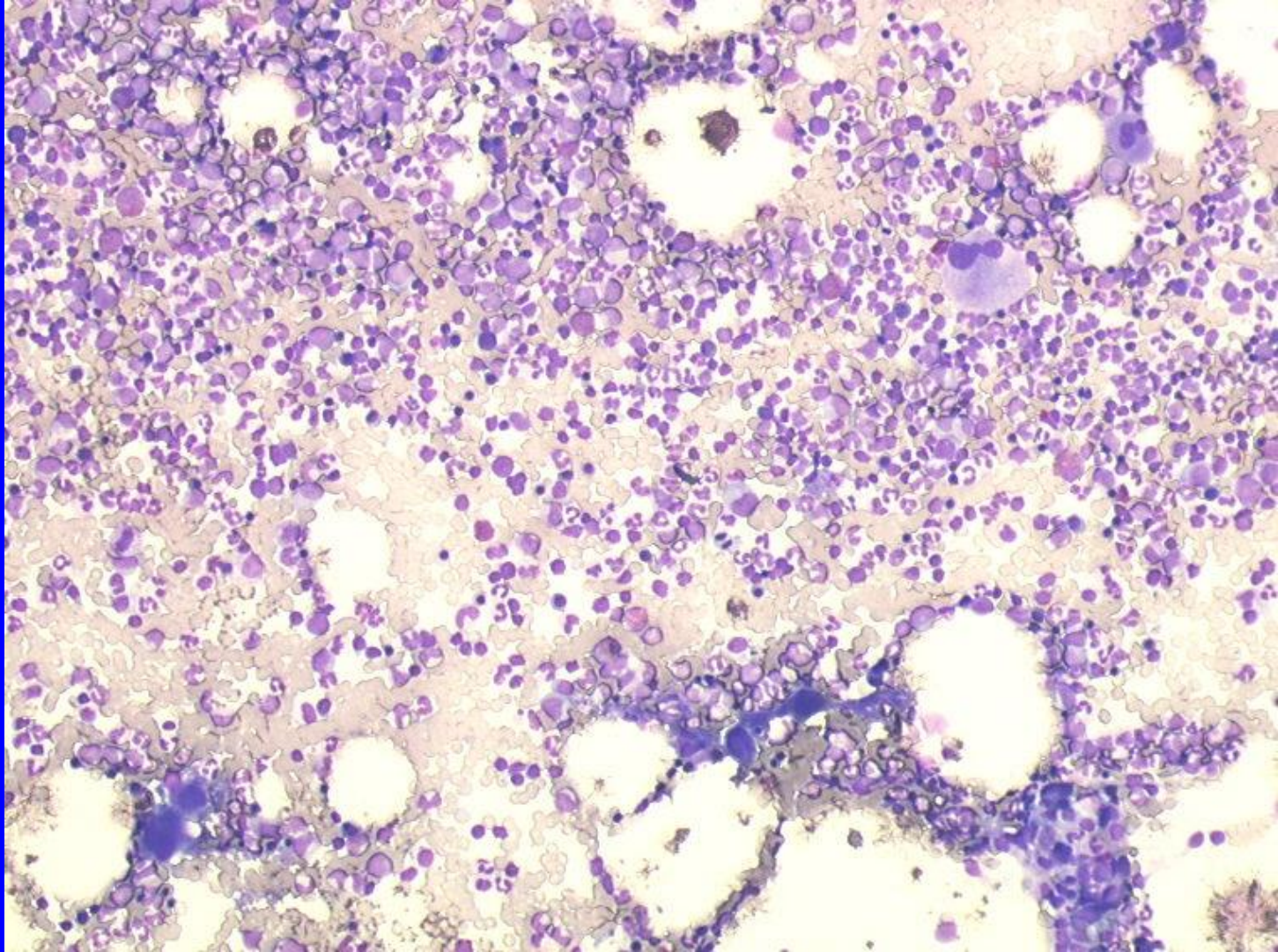
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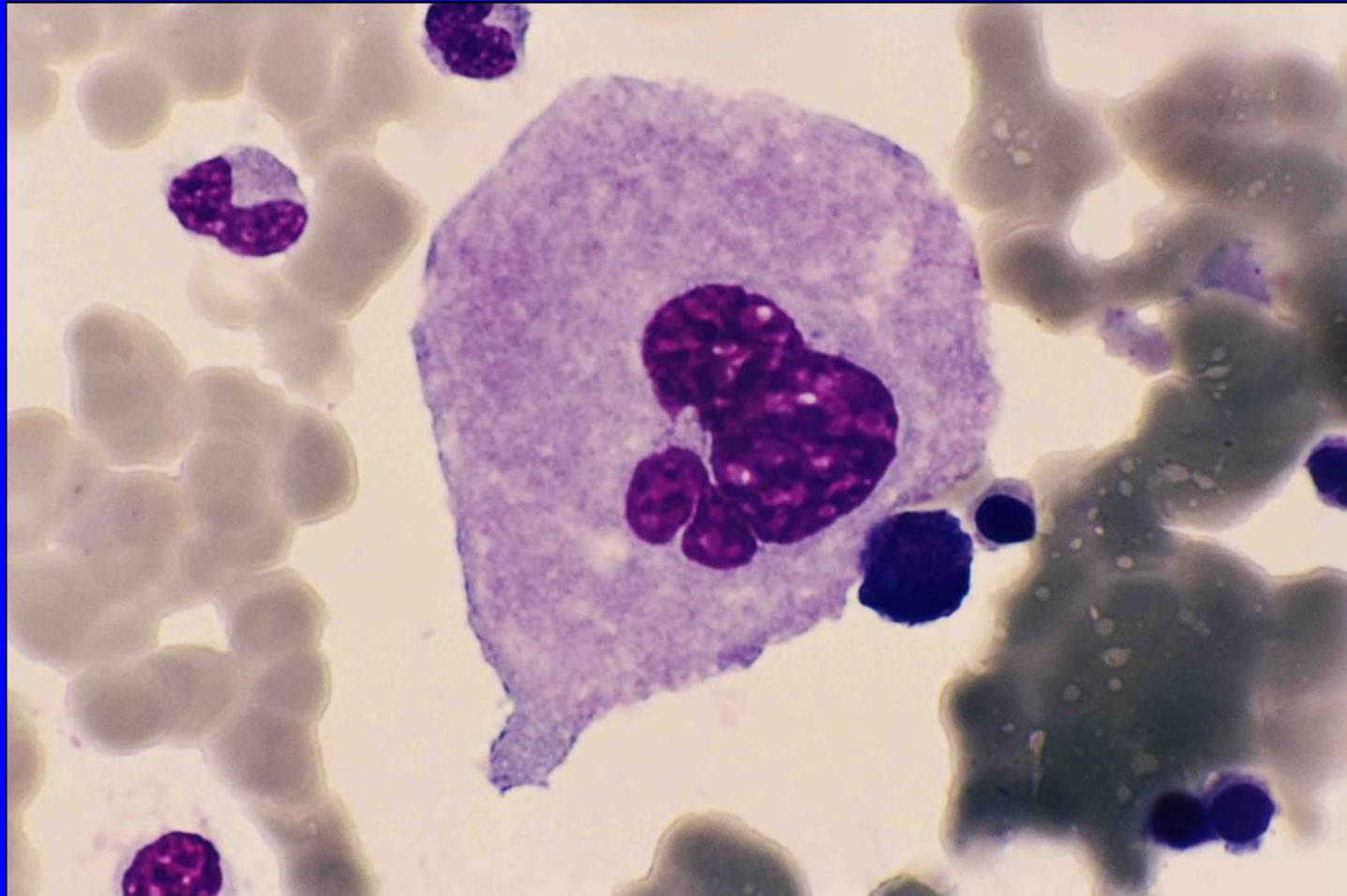
1994: *mpl* et Thrombopoïétine

2016: rupture mégacaryocytaire (IL-1^α)

1910: Megakaryocyte (Wright)



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A humoral factor controls platelet production.

1967: Mesure de la production plaquettaire (Odell)

Méthode isotopique

LA PRODUCTION DES PLAQUETTES

EST CONTROLEE

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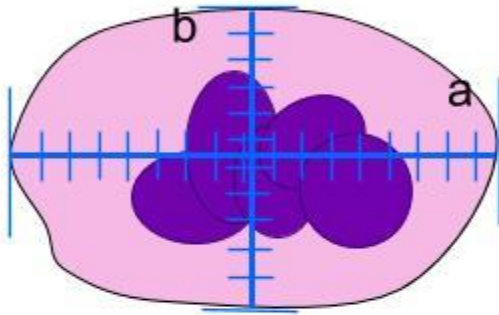
1994: *mpl* et Thrombopoïétine

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Morphometry of Megakaryocytes

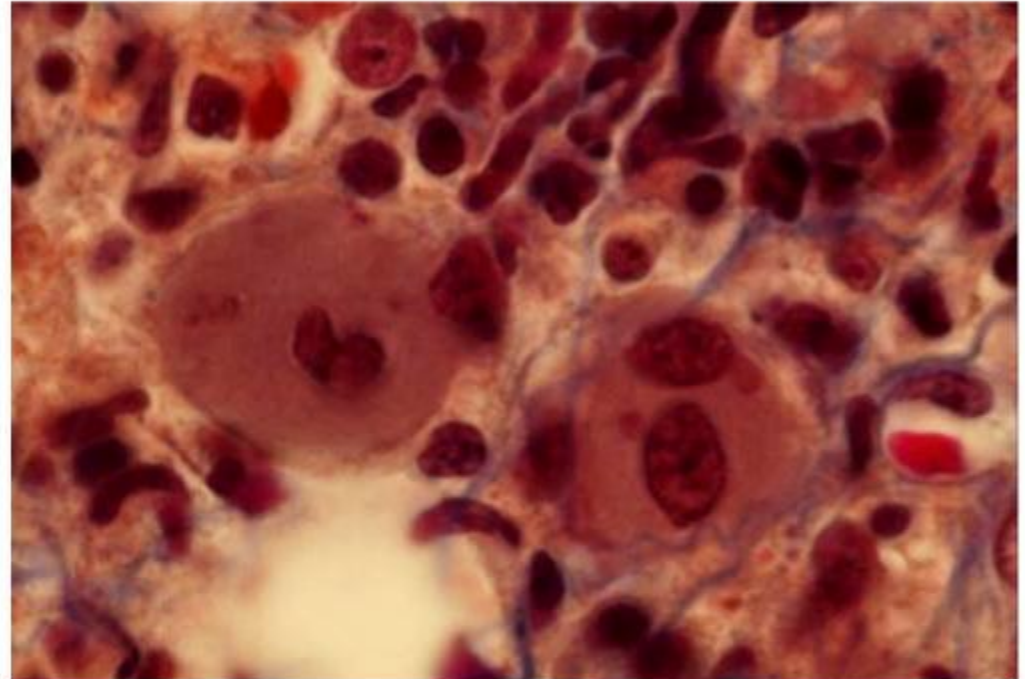
Mean volume of megakaryocyte

Biopsy



a = largest diameter of MK

b = largest perpendicular diameter of a

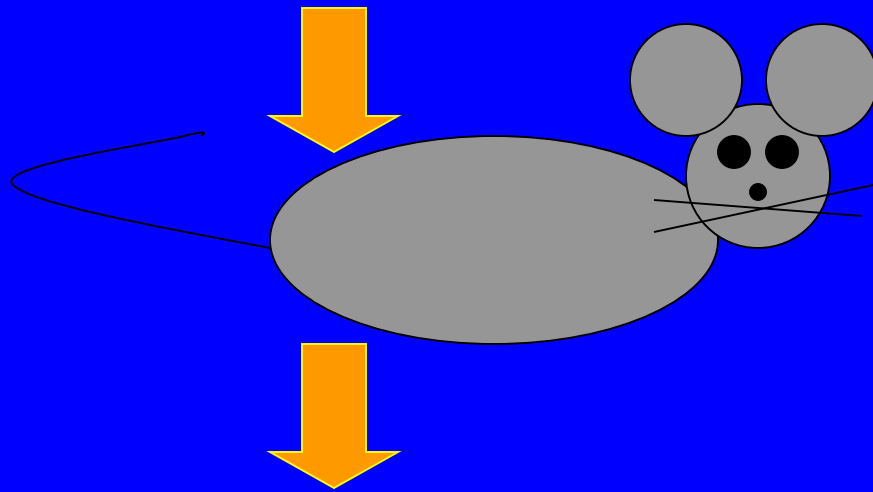


1. Elliptic mean* =
$$\sqrt{\frac{(a^2 + b^2)}{2}}$$

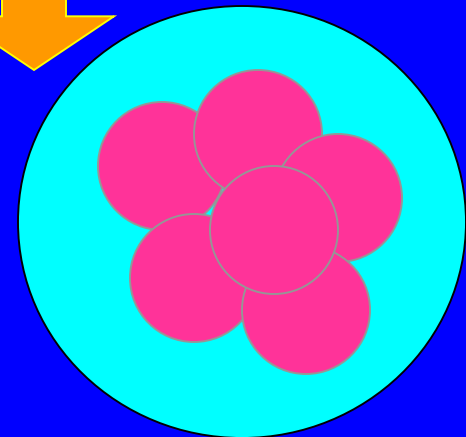
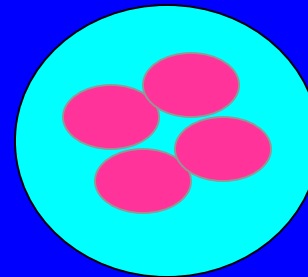
* For a minimum of 50 Megakaryocytes

1968: Le Nombre, la Taille et la Ploïdie des mégacaryocytes sont sous contrôle (Harker)

Sérum anti-plaquettaire

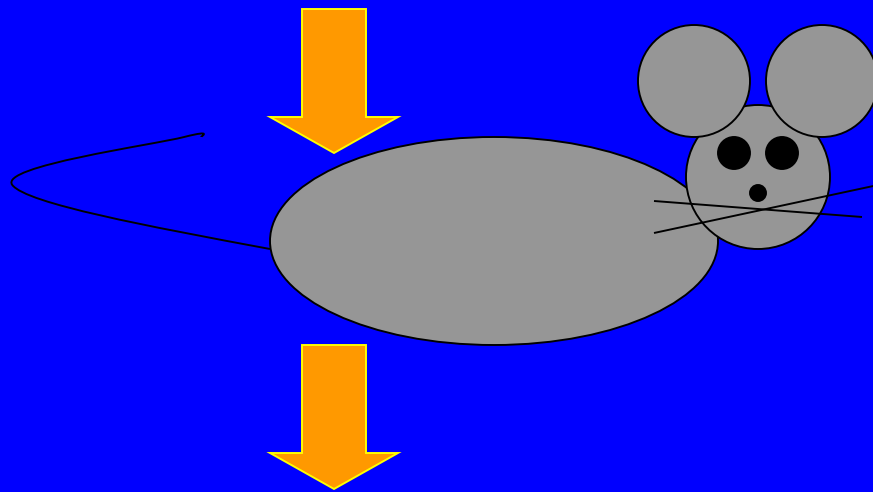


Thrombocytopénie

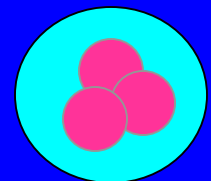
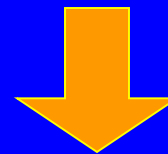
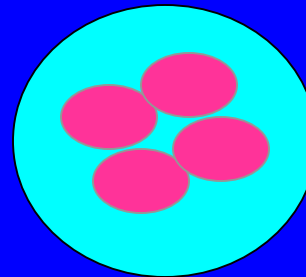


1968: Le Nombre, la Taille et la Ploïdie des mégacaryocytes sont sous contrôle (Harker)

