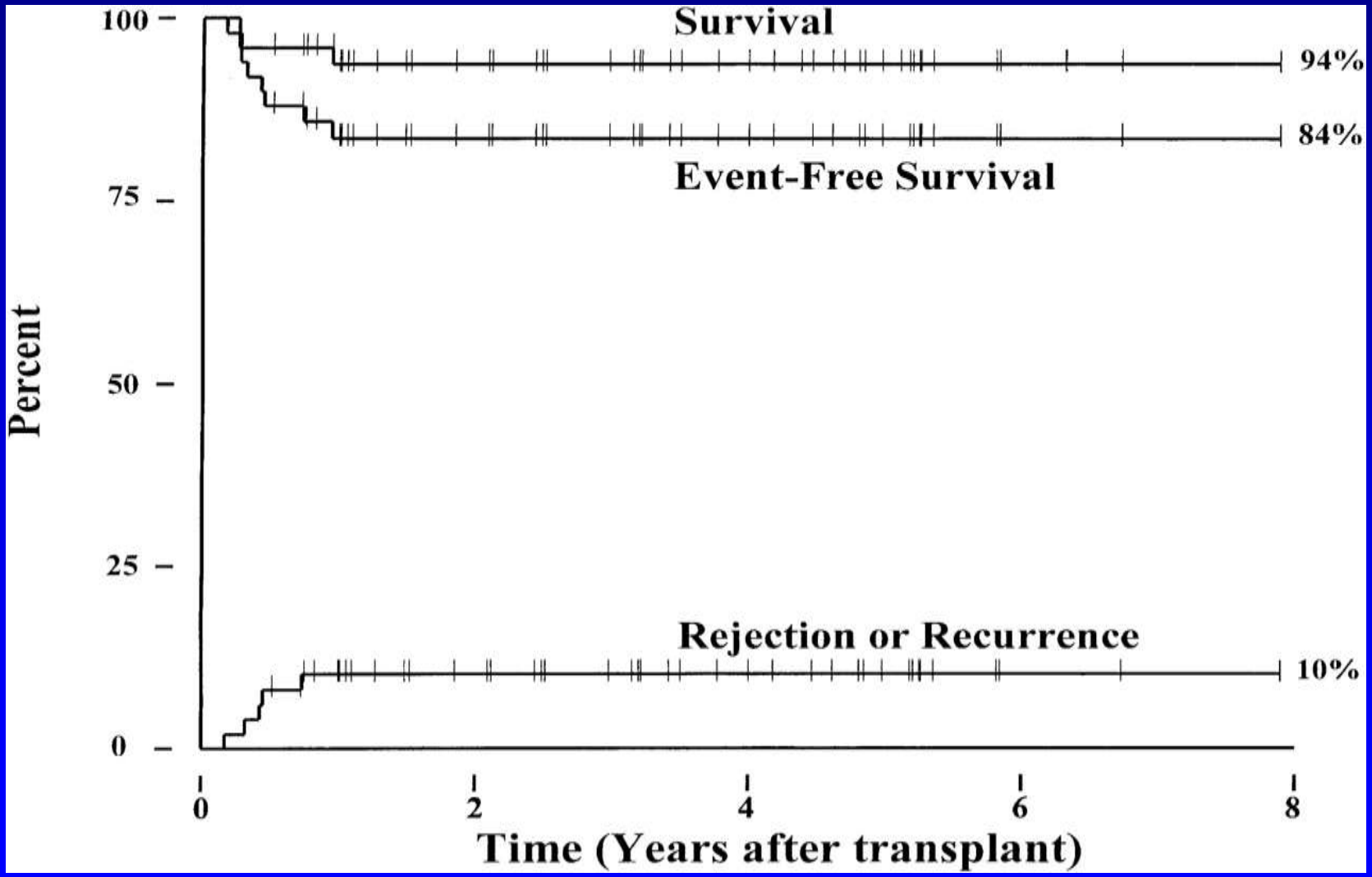
CURE IS PRACTICAL BUT ONLY AVAILABLE TO A FEW



Cure Is Practical

Table 1. Hematopoietic cell transplantation

Location	Belgium		Pesario	France	Multicenter	Other US/Europe	Total
Regimen	BU,CY (30) BU,CY,TLI (6) BU,CY,ATG (14)		BU,CY (17) BU,CY,ATG (2)	BU,CY (12) BU,CY,TLI (1) BU,CY,ATG (21)	BU,CY,ATG	BU,CY,ATG (13), CY/TBI (3)	
Number of patients	36	14	19	34	59	16*	175†
Median age (range)	8.6 (1.7–23)	2.0 (0.9–15)	7 (4–38)	8.6 (2.3–17.2)	9.9 (3.3–15.9)	–	
Asymptomatic	0	14	3	0	0	–	
Stroke/CNS	6	0	1	16	31	2	
ACS	20	0		15‡	20	1	
VOC	36‡	0	15	18	8	1	
Other/unknown						11	
MM donor			1				
Survival (%)	34 (94)	14 (100)	14 (74)	31 (91)	55 (94)	13 (81)	159 (91)
Deaths	2	0	5	3†	4	3	
Graft rejection/ recurrent SCD (%)	4	1	1	4	5	1	16 (9)
Stable mixed chimerism	6§	–	5	1	10	–	11%
Disease-free survival (%)	30 (83)	13 (93)	13 (68)	27 (79)¶	50 (85)	12 (80)¶	143 (82)
aGVHD	15**	5	4	6 (> grade II)	11 (grade I–III)	2	25%
cGVHD	8	2	2	2	5	1	12%
Seizures	18		1	7/26	13	1	25%

Hoppe & Walters. Oncology 2001;13:85-90.