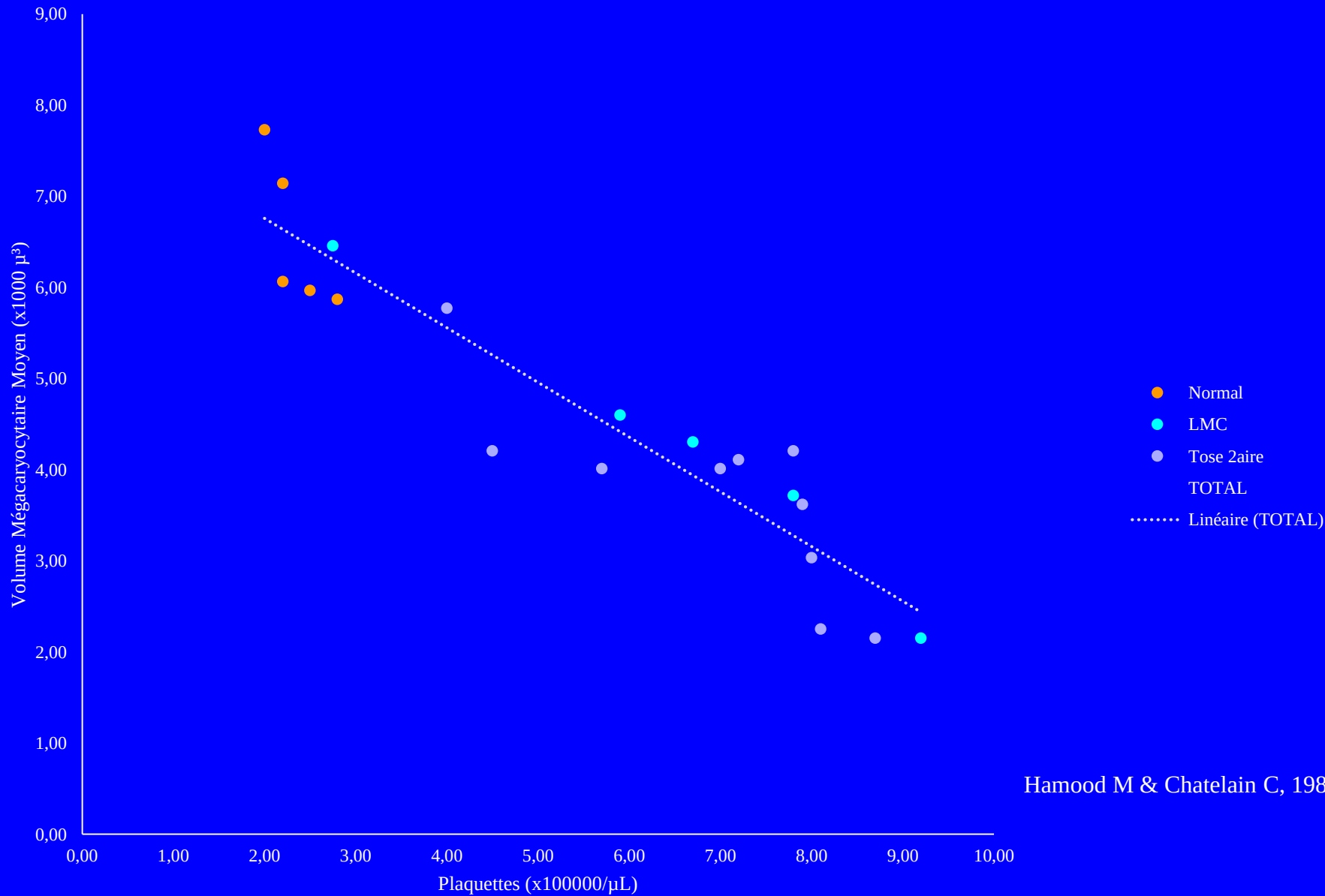
Transfusion de plaquettes



Thrombocythémie

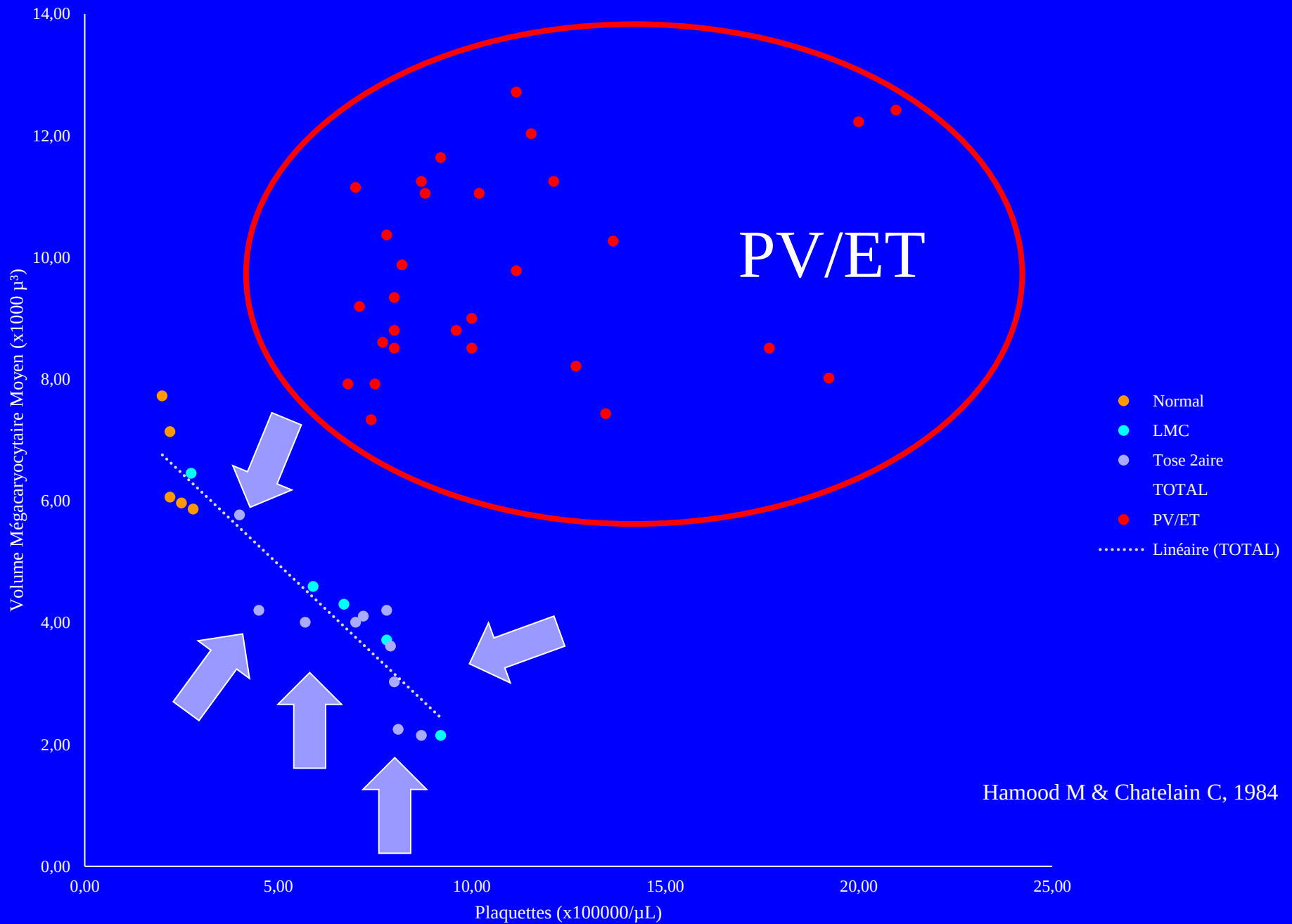


Morphométrie



Hamood M & Chatelain C, 1984

Morphométrie



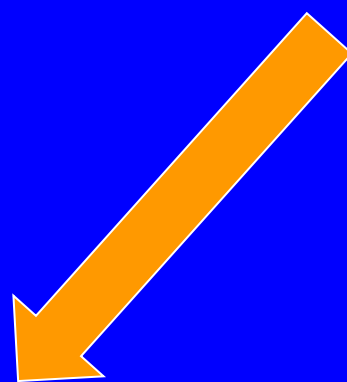
HYPERPLAQUETTOSE REACTIONNELLE vs PRIMITIVE



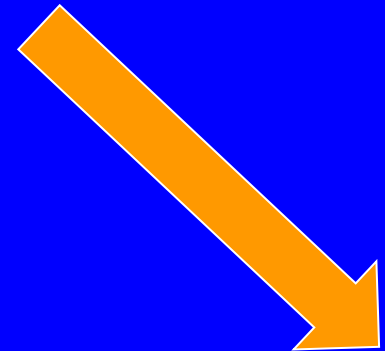
Effort, stress, adrénaline
Infection, inflammation
Carence en fer
Cancer
Vincristine
Asplénie



SMP



LMC



TE
Vaquez

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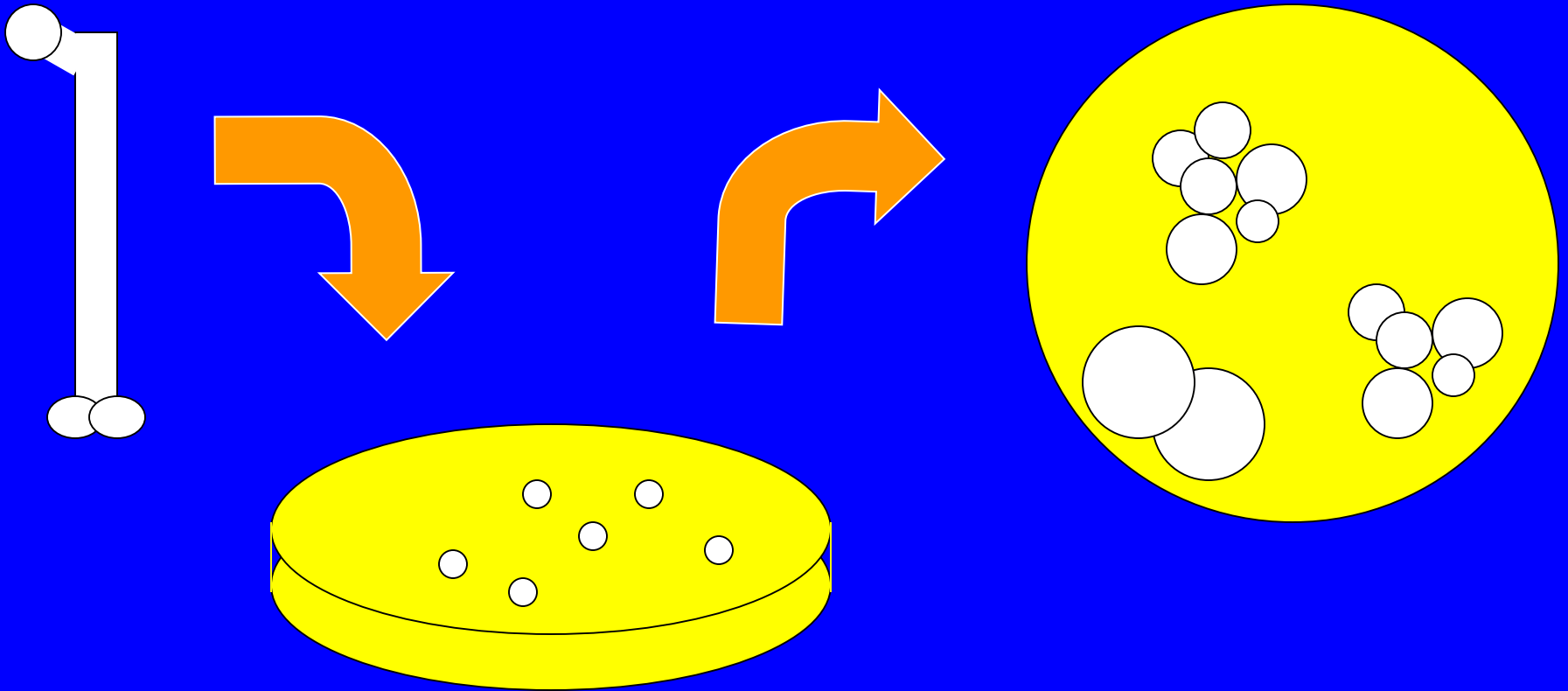
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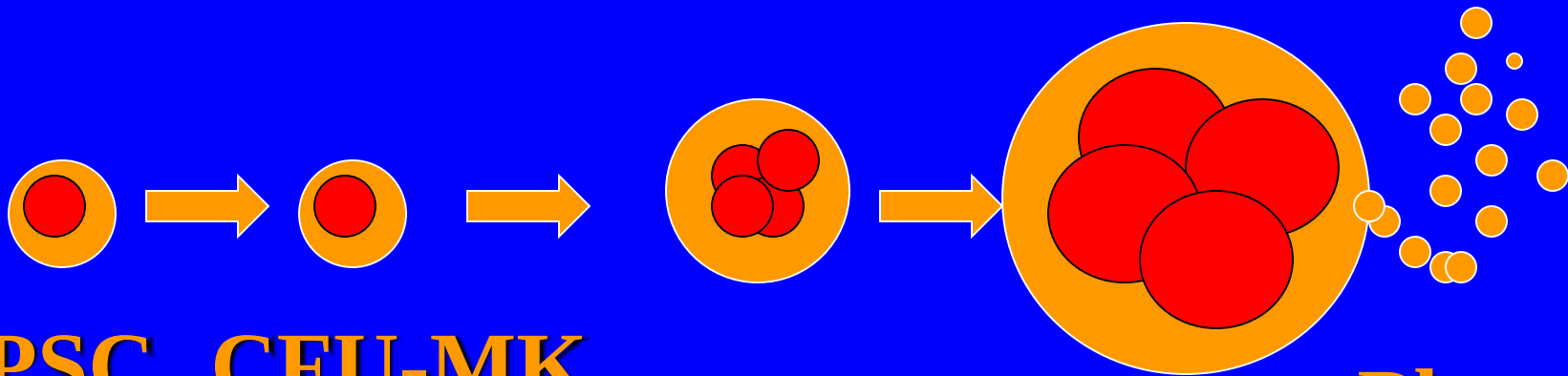
1994: *mpl* et Thrombopoïétine

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Hiérarchie cellulaire



PSC **CFU-MK**

Mégacaryocytes

Plaquettes

Lithium Enhancement of Megakaryocytopoiesis in Culture: Mediation via Accessory Marrow Cells

By Christian Chatelain, Samuel A. Burstein, and Laurence A. Harker

Blood, Vol. 62, No. 1 (July), 1983: pp. 172–176

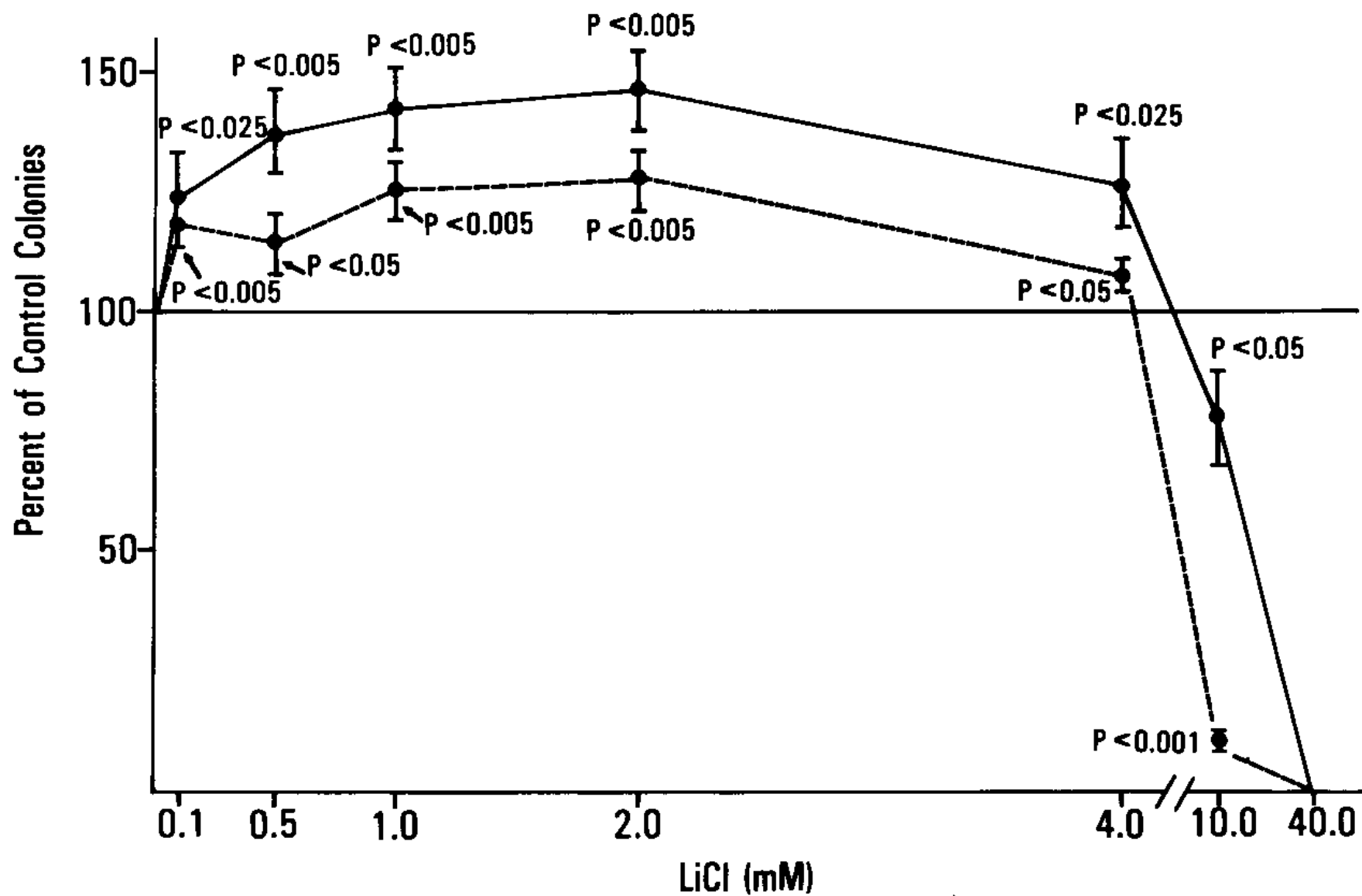
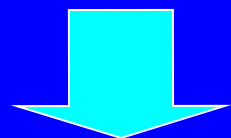
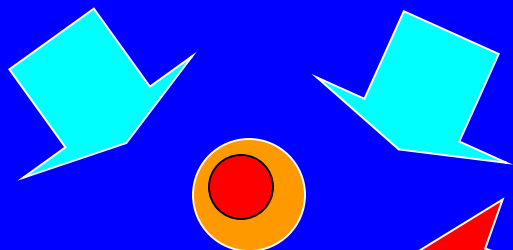


Table 1. The Influence of CyA on Lithium-Stimulated Colony Growth

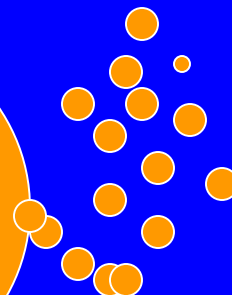
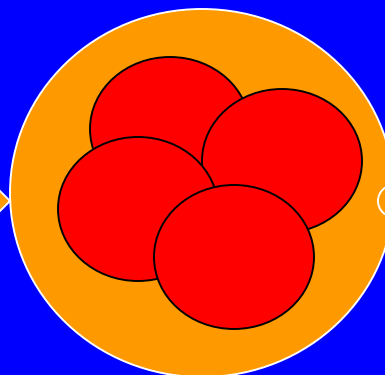
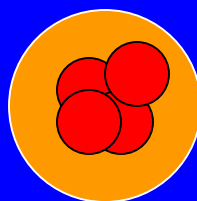
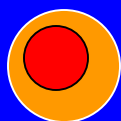
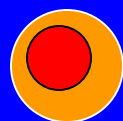
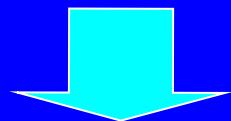
	CFU-M	CFU-C
Control	24 $\pm$ 1*	80 $\pm$ 11
CyA (3 μ g/ml)	24 $\pm$ 1	78 $\pm$ 10
Li ⁺ (2 mM LiCl)	32 $\pm$ 1	117 $\pm$ 13
Li + CyA	24 $\pm$ 1	82 $\pm$ 13

LITHIUM

ACETYLCHOLINE



IL-3 GM-CSF



CYCLOSPORINE A

PSC CFU-MK

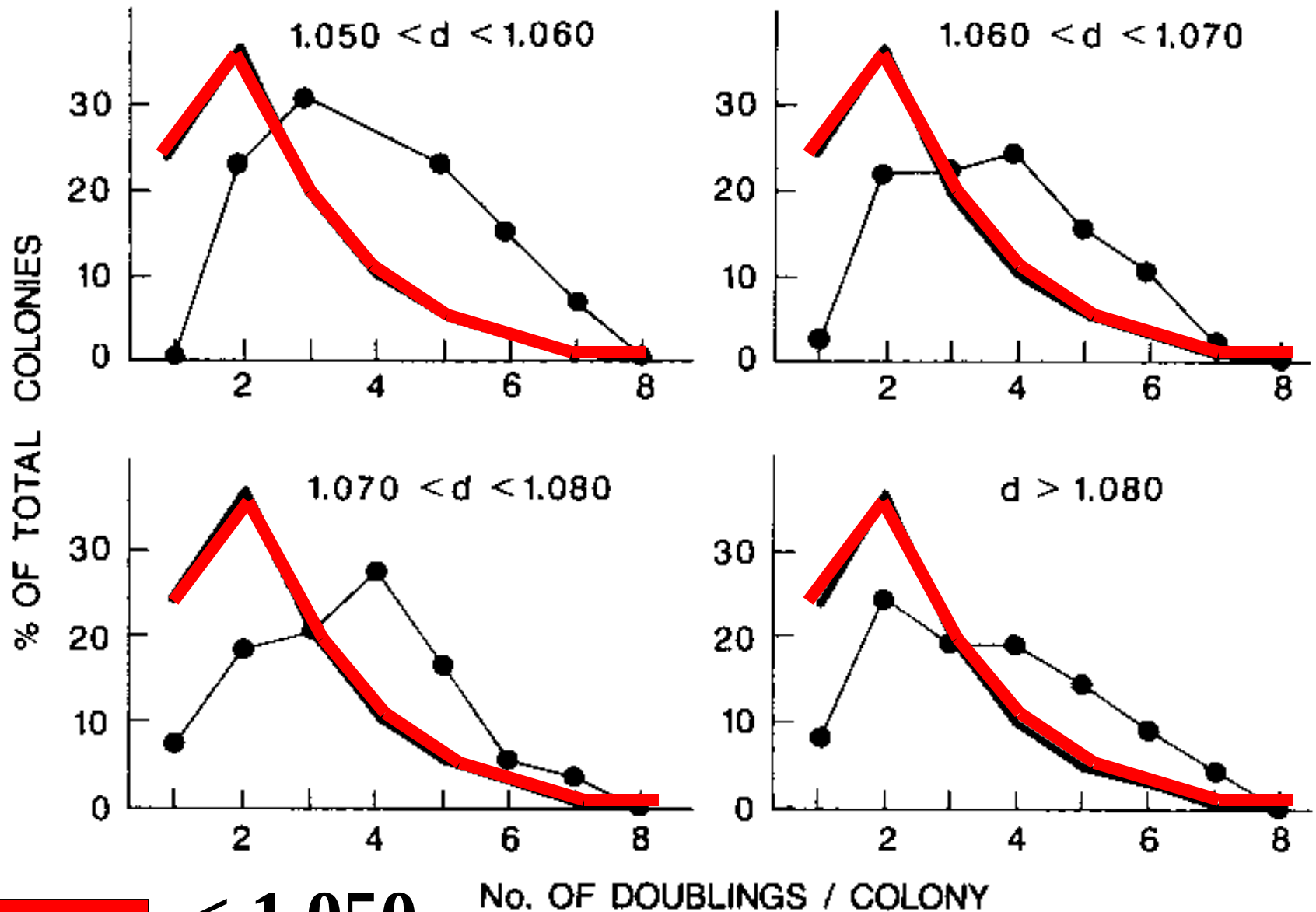
Mégacaryocytes Plaquettes

Identification of a Light Density Murine Megakaryocyte Progenitor (LD-CFU-M)

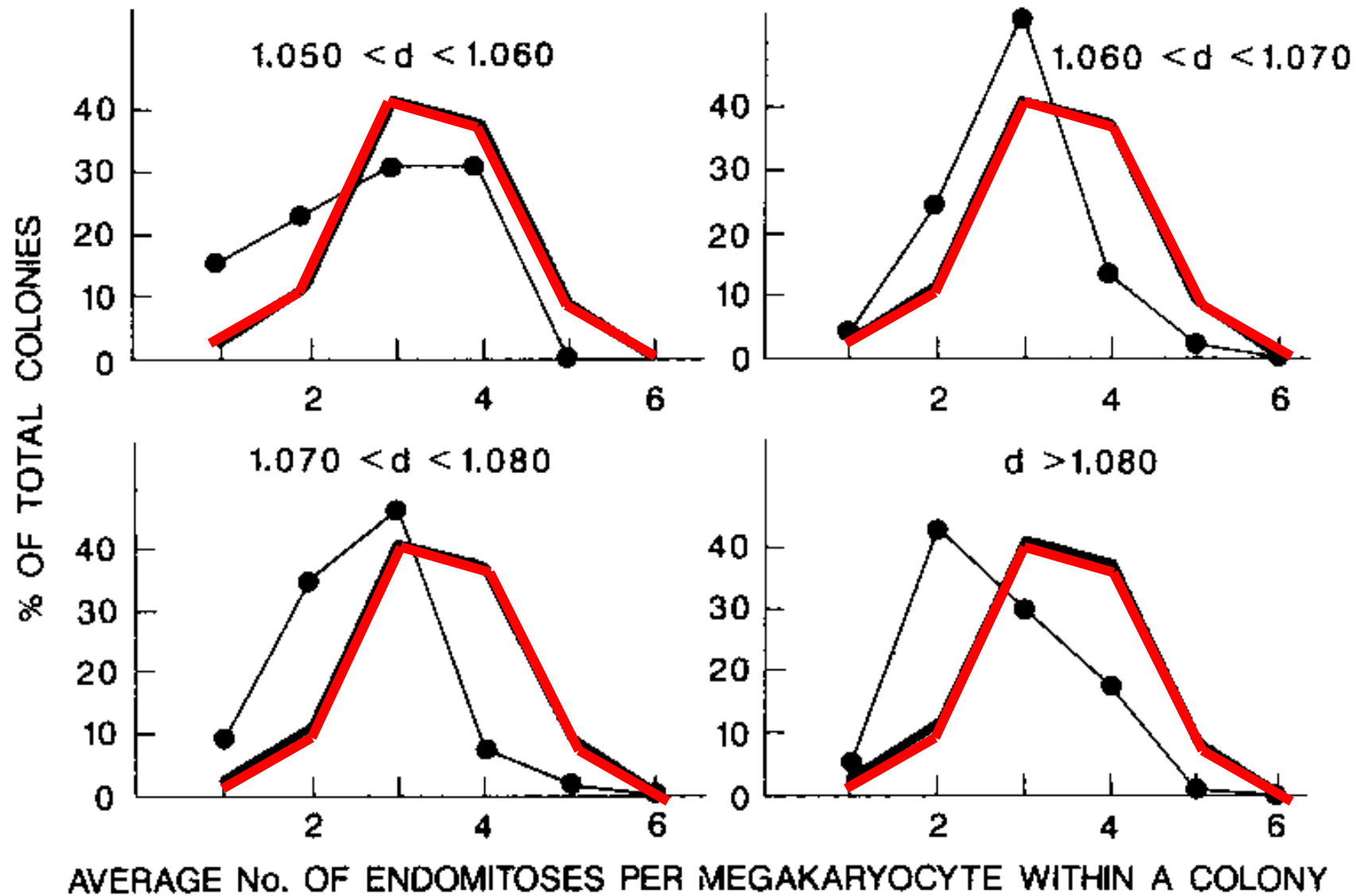
By Christian Chatelain, Marc De Bast, and Michel Symann

Blood, Vol 72, No 4 (October), 1988: pp 1187-1192

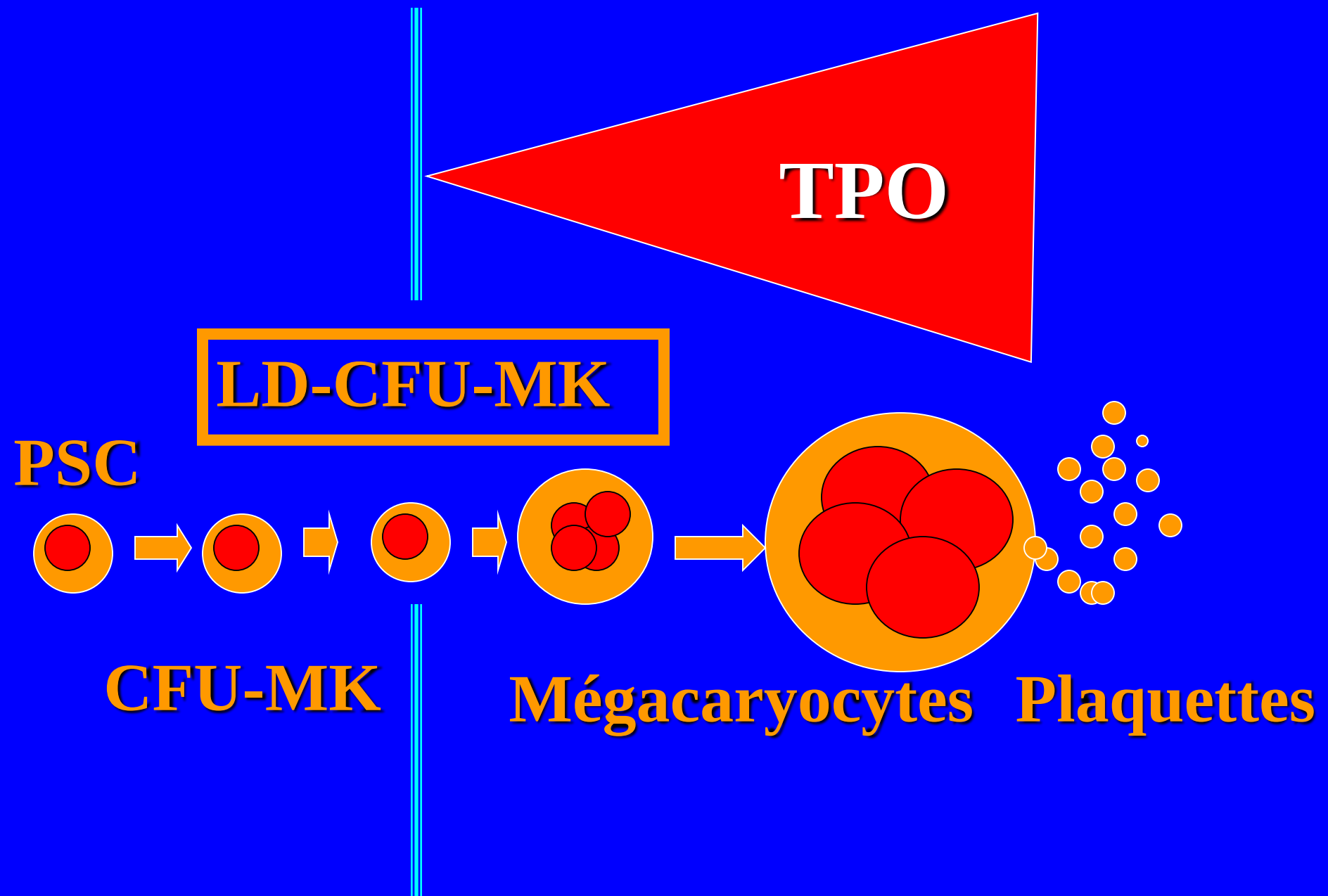
LD-CFU-MK



LD-CFU-MK



< 1.050



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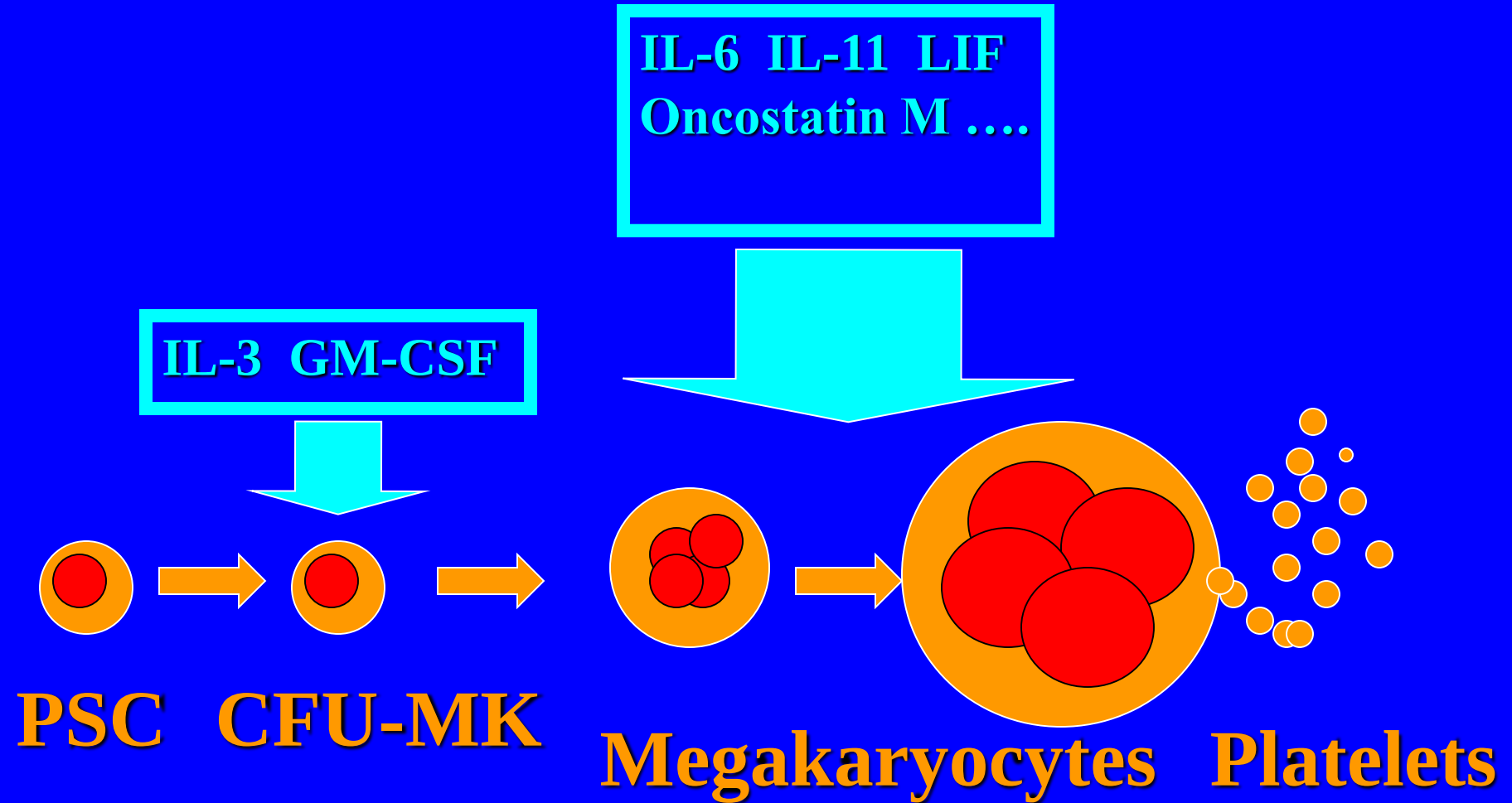
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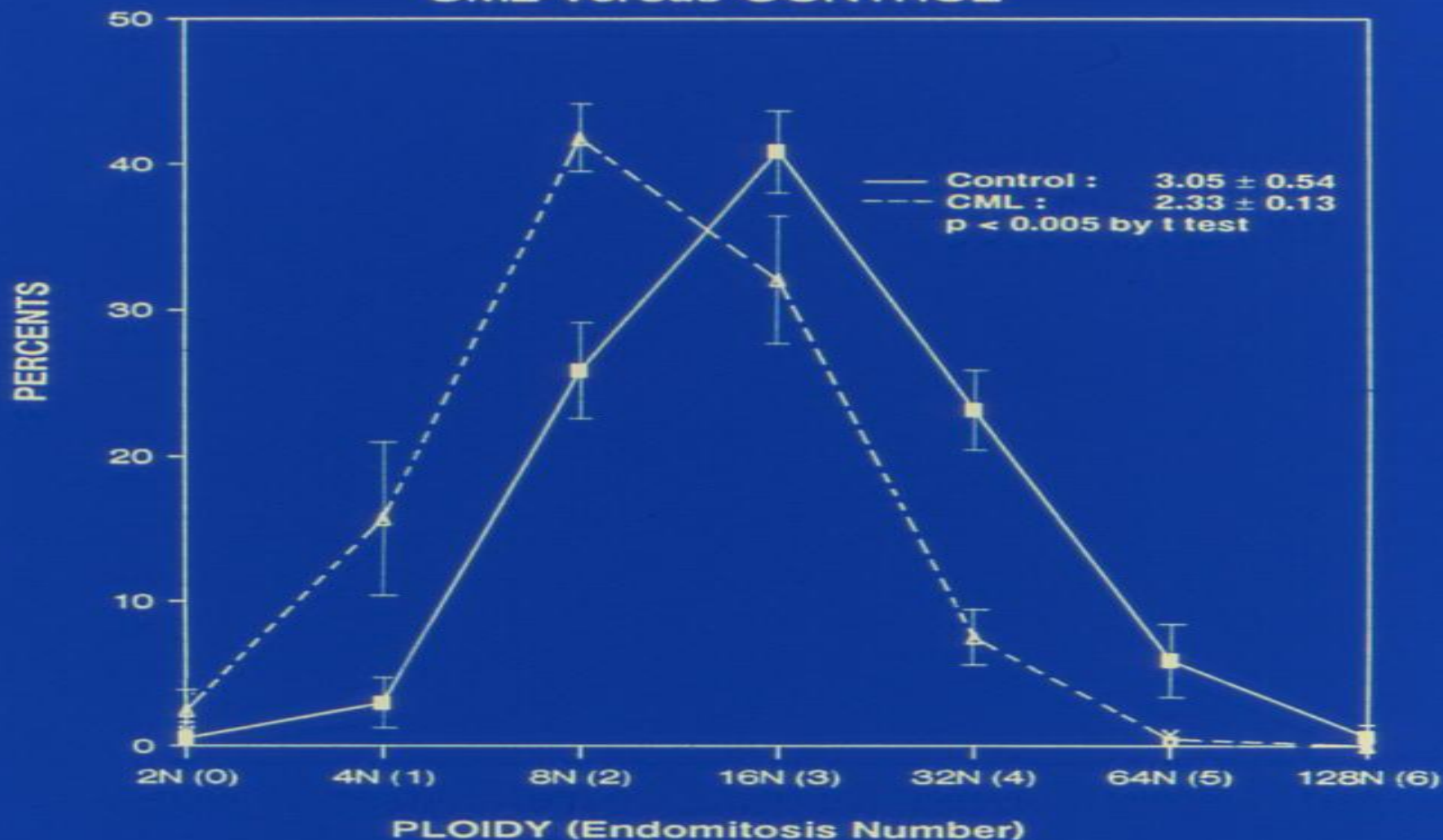


1983: Cytokines (Metcalf, Quesenberry,...)