Non-Myeloablative BMT in Adults

Table 1. Characteristics of 10 Patients Undergoing Nonmyeloablative Hematopoietic Stem-Cell Transplantation (HSCT).*

Patient No.	Age at HSCT	Sex	Type of Sickle Hemoglobin	Coexisting Conditions and Indications for HSCT	Medical Management before HSCT
	yr				
1	24	F	SS	Recurrent TIA and stroke, elevated TRV	Simple and exchange red-cell transfusions
2	27	M	SS	Frequent VOC, priapism, proteinuria (1.7 g/24 hr)	Hydroxyurea, simple and exchange red-cell transfusions
3	21	F	SS	TIA, frequent VOC, acute chest syndrome	Hydroxyurea, exchange red-cell transfusions
4	16	M	SS	Frequent VOC, acute chest syndrome, narrow CNS arteries on MRA	Hydroxyurea, exchange red-cell transfusions
5	21	M	SS	Frequent VOC, acute chest syndrome	Hydroxyurea
6	40	M	SC	Frequent VOC, priapism, narrow CNS arteries on MRA, lacunar infarcts	Hydroxyurea
7	26	F	SS	Frequent VOC, elevated TRV	Hydroxyurea
8	26	F	SS	Frequent VOC, elevated TRV	Hydroxyurea and simple red-cell transfusions
9	45	F	SS	Sickle-cell–related FSGS (baseline creatinine, 2.5–2.7 mg/dl [221–239 μmol/liter]), elevated TRV, acute chest syndrome, frequent VOC, red-cell alloimmunization, hepatitis C	Hydroxyurea, simple and exchange red-cell transfusions, darbepoetin
10	26	M	SS	Sickle-cell–related nephrotic syndrome, elevated TRV, acute chest syndrome	Hydroxyurea, simple red-cell transfusions, prednisone

Hsieh et al. New Engl J Med 2010;361:2009-2017.

Non-Myeloablative BMT in Adults

Table 2. Hematopoietic-Graft Composition and Outcome after Hematopoietic Stem-Cell Transplantation (HSCT).*

Patient No.	Composition of Infused Graft		Months after Transplantation	Duration of ANC $<0.50\times10^{-9}$/liter	Duration of ALC $<0.75\times10^{-9}$/liter	Donor CD3+ Cells	Donor CD14+15+ Cells	Hemoglobin	Hemoglobin S	
	CD34+ Cells	CD3+ Cells							Donor	Recipient
	$\times10^{-6}$†	$\times10^{-8}$†		*days*	*months*		%	*g/dl*	%	
1	5.72	3.21	54	21	3.5	7	48	12.0	0	0
2‡	7.56	2.27	36	18	2.5	63	19	11.1	40.5	51.6
3	10.0	3.42	42	12	6	61	100	14.8	35.2	35.2
4 ‡	8.3	5.35	33	29	6	0	0	11.4	0	45.9§
5	5.51	3.71	30	10	4	72	100	14.3	0	0
6	23.8	2.81	32	10	6	35	97	14.7	38.2	37.0
7	18.8	3.32	29	19	8	62	100	12.2	36.6	35.4
8	20.1	3.04	30	11	1.5	63	100	12.1	0	0
9	16.6	3.7	16	15	3.5	23	97	11.7¶	0	0
10	15.1	3.64	15	18	4	75	100	10.5¶	35	34.6

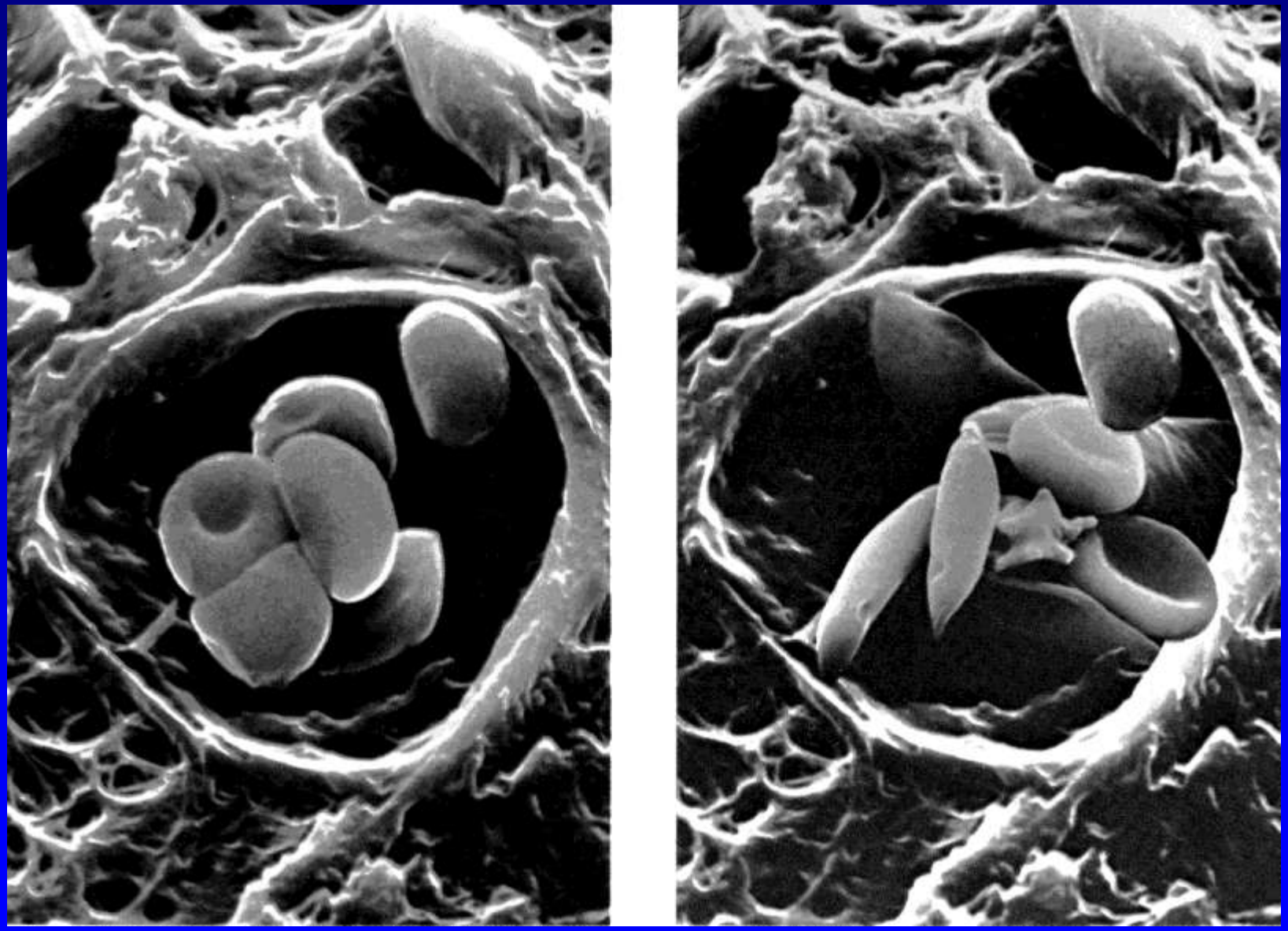
* Results are from the most recent follow-up assessment. ALC denotes absolute lymphocyte count, and ANC absolute neutrophil count.
† Values are per kilogram of the recipient's body weight.
‡ The results shown are from a second transplantation.
§ The patient had received an exchange transfusion within the previous 2 months.
¶ The patient was receiving supportive treatment with erythropoietin owing to renal insufficiency.

Hsieh et al. New Engl J Med 2010;361:2009-2017.

APPROACH TO TREATMENT

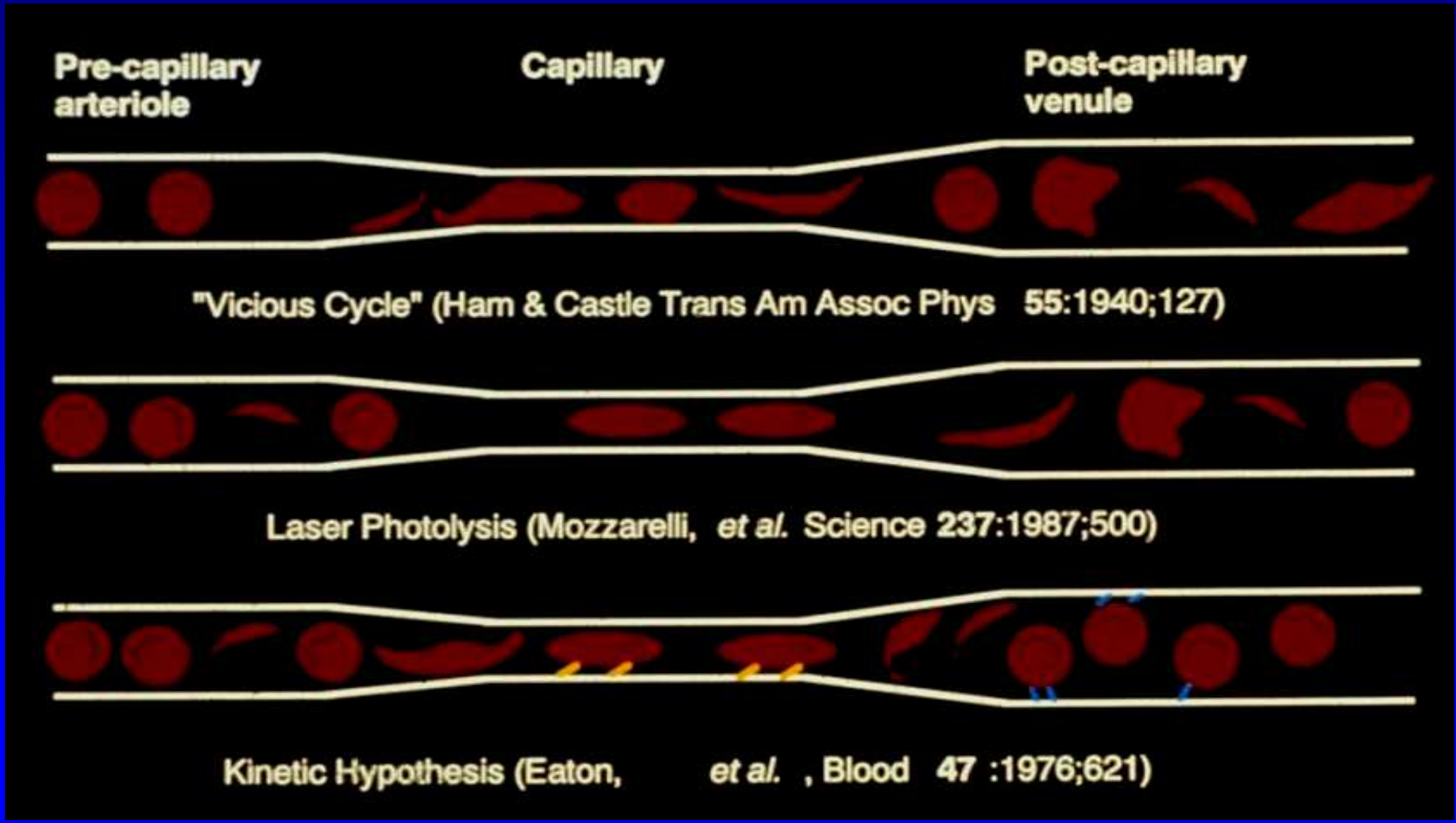
- Complications precipitated by extra erythrocytic factors, not directly related to hemoglobin
  - Increased cell/cell and endothelial adherence
  - Activation of thrombosis
  - Decrease vasoconstriction