MEGAKARYOCYTE PLOIDY DISTRIBUTION

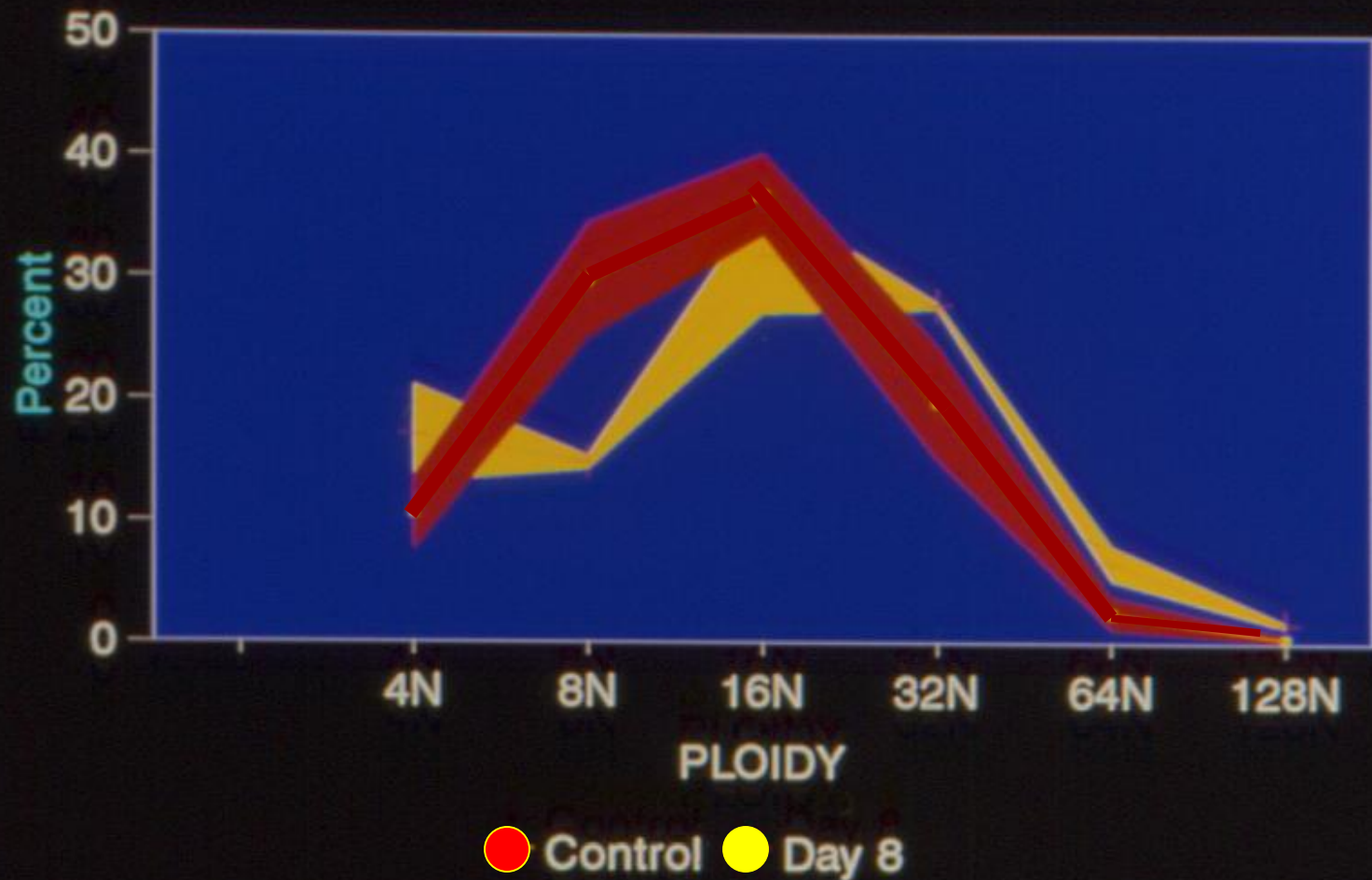
CML versus CONTROL



IL-6

MEGAKARYOCYTE PLOIDY DISTRIBUTION

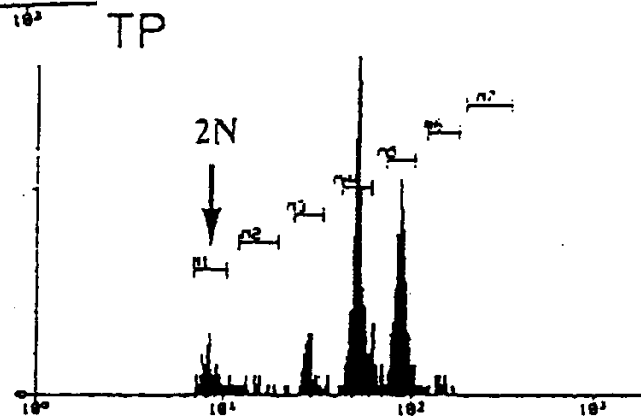
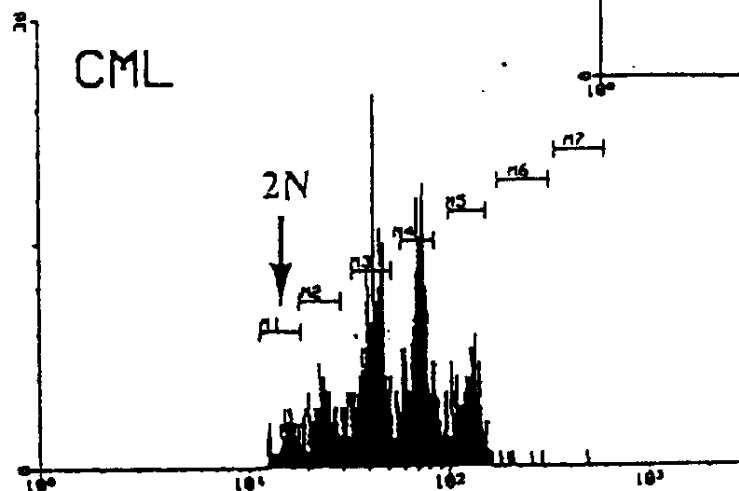
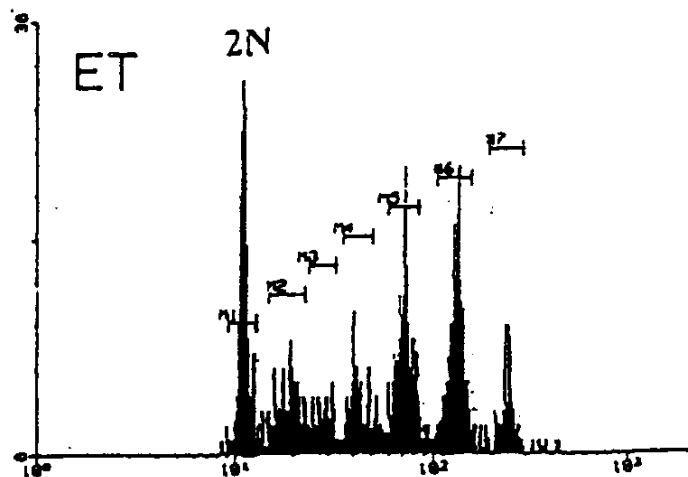
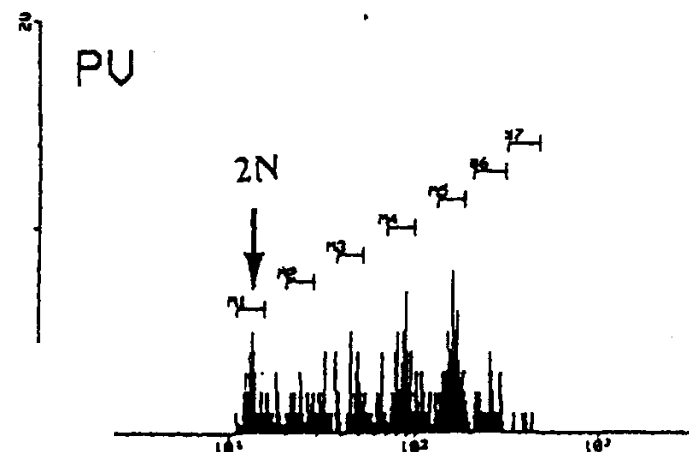
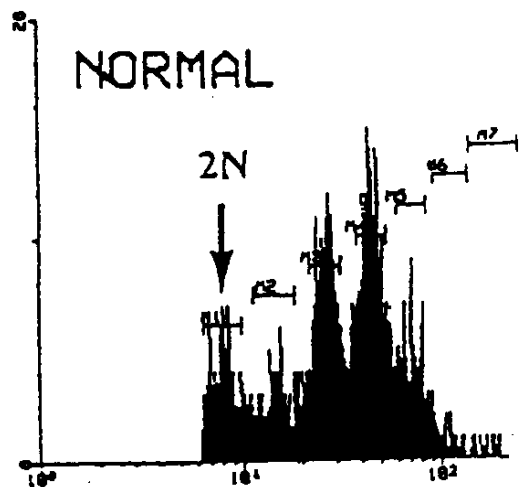
2 μ g

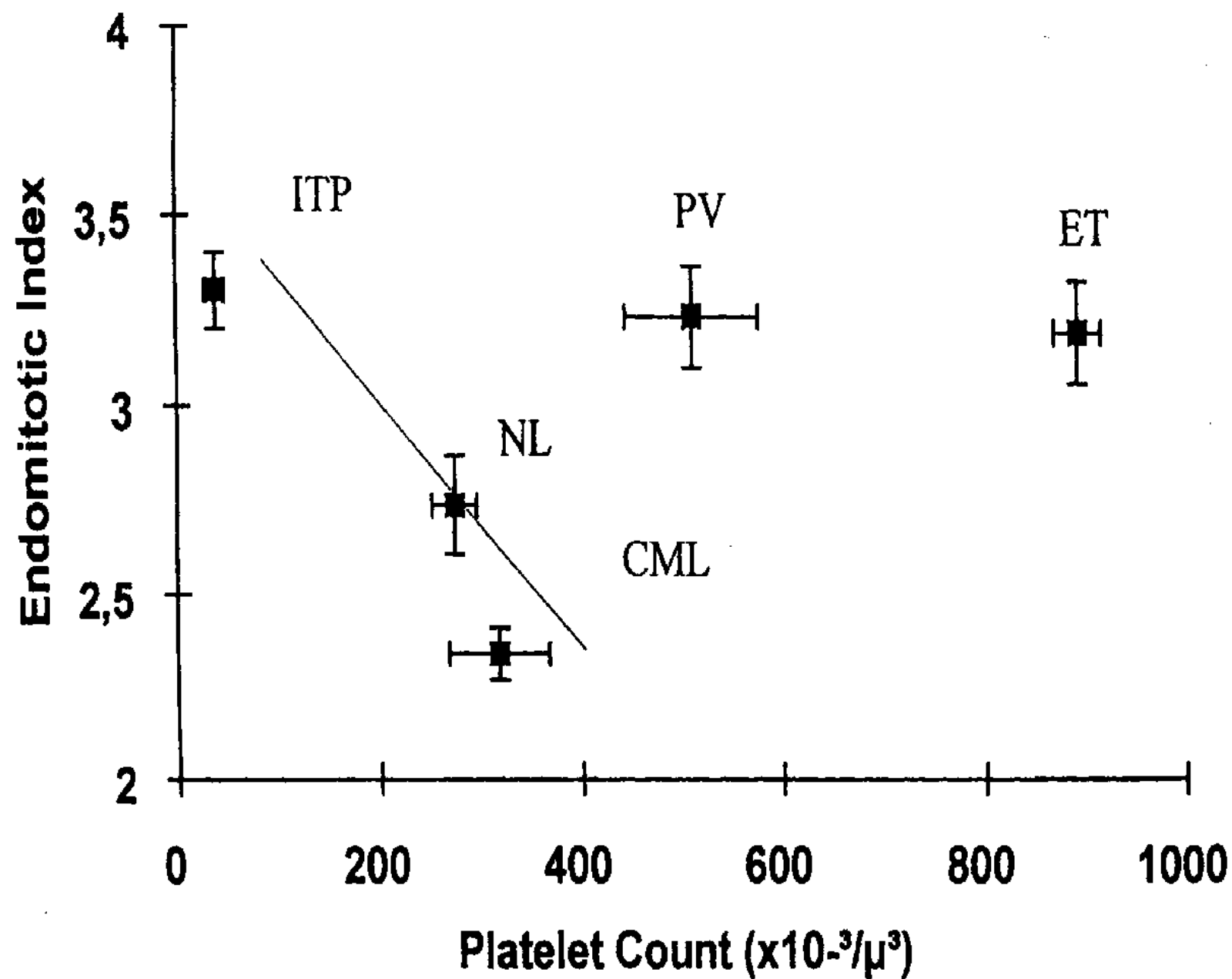


ANTICANCER RESEARCH 18: 3347-3354 (1998)

Endomitotic Index of Megakaryocytes Measured by Flow Cytometry Helps to Diagnose Hematological Disorders with Abnormal Platelet Counts

SARAH BAATOUT, BERNARD CHATELAIN, PHILIPPE STAQUET, MICHEL SYMANN
and CHRISTIAN CHATELAIN





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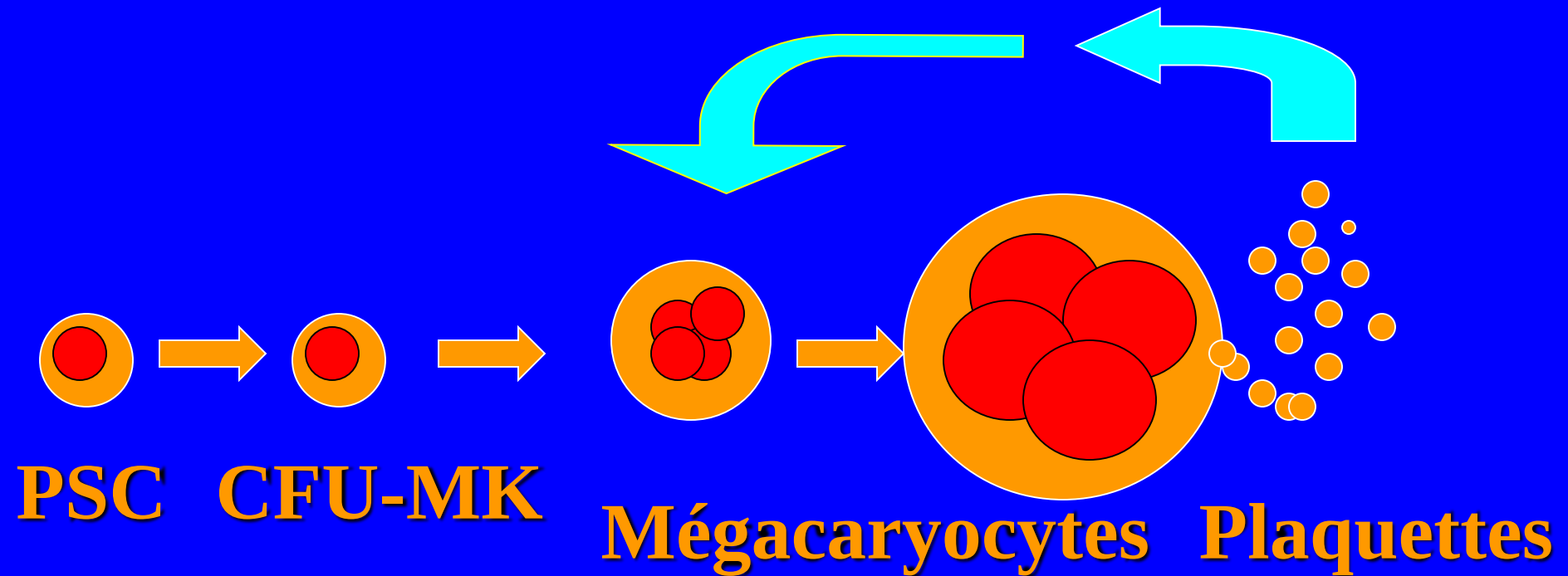
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2016: rupture mégacaryocytaire (IL-1^α)

1994: THROMBOPOIETINE (mpl ligand)

THROMBOPOIETINE



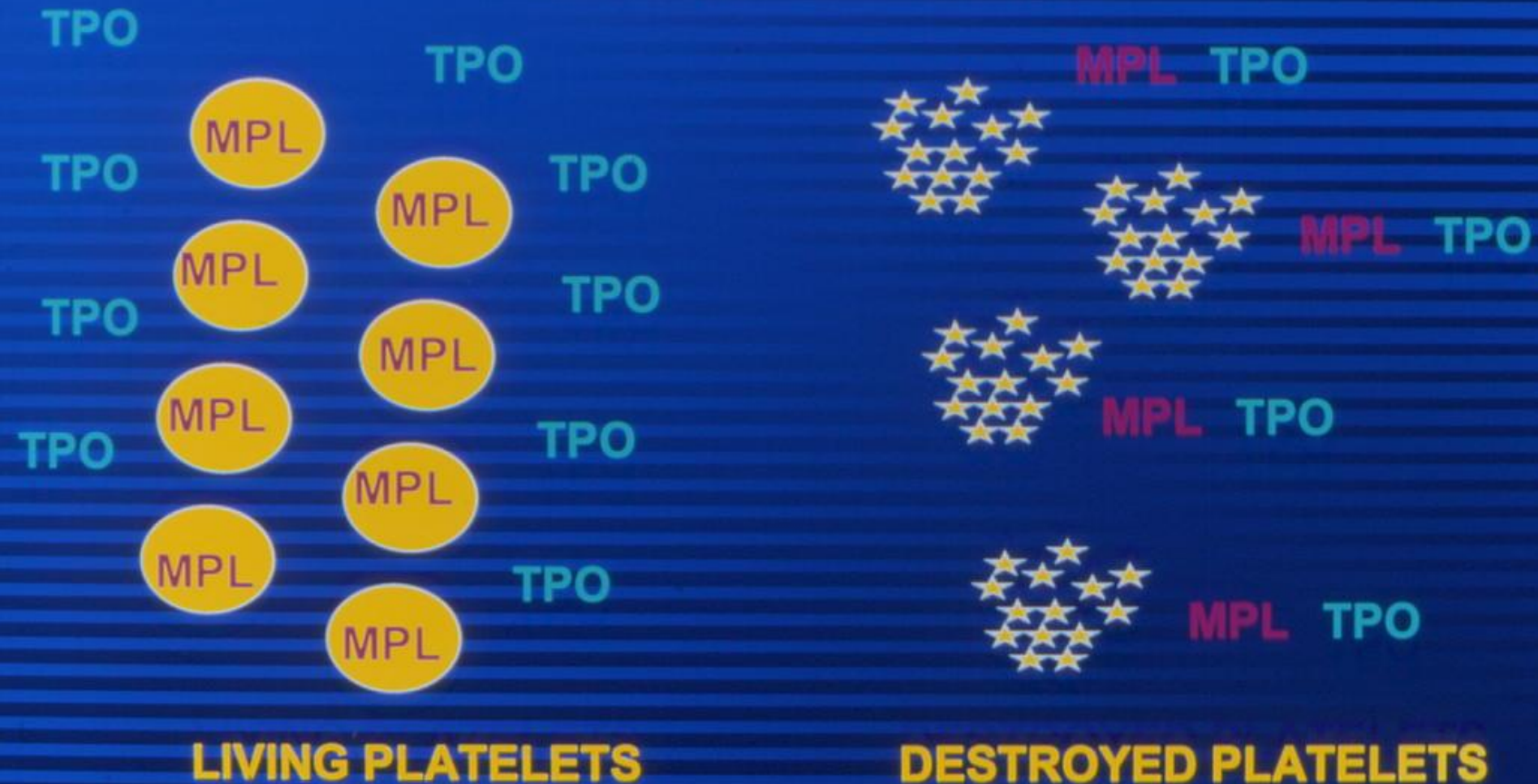
THROMBOPOIETINE

1. mpl oncogene
2. Production constante
3. Stimulates proliferation
4. Contrôle POLYPLOIDISATION
5. LD-CFU-MK
6. Régulation ‘ par produit final ’
c.a.d par les plaquettes

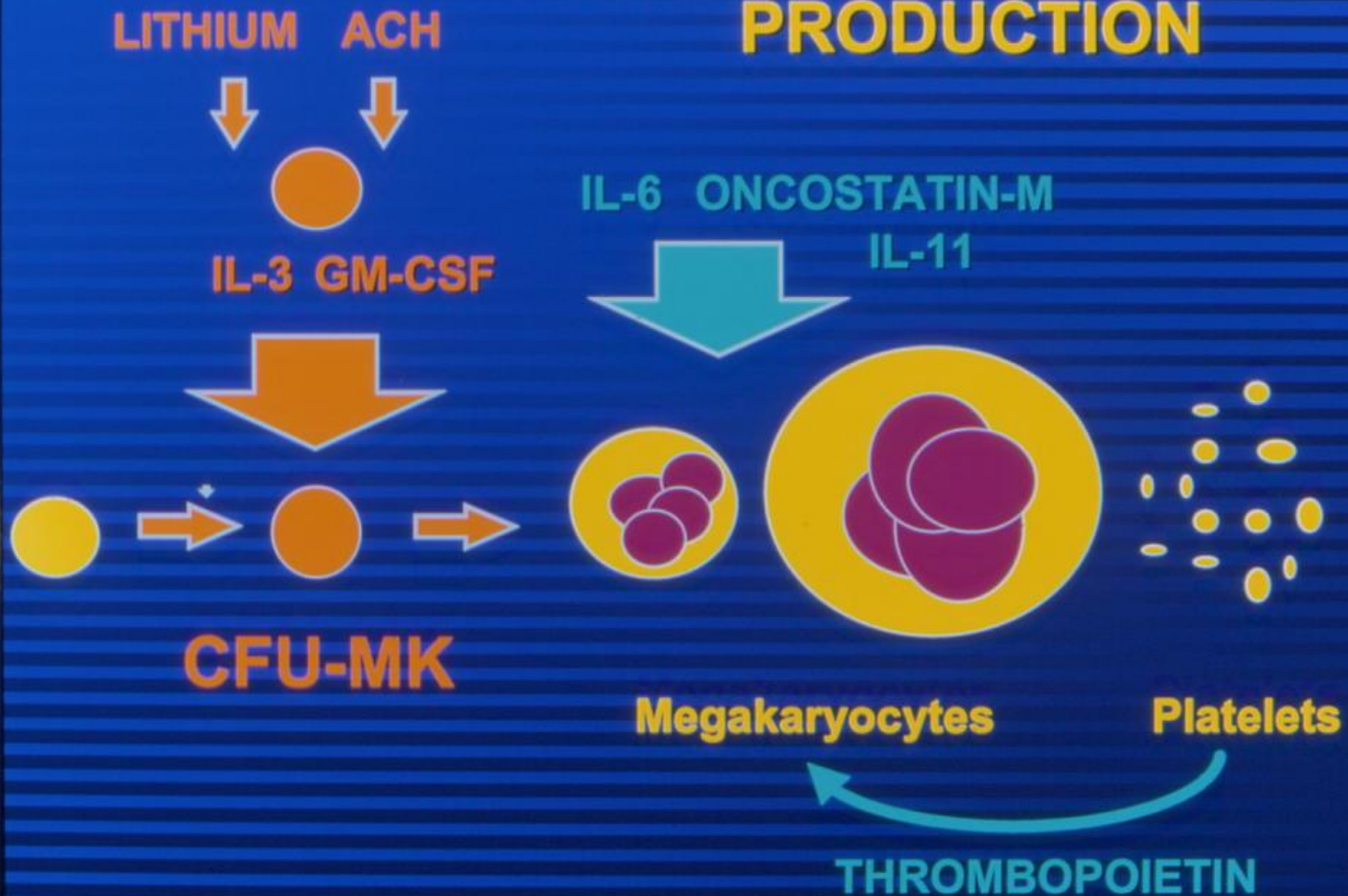
THROMBOPOIETINE



THROMBOPOIETIN REGULATION



CONTROL OF PLATELET PRODUCTION



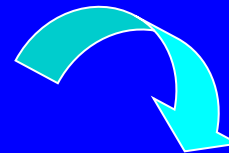
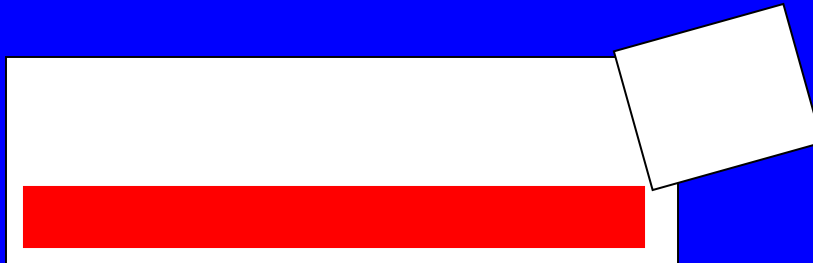
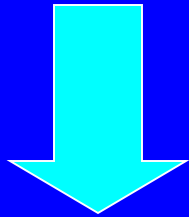
APPLICATION CLINIQUE DE LA THROMBOPOIETINE

1. rh-TPO: déception
2. Dosage : ITP, ...
3. Analogues TPO: Nplate® (Romiplostim)
et Revolade® (Eltrombopag) PTI
4. Production *in vitro* de plaquettes