SICKLE CELLS ARE STICKY



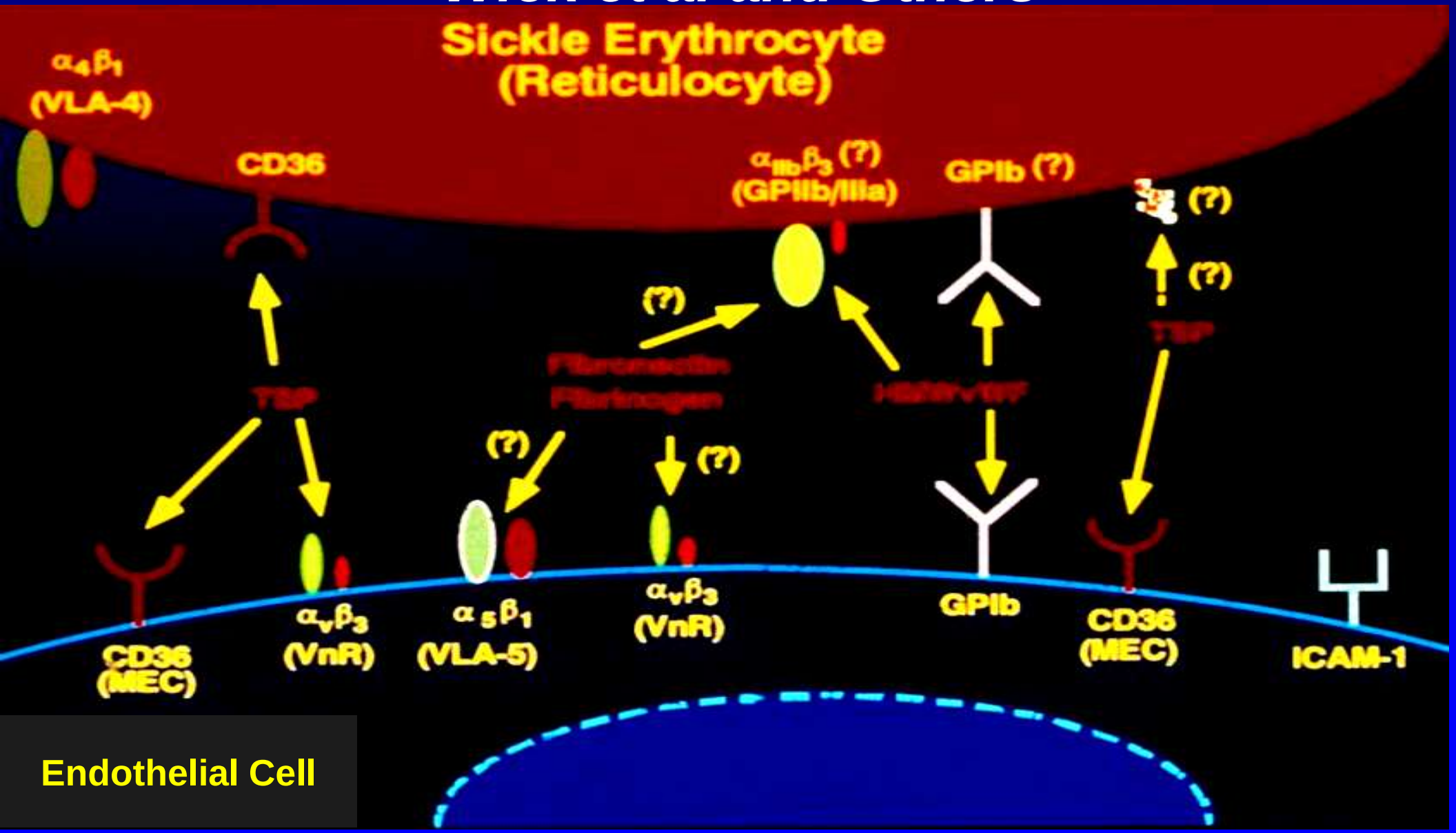
VASO – OCCLUSION

Wick et al

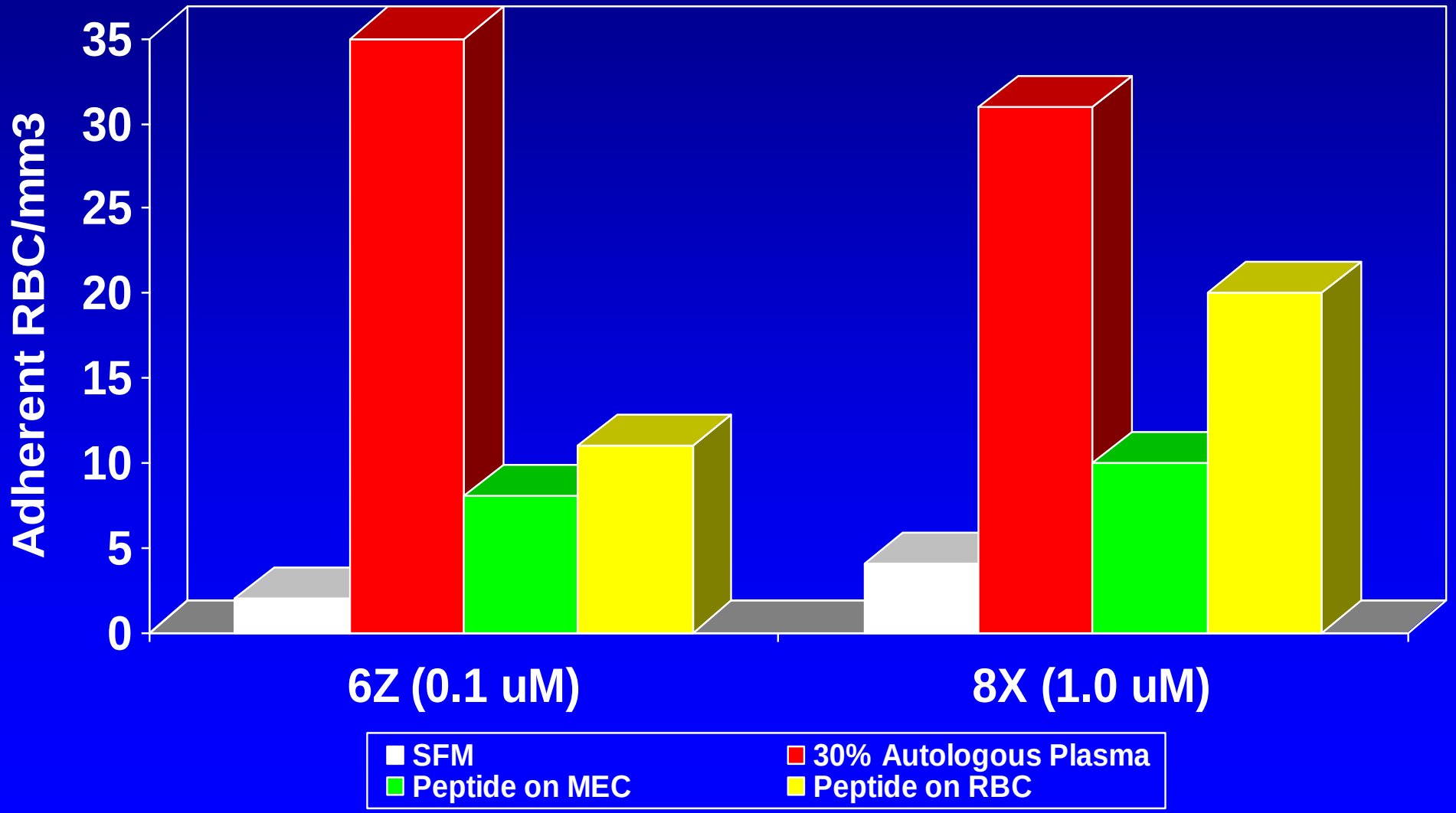


MULTIPLE SPECIFIC PATHWAYS

Wick et al and Others