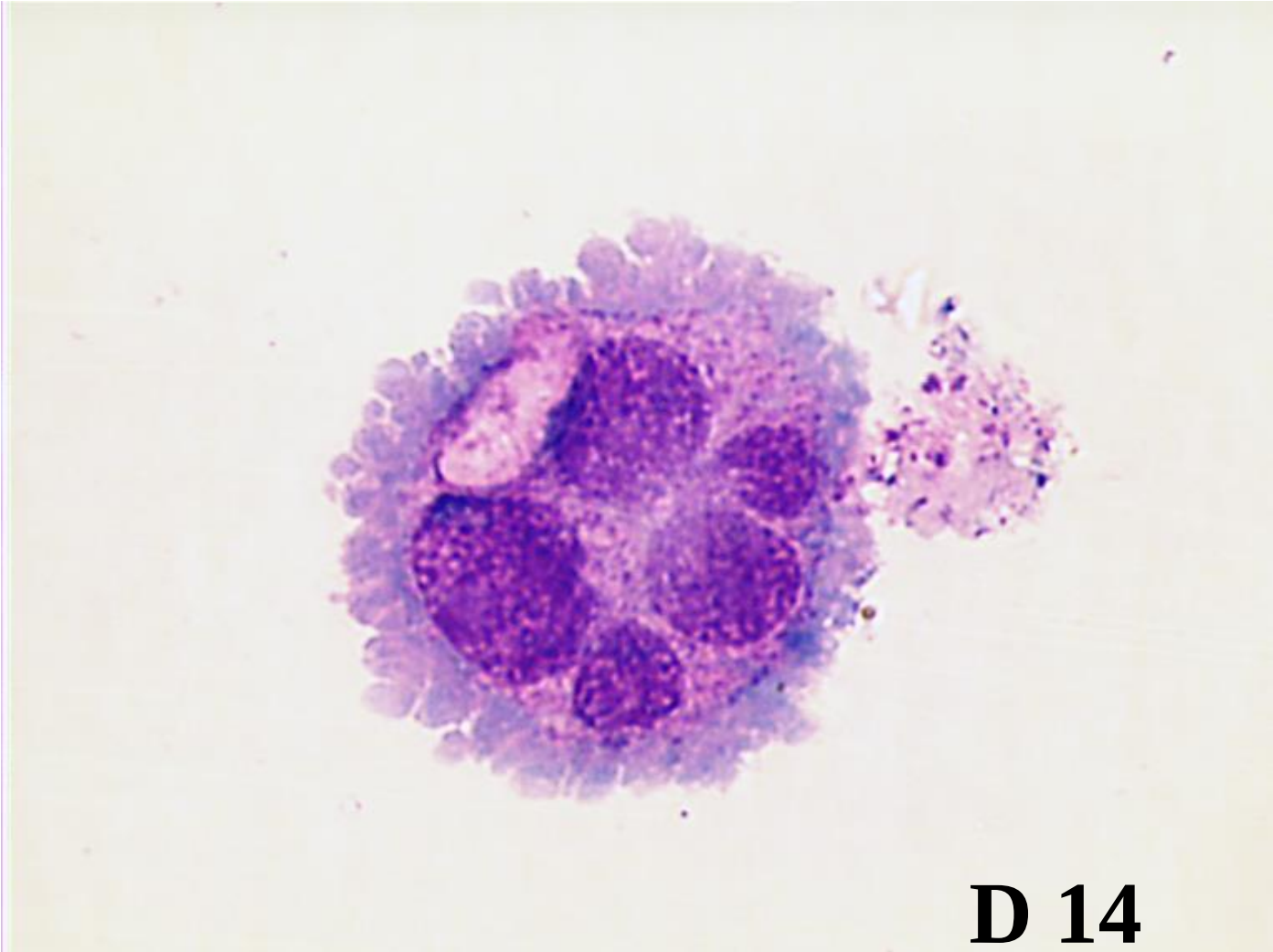
Platelet production in vitro

CD34 + cells

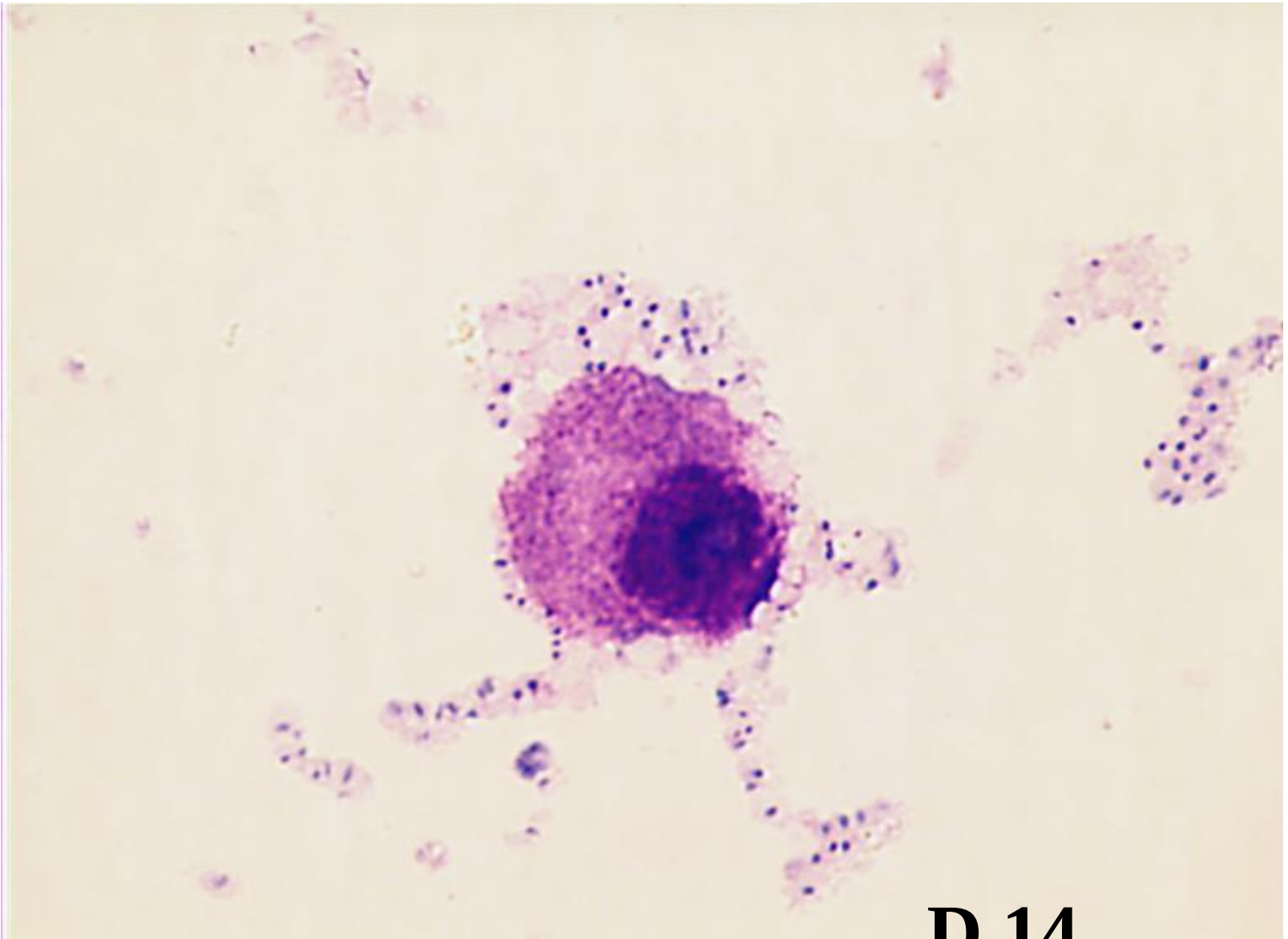
7-14 days



Platelets



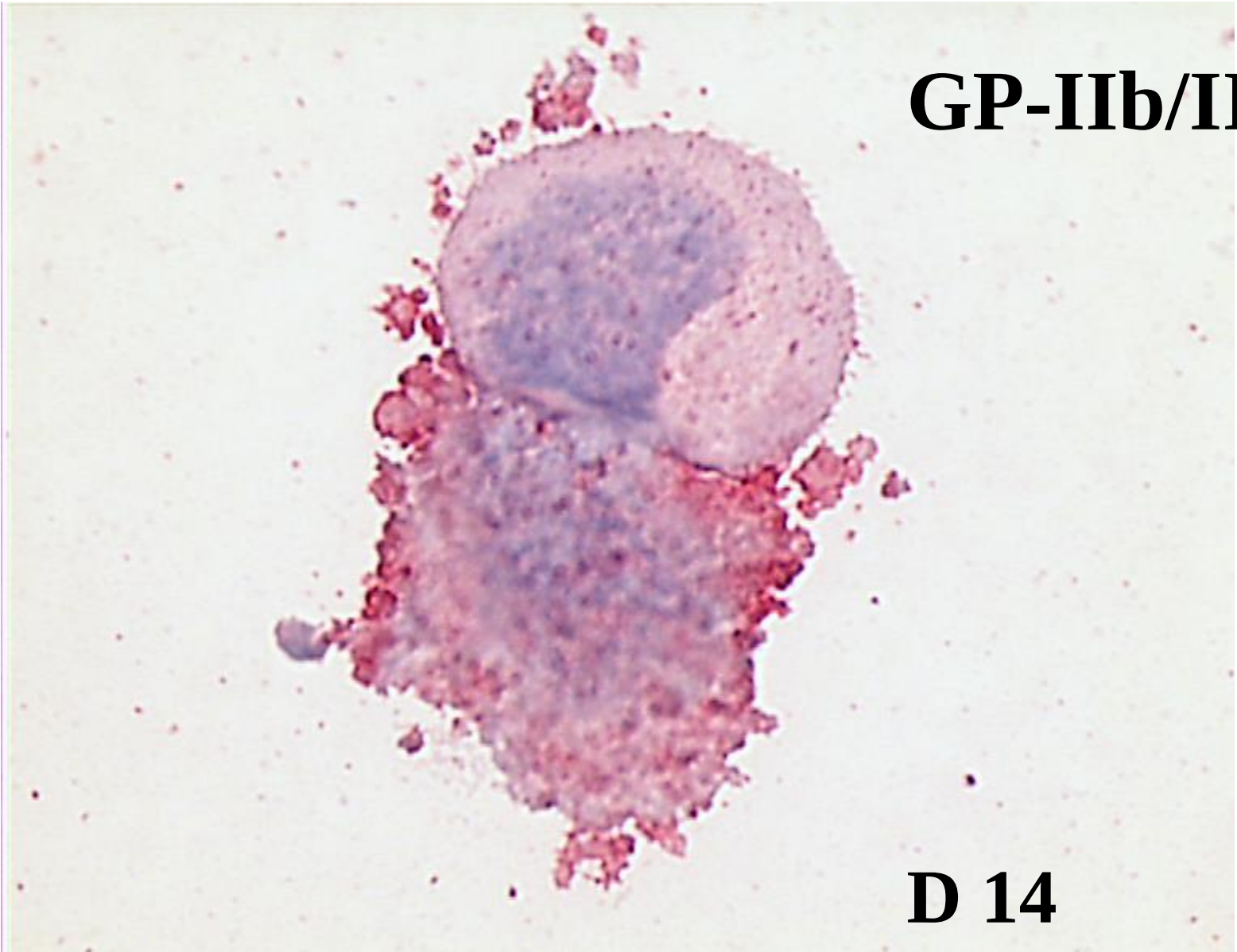
D 14

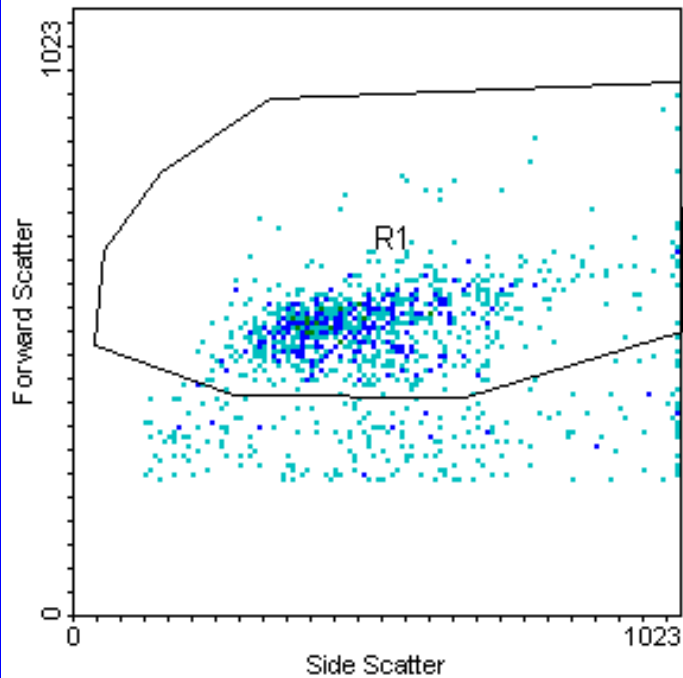


D 14

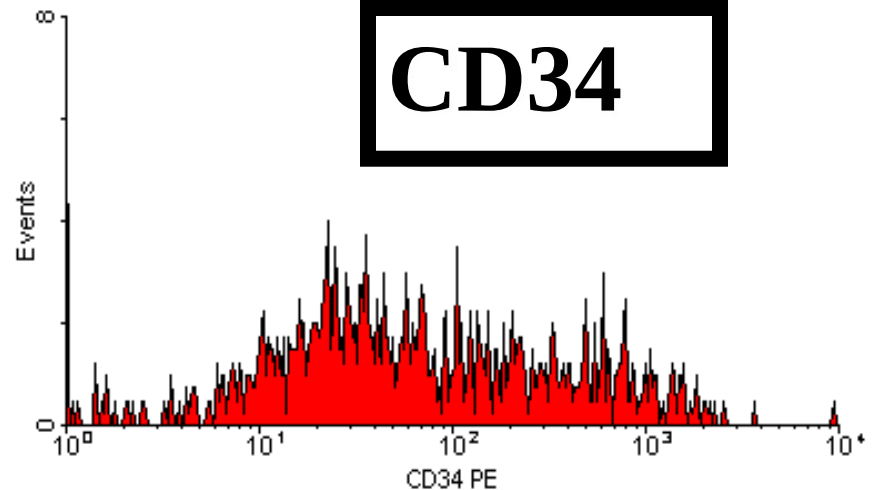
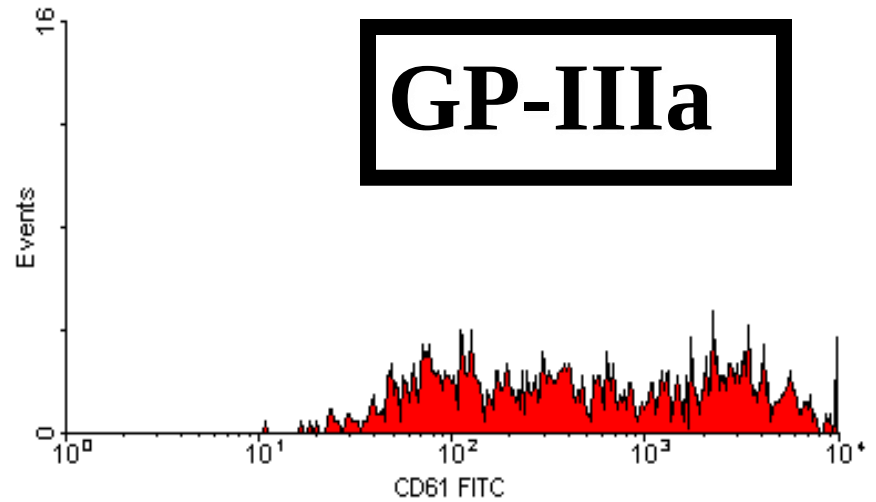
GP-IIb/IIIa

D 14

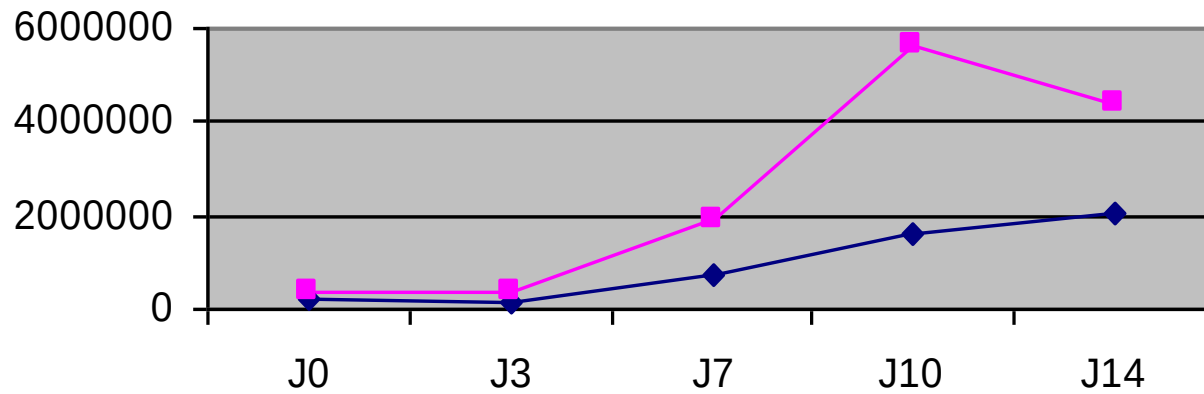




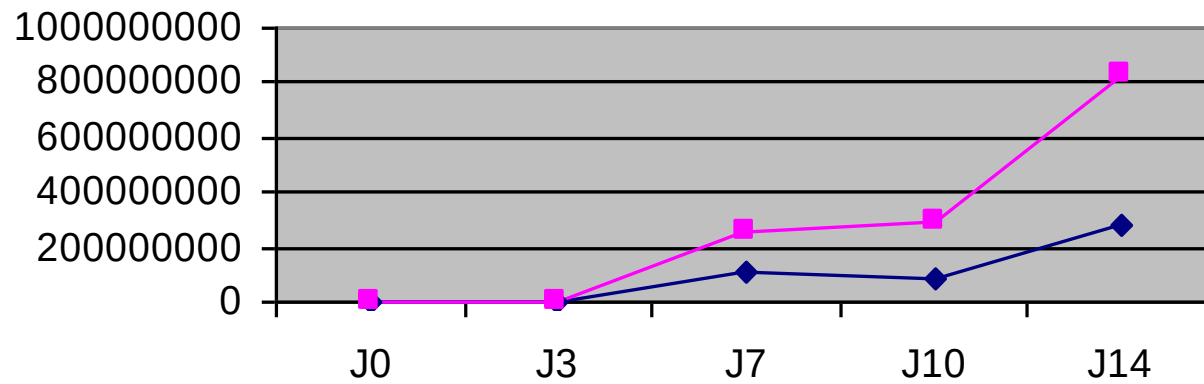
**Forward vs side
Scatter (d14)**



Cells



Platelets



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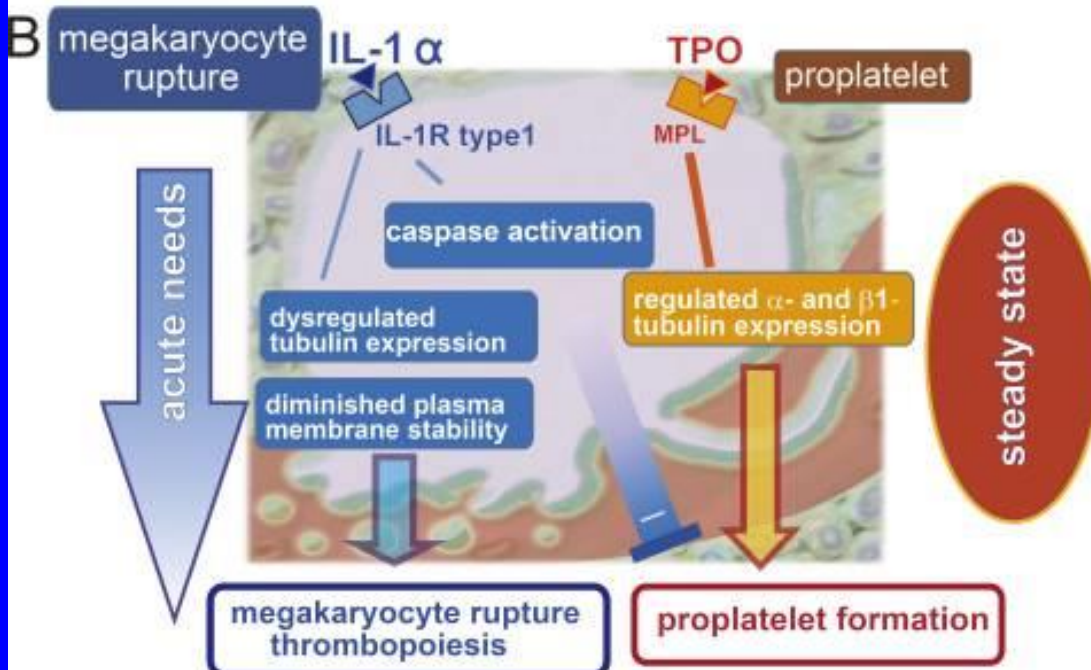
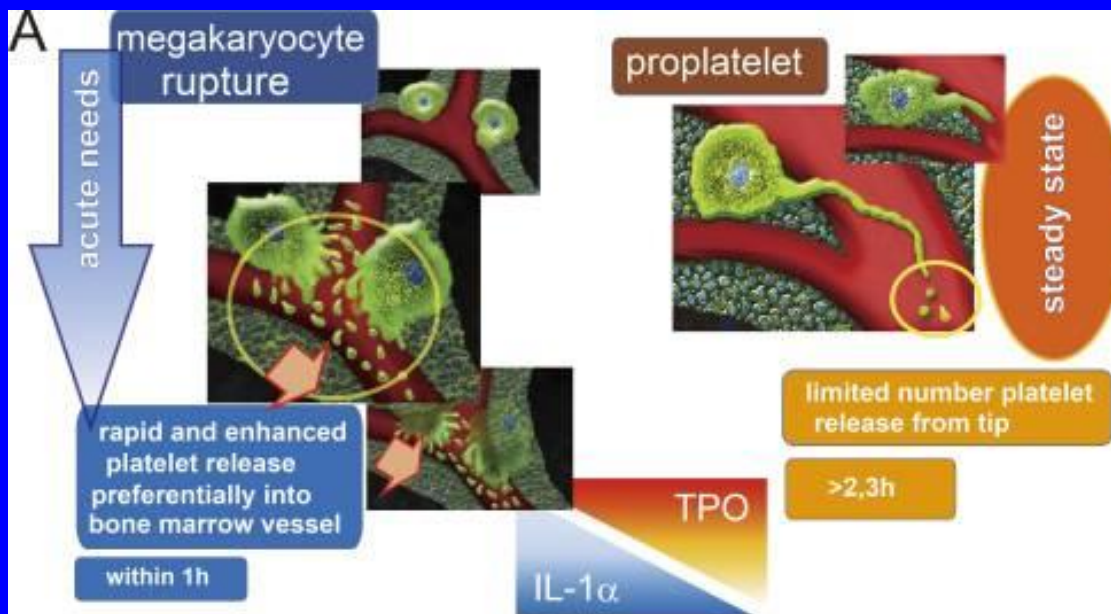
2016: rupture mégacaryocytaire (IL-1^α)

RUPTURE MEGACARYOCYTAIRE

IL-1 α induces thrombopoiesis through megakaryocyte rupture in response to acute platelet needs.

Nishimura S¹, Nagasaki M², Kunishima S³, Sawaguchi A⁴, Sakata A⁵, Sakaguchi H⁶,
Ohmori T⁵, Manabe I⁷, Italiano JE Jr⁸, Ryu T⁹, Takayama N¹⁰, Komuro I²,
Kadowaki T², Eto K¹¹, Nagai R⁵.

J Cell Biol. 2015 May 11;209(3):453-66.



En guise de conclusion

DIAGNOSTIC D'
HYPERPLAQUETTOSE

MEGAKARYOCYTE SIZE AND PLOIDY



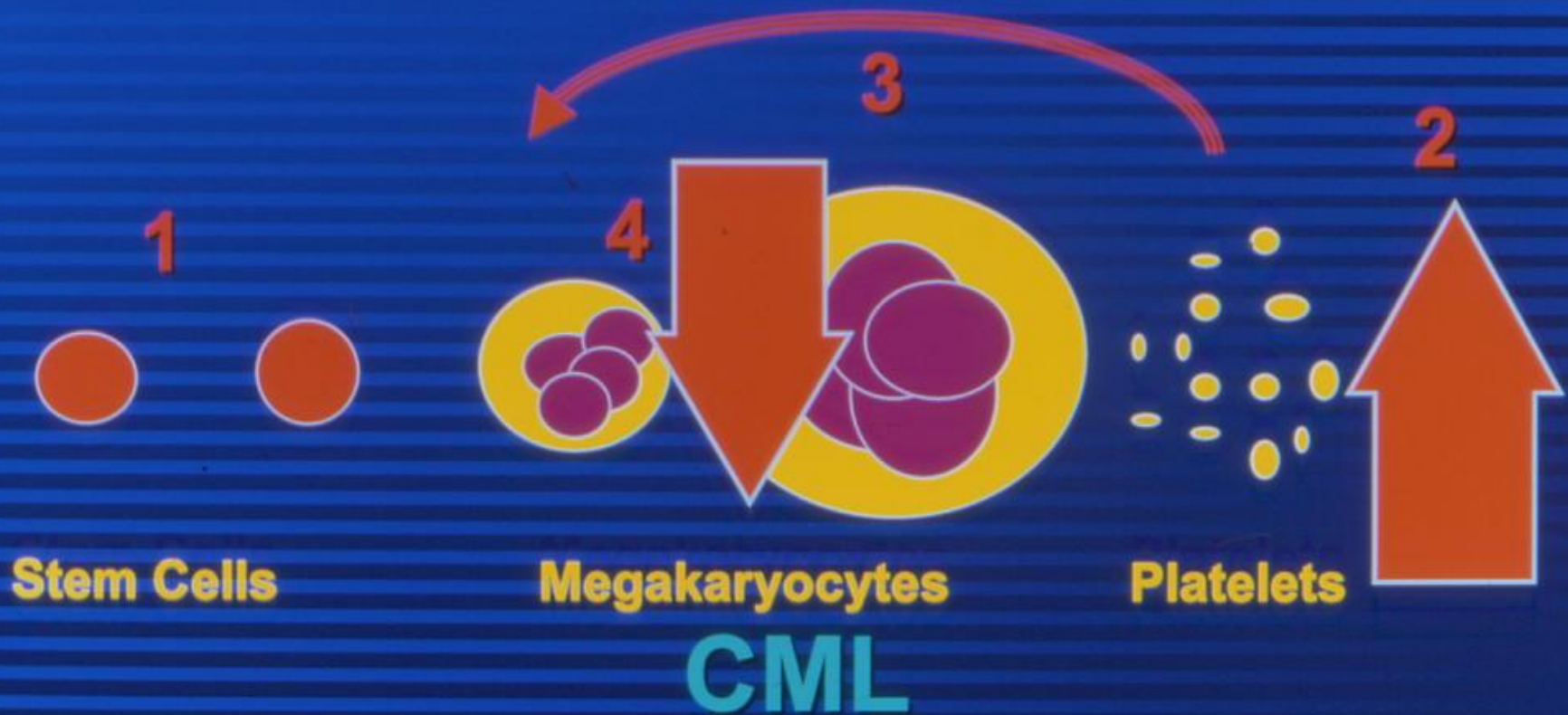
R.T.

MEGAKARYOCYTE SIZE AND PLOIDY



E.T.

MEGAKARYOCYTE SIZE AND PLOIDY



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Jeudis de Fleurus 2016

Prof. Christian CHATELAIN

NTHC

Université de Namur

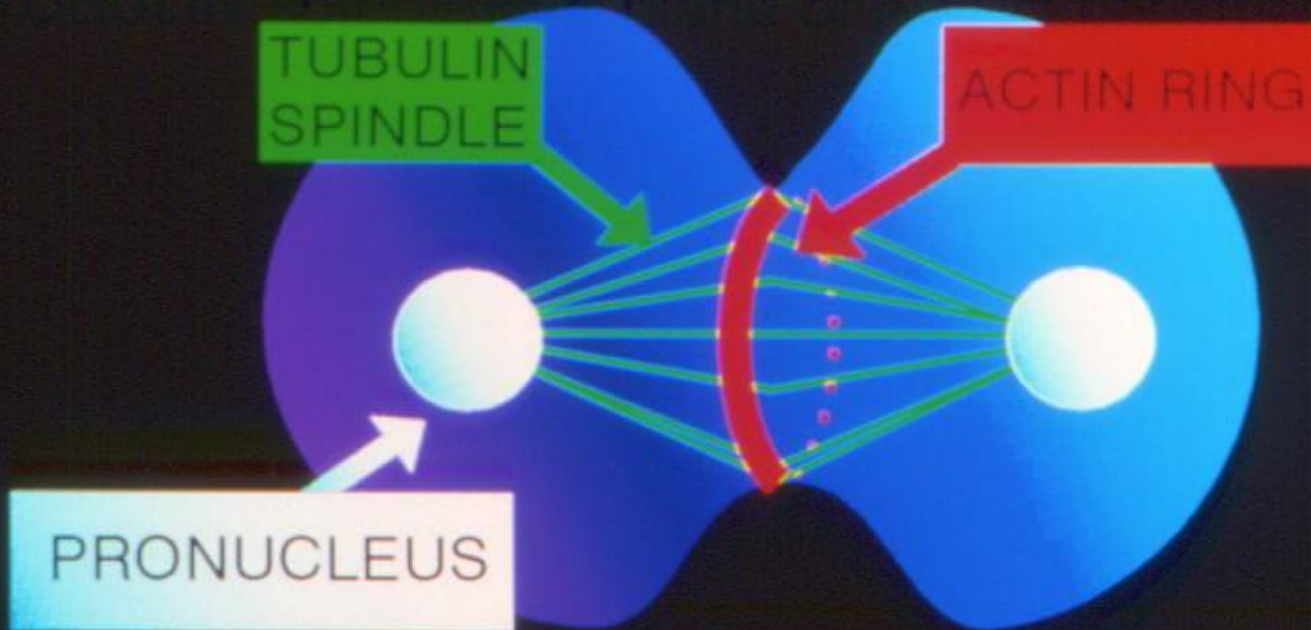
POLYPLOIDISATION MECHANISM

Role of cytoskeleton

Inhibition of ACTIN polymerization

→ Polyploidization of MK cell lines

TUBULIN spindle → plane of ACTIN constriction ring

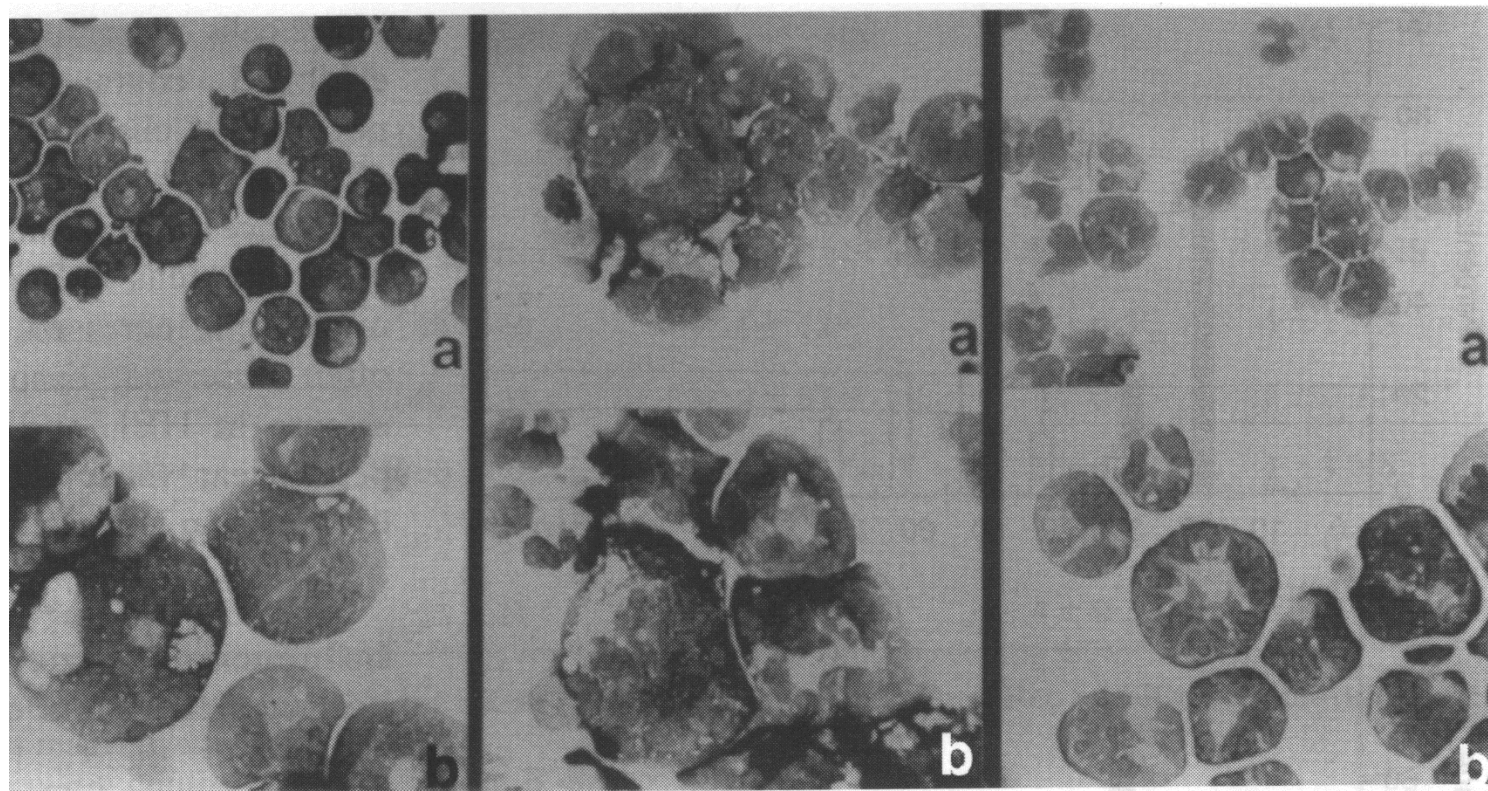


Inhibition of TUBULIN spindle ? POLYPLOIDIZATION
ACTIN content

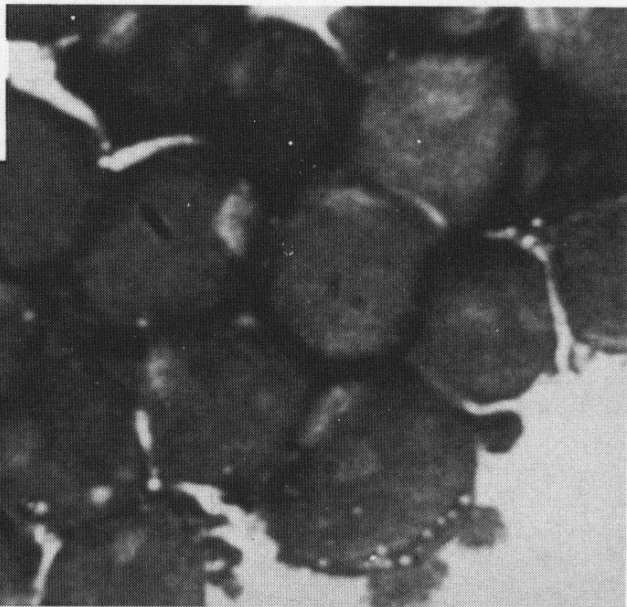
Induction and enhancement of normal human megakaryocyte polyploidization are concomitant with perturbation in the actin metabolism

S. Baatout, B. Chatelain, P. Staquet, M. Symann and C. Chatelain

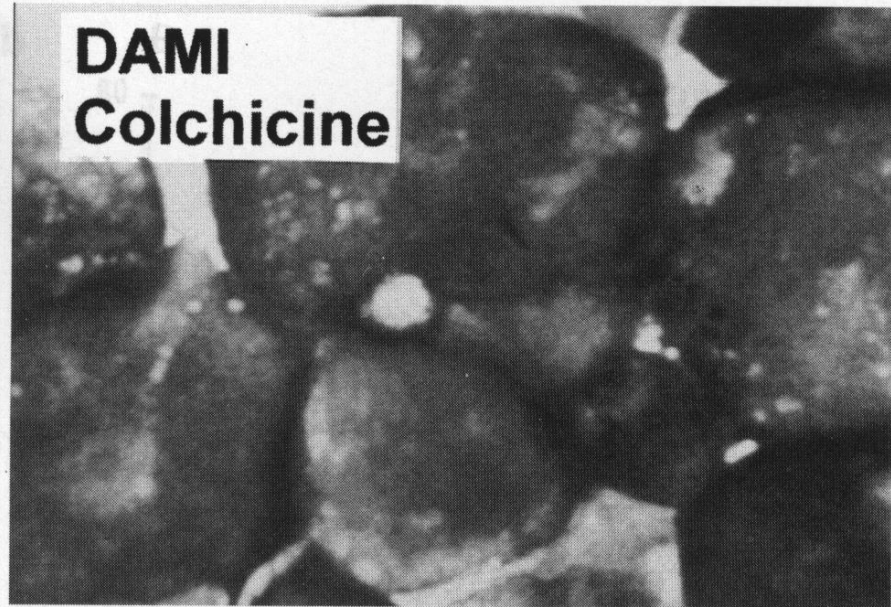
UCL, Brussels and Mont-Godinne, Belgium



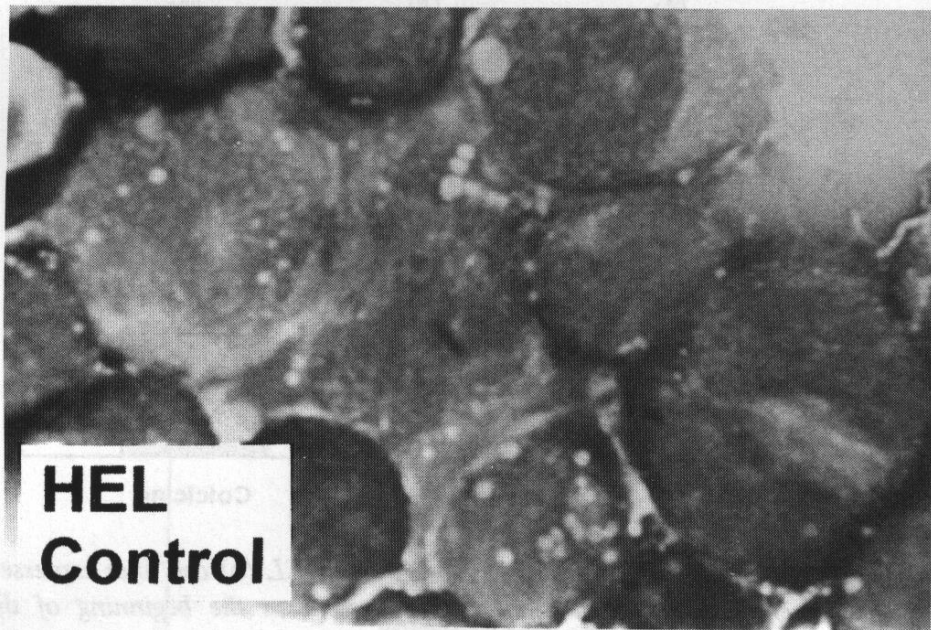
**DAMI
Control**



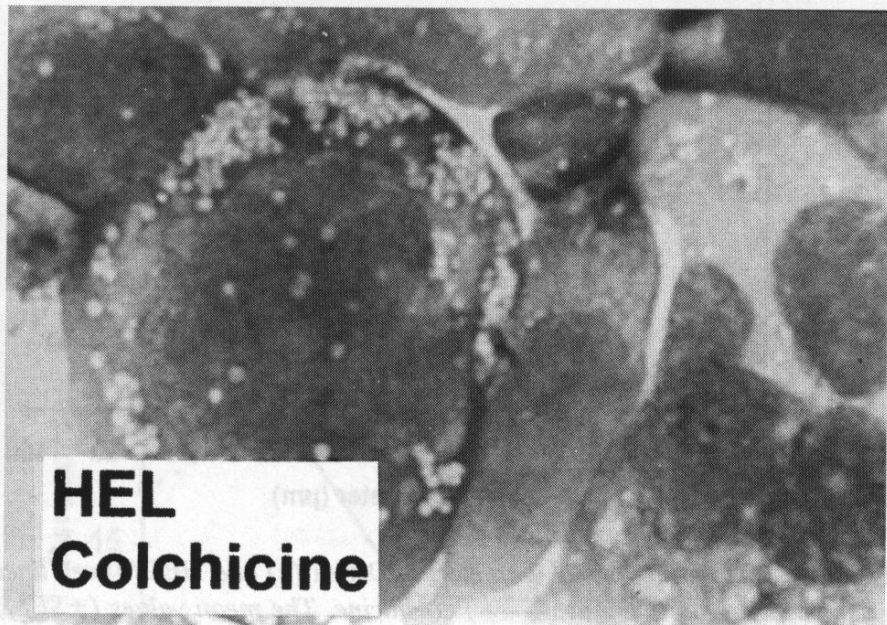
**DAMI
Colchicine**

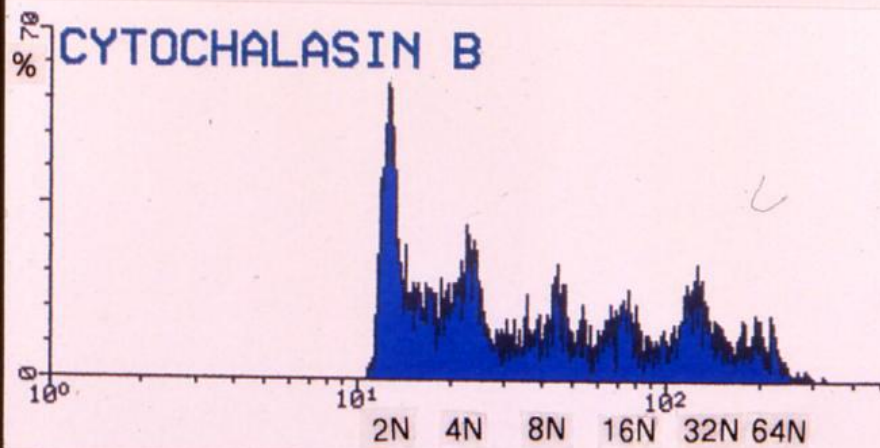
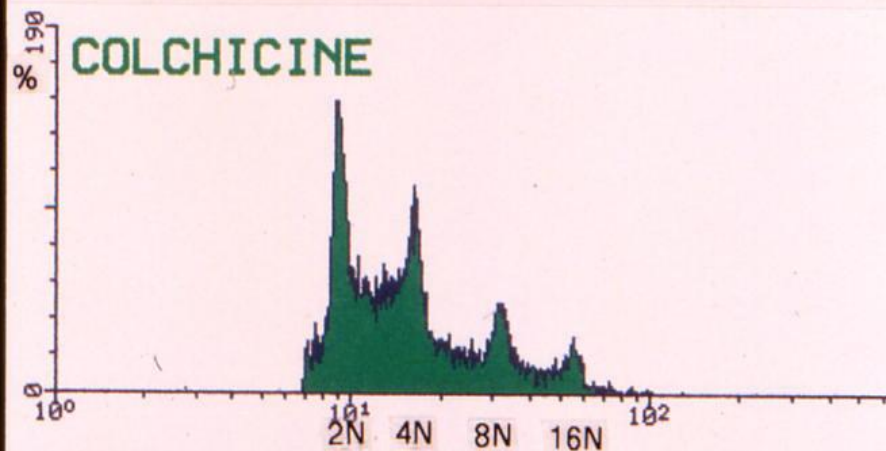
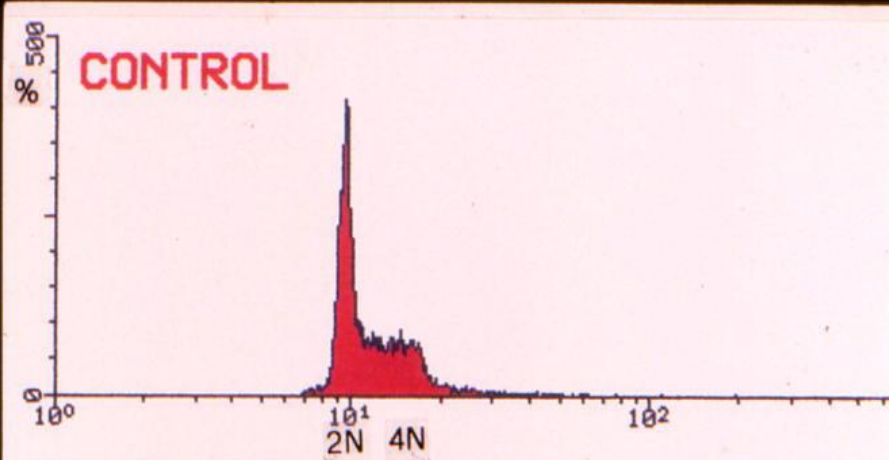