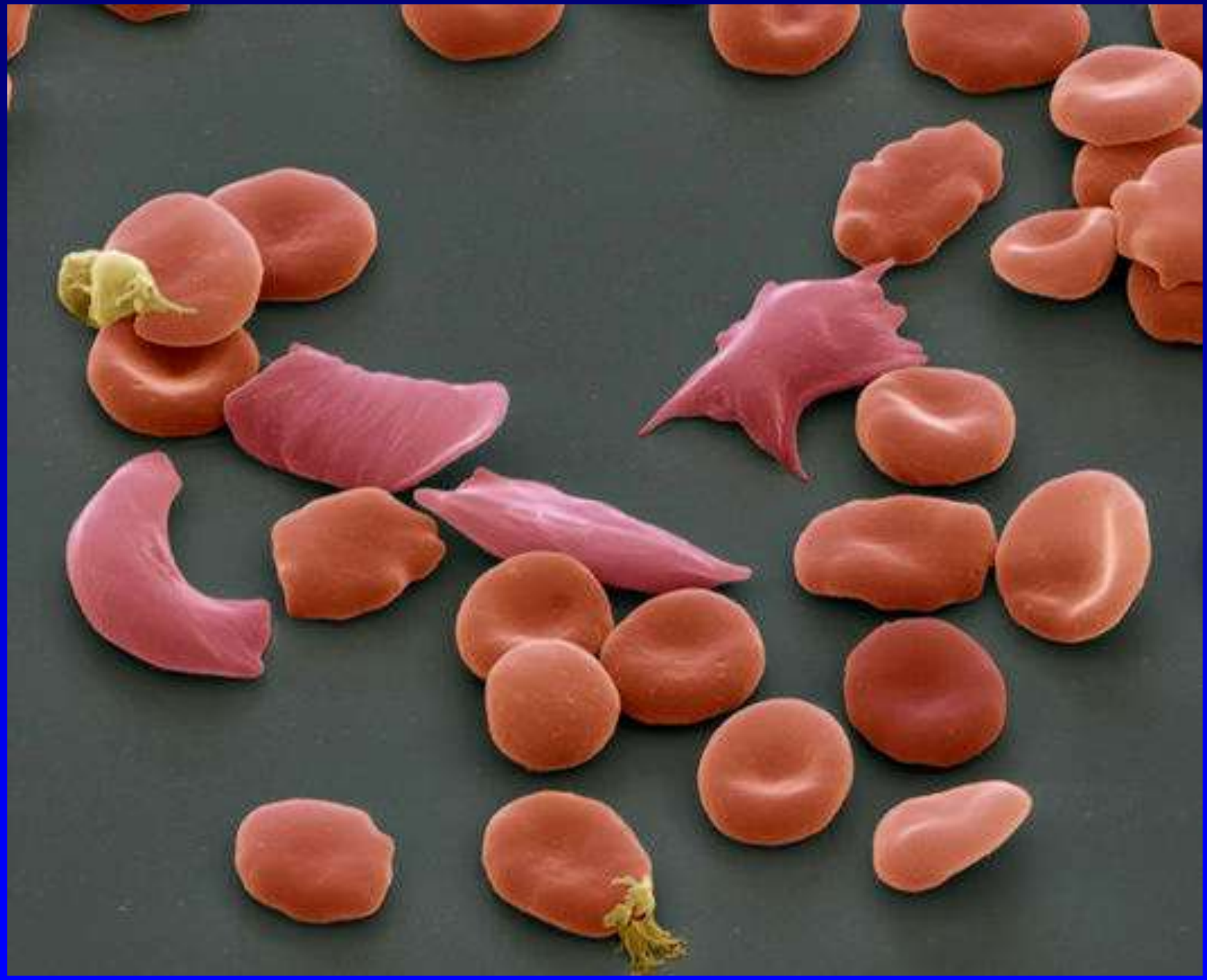
RGD Peptides Inhibit Plasma Dependent SRBC Endothelial Adherence



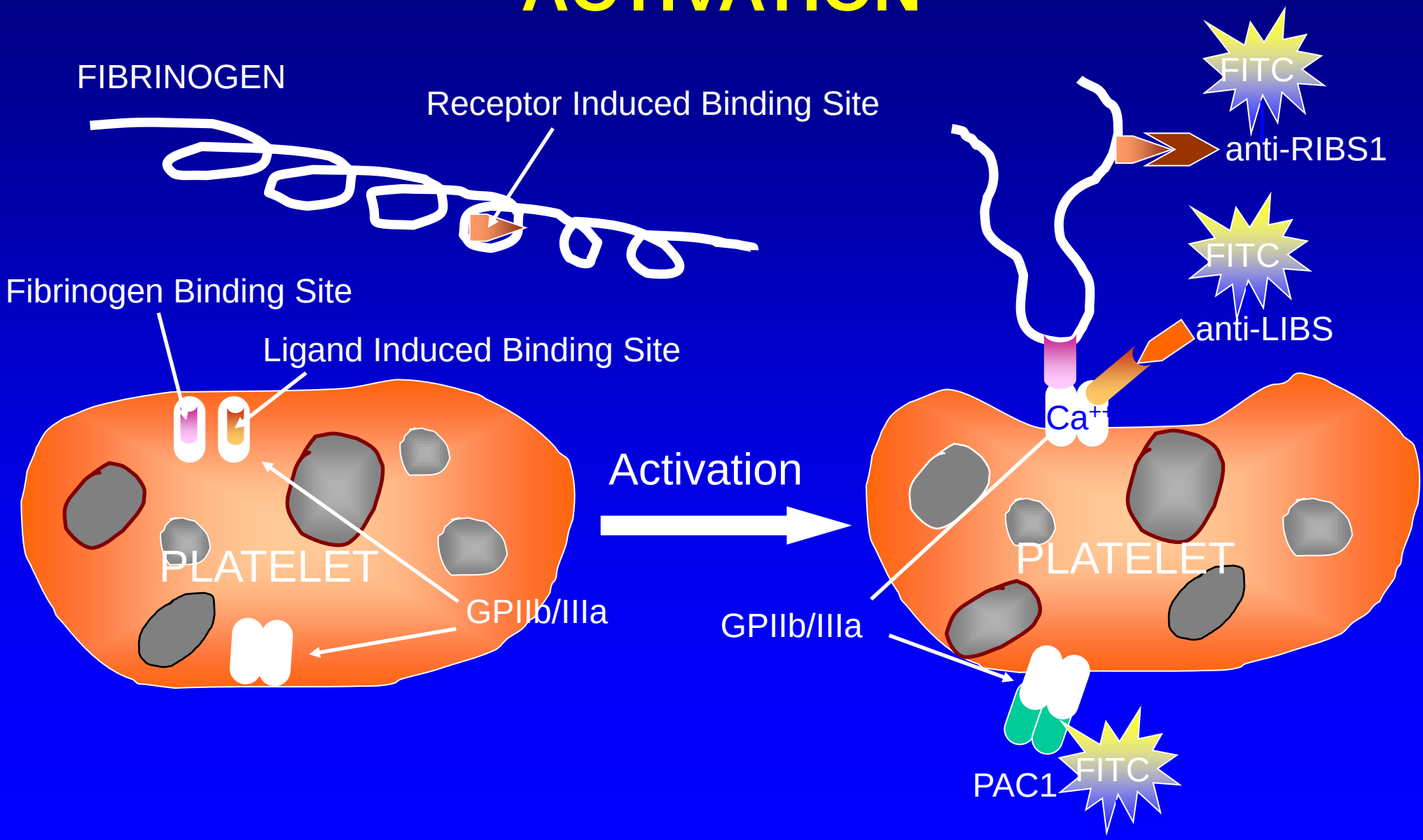
SICKLE CELL DISEASE:

A Hypercoagulable State ?

- Increased platelet count
- Decreased platelet survival
  - Haut et al J Lab Clin Med 82:44, 1973.
  - Semple et al. Thromb Haemostasis 51:303, 1984.
- Drop in count during crisis
  - Alkjaersig et al J Lab Clin Med 88:440,1976.
- Increased F VIII & vWF
  - Richardson et al Br J Haematol 41:95, 1979.
  - Leslie et al. Br J Haematol 30:159, 1975.

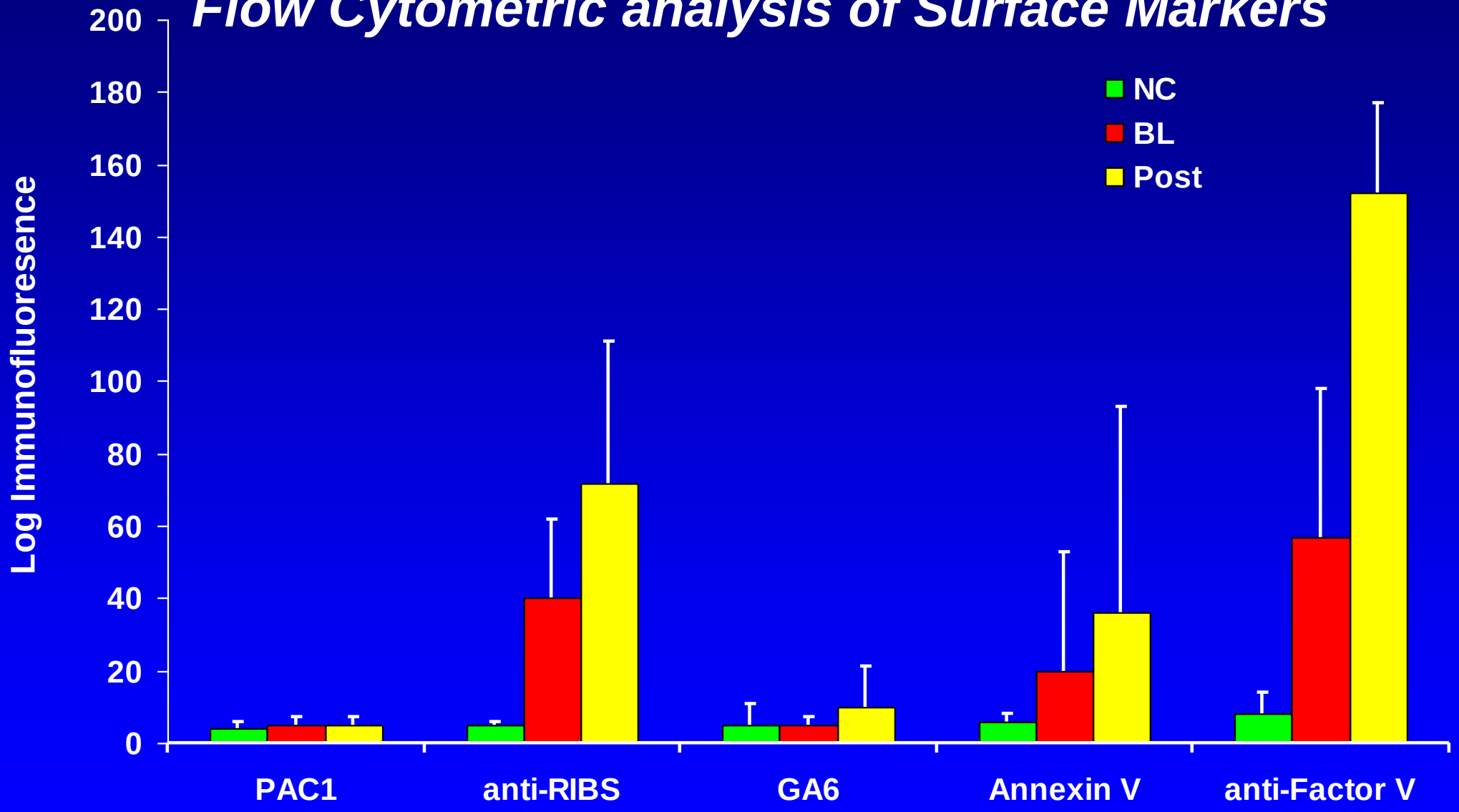


FLOW CYTOMETRIC ANALYSIS OF PLATELET ACTIVATION