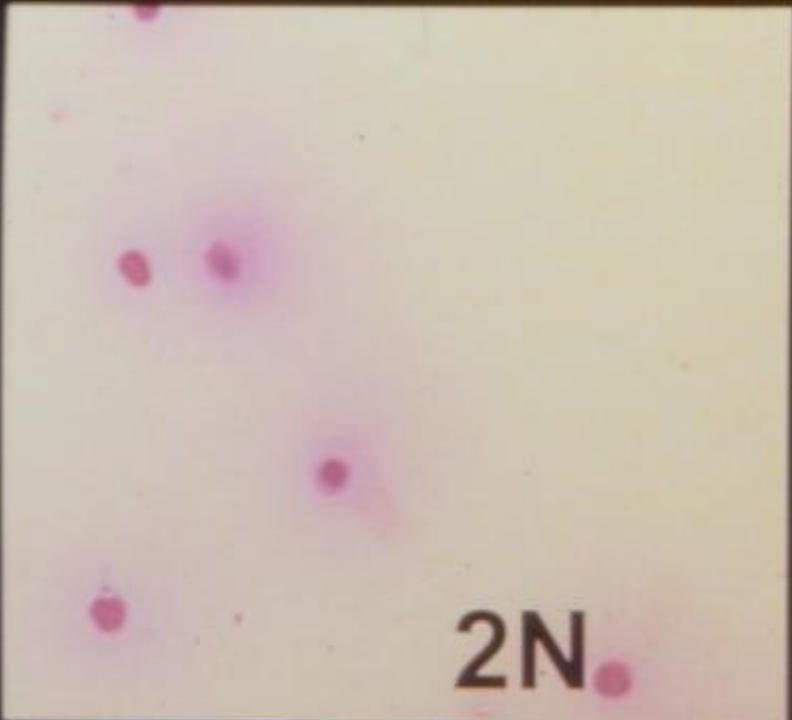
**HEL
Control**



**HEL
Colchicine**

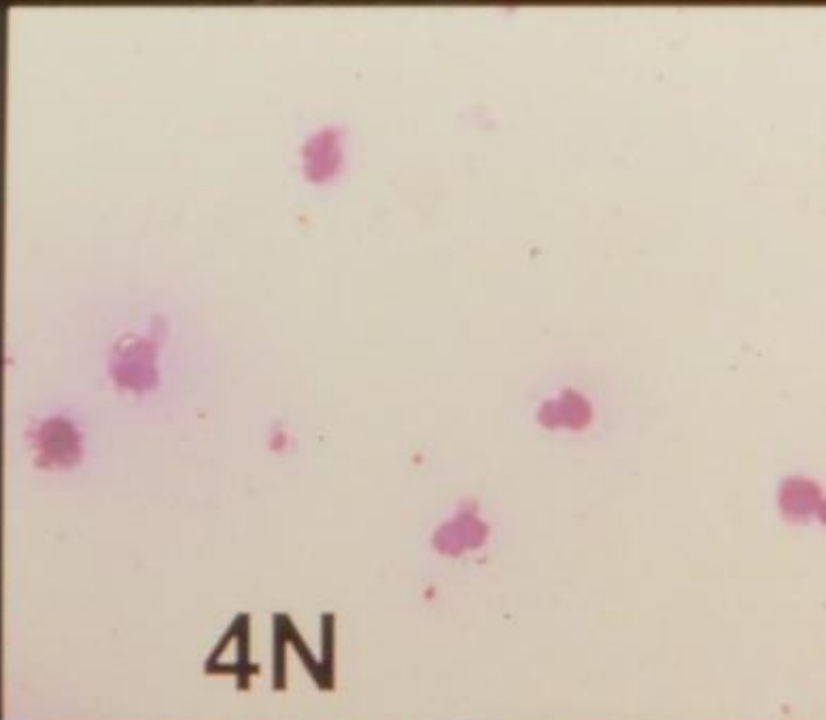






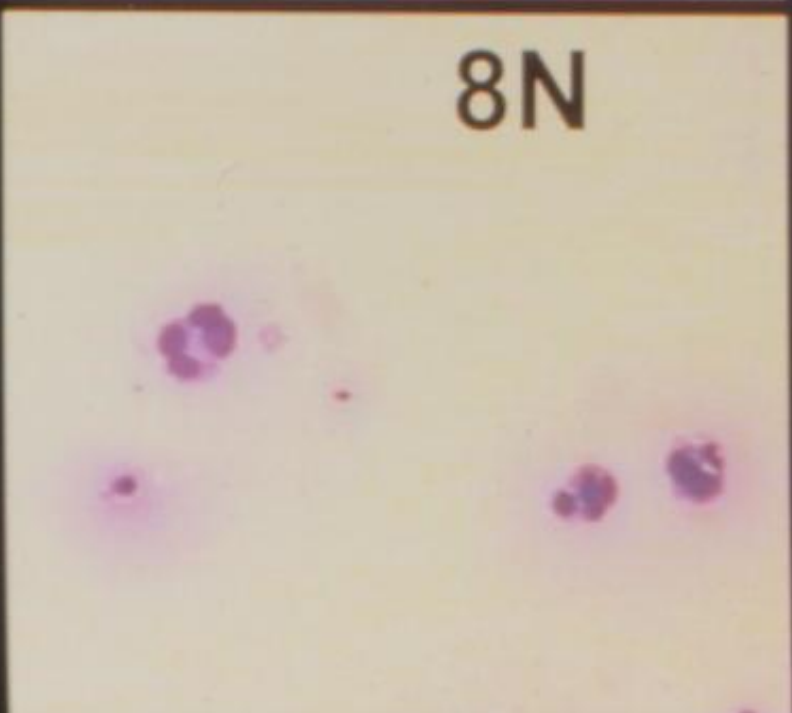
2N

This micrograph shows several cells with small, dark, spherical nuclei. The cells are sparsely distributed across the field of view.



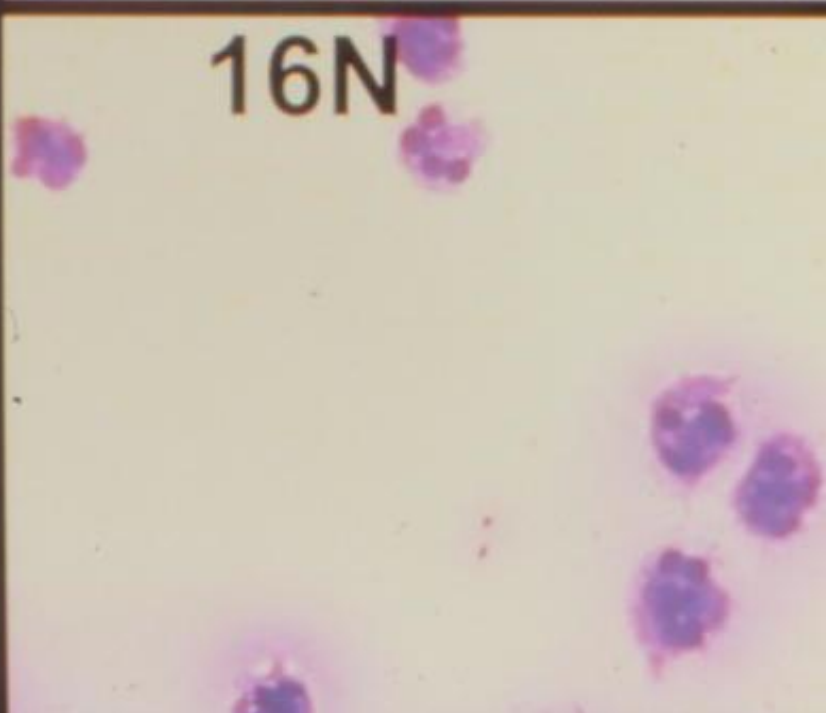
4N

This micrograph shows cells with larger, more complex nuclei compared to the 2N stage. Some nuclei appear to have internal structures or are more irregular in shape.



8N

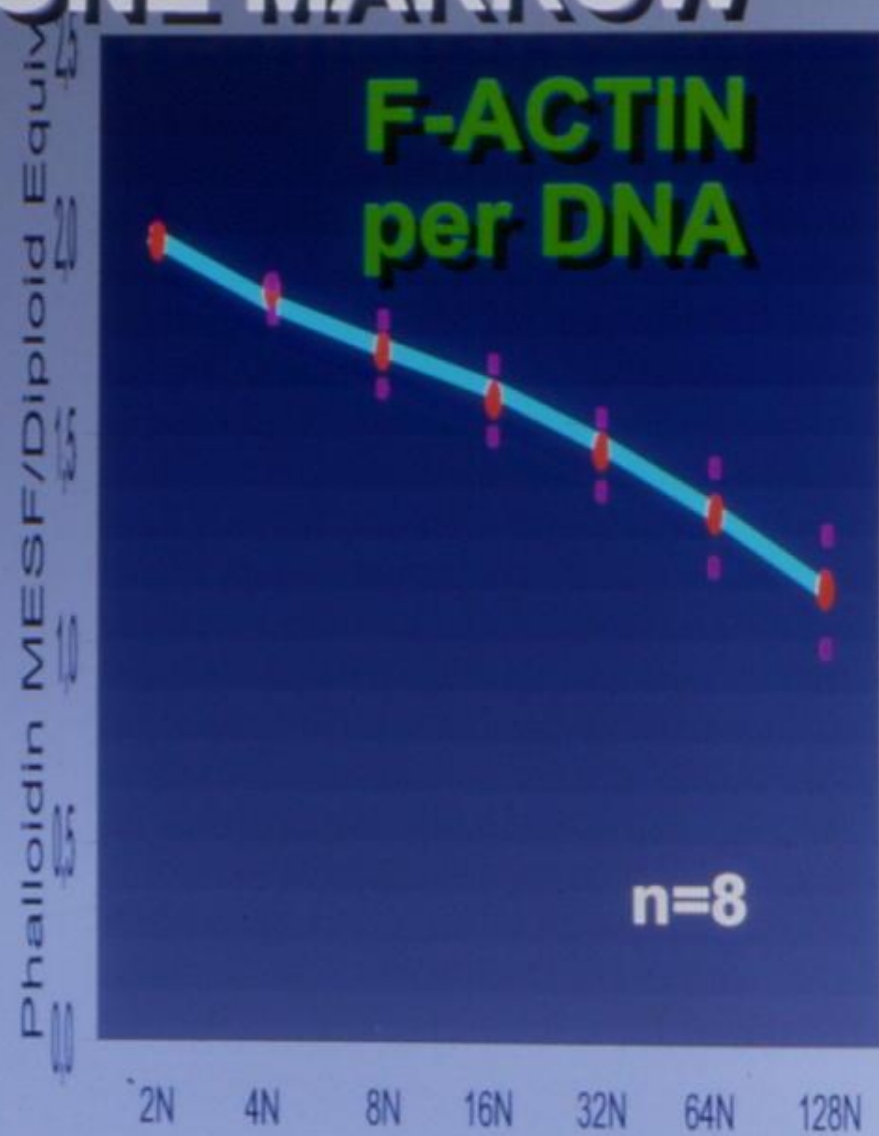
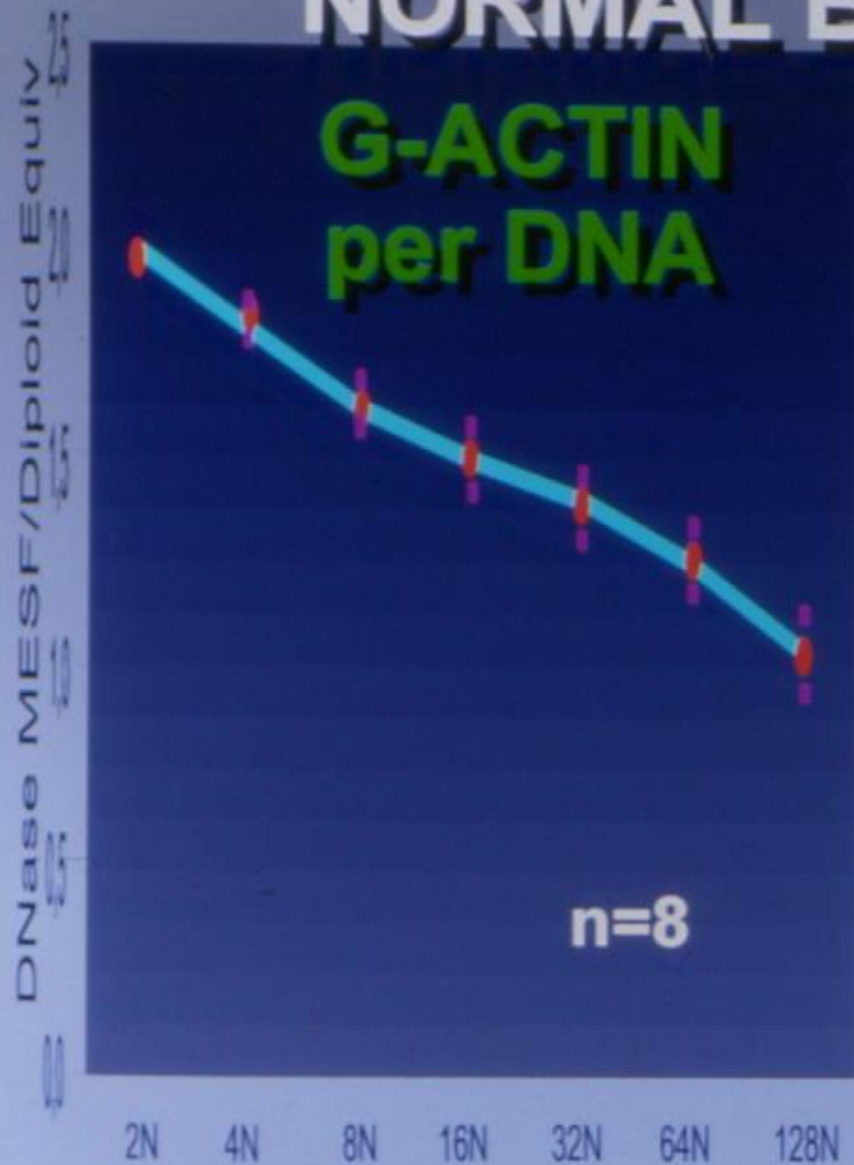
This micrograph shows cells with very large, complex nuclei. Some nuclei appear to be multinucleated or have multiple distinct nucleoli, indicating a high level of chromatin condensation.



16N

This micrograph shows cells with extremely large, complex nuclei. The nuclei are highly condensed and often appear to be multinucleated, representing a very high level of chromatin condensation.

NORMAL BONE MARROW



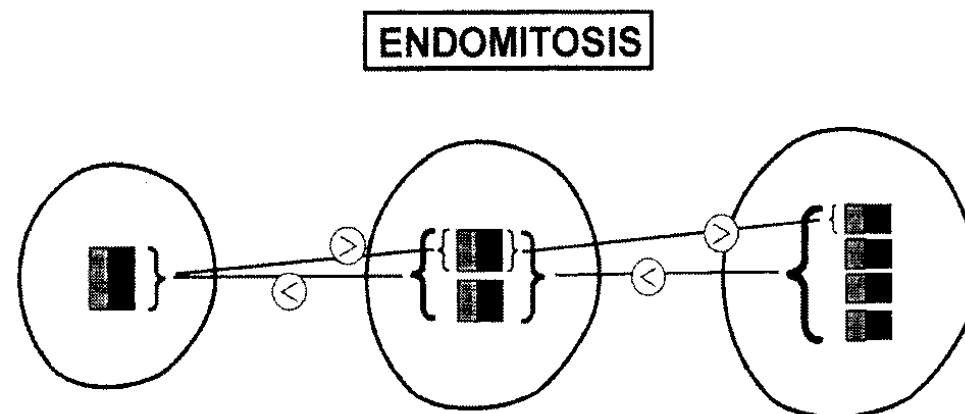
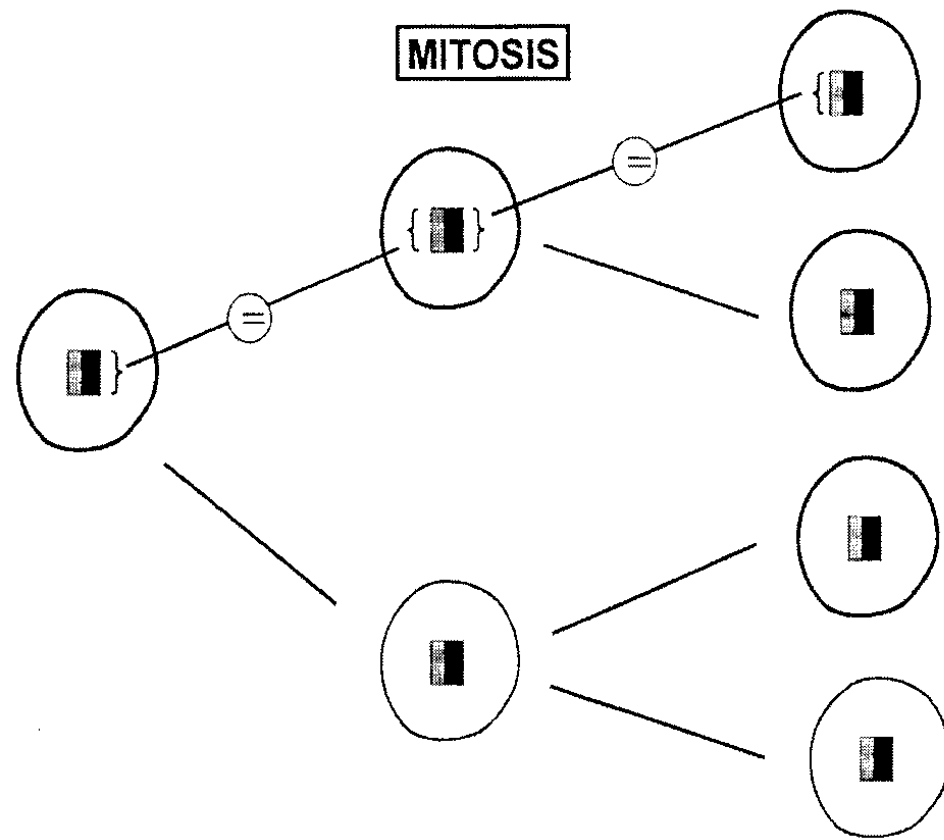


Figure 1. Modeling of the genetic content in normal mitosis (upper part)

TREATMENT OF ESSENTIAL THROMBOCYTHEMIA:

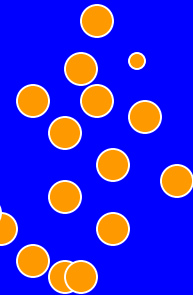
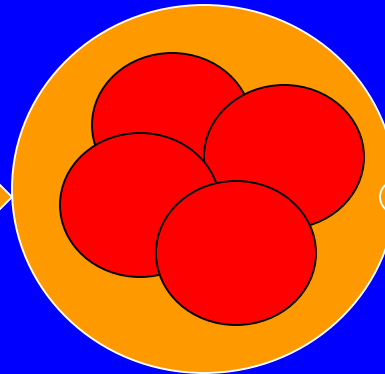
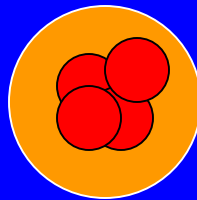
**HYDROXYUREA DECREASES
PROLIFERATION**

**ANAGRELIDE DECREASES
POLYPLOIDIZATION**

THERAPY OF E.T.

ANAGRELIDE

HUDROXYUREA



PSC CFU-MK

Megakaryocytes Platelets

TREATMENT OF ESSENTIAL THROMBOCYTHEMIA:

**Do not forget HYPERURICEMIA
(Allopurinol)**

What about PLATELET FUNCTIONS?

Pathogeny and treatment of
THROMBOCYTHEMIA:
UNDERSTANDING
MEGAKARYOCYTOPOIESIS

2004

Prof. Christian CHATELAIN
UCL MONT-GODINNE