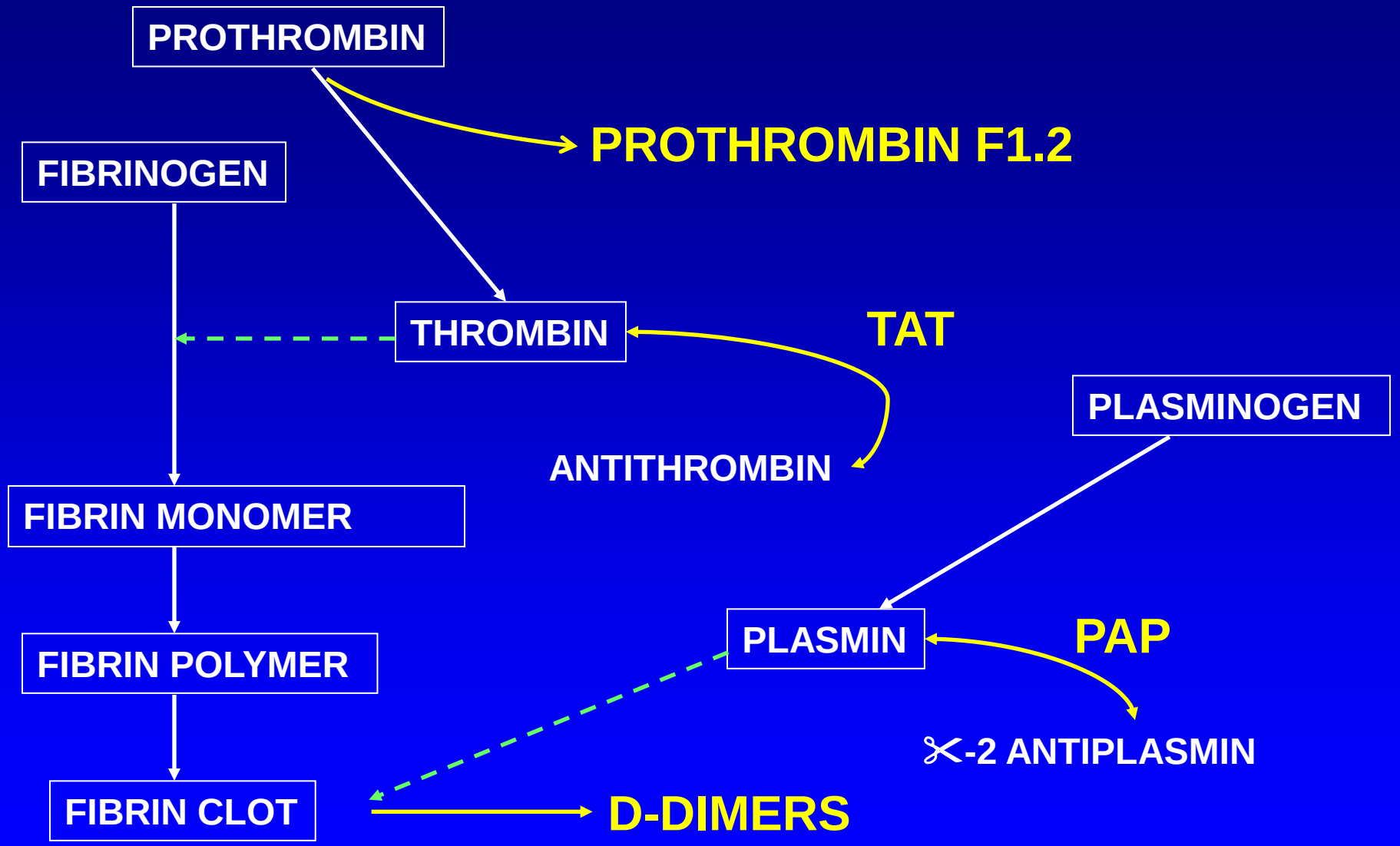


PLATELET ACTIVATION

Flow Cytometric analysis of Surface Markers

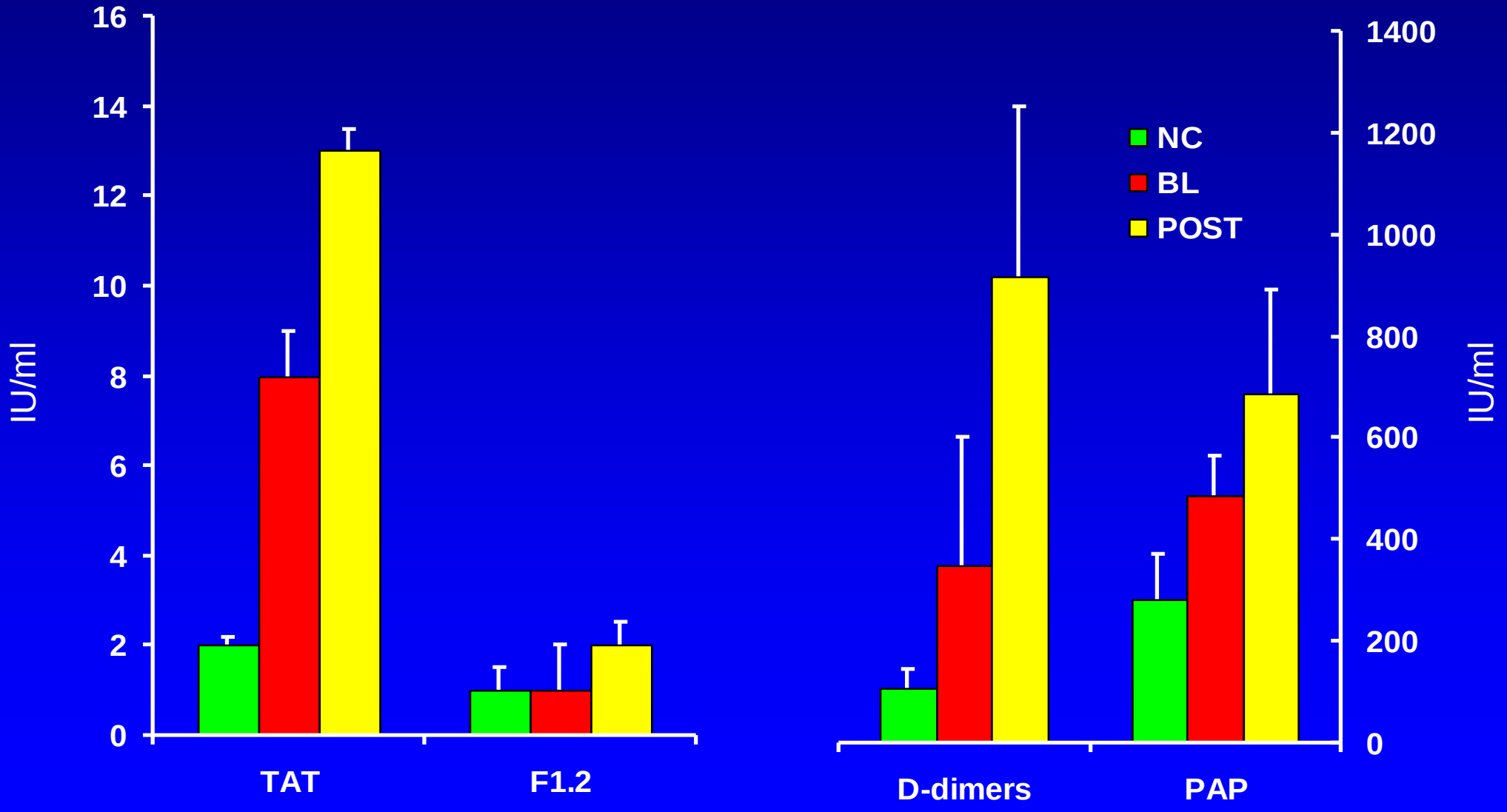


THROMBOSIS and FIBRINOLYSIS

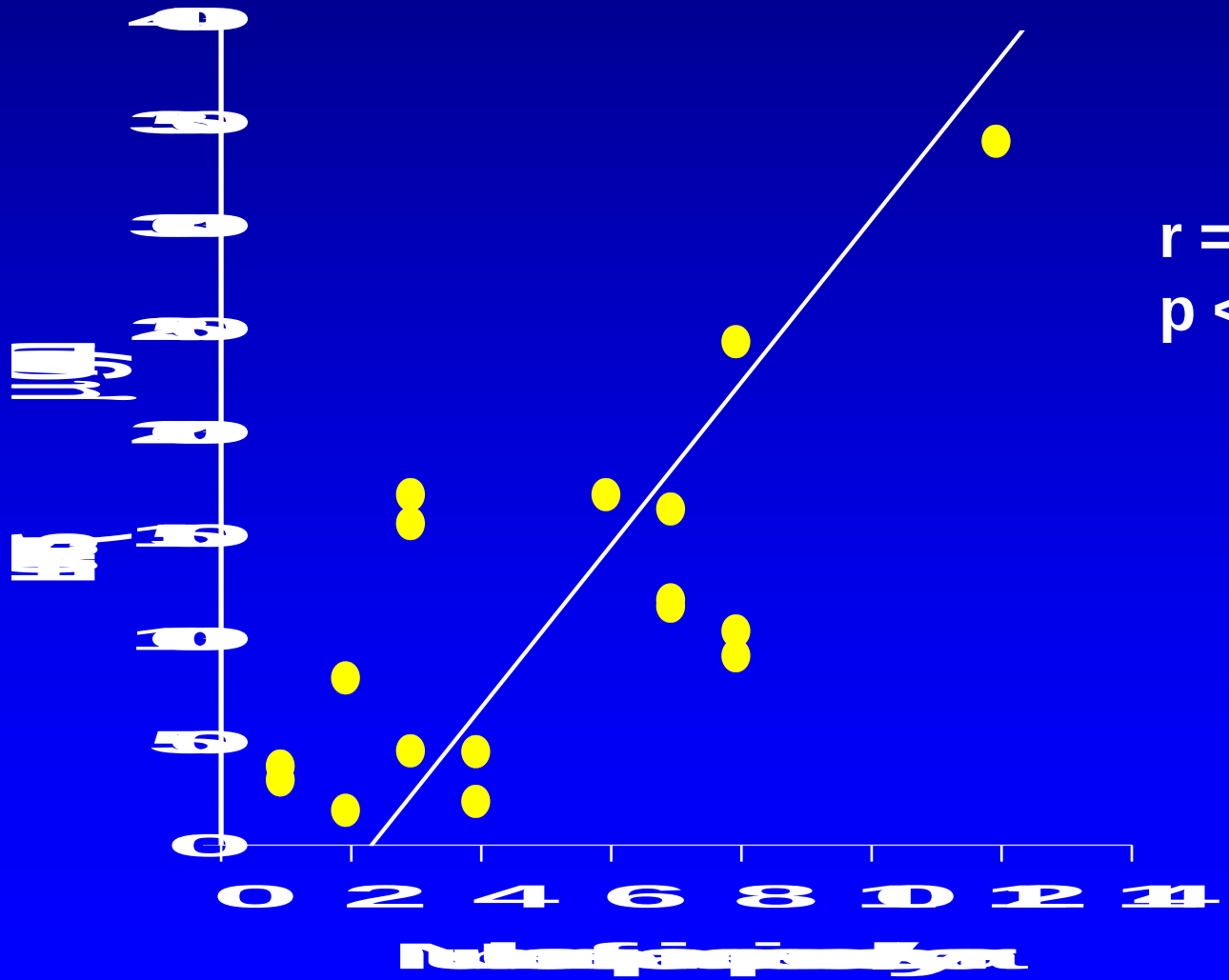


THROMBOGENIC ACTIVITY

Circulating Plasma Markers



Correlation Between Plasma Level of D-dimers Fragments and Frequency of Pain Episodes in SCD



r = 0.74
p < 0.01

INUIT NATIVE AMERICANS

N 3 FATTY ACIDS

n-3 FATTY ACIDS

- Attenuate platelet reactivity
- Increase blood fluidity
  - Increase RBC deformability
  - Decrease blood viscosity
- Decrease VLDL
- Decrease release of proinflammatory mediators LTB 4 and IL 1β
- Cause vasodilation
- Decrease re-infarction rate in CAD

Frequency of Pain Crisis

	Total	n-3FA	placebo	
Patients:	9	5	4	*P***
Pain episodes / year				
pre treatment		7.8	7.6	>0.05
on treatment		3.8	7.1	<0.01
*P**		< 0.01	> 0.05	

* for comparison between pre treatment v treatment
** for comparison between n-3fas v placebo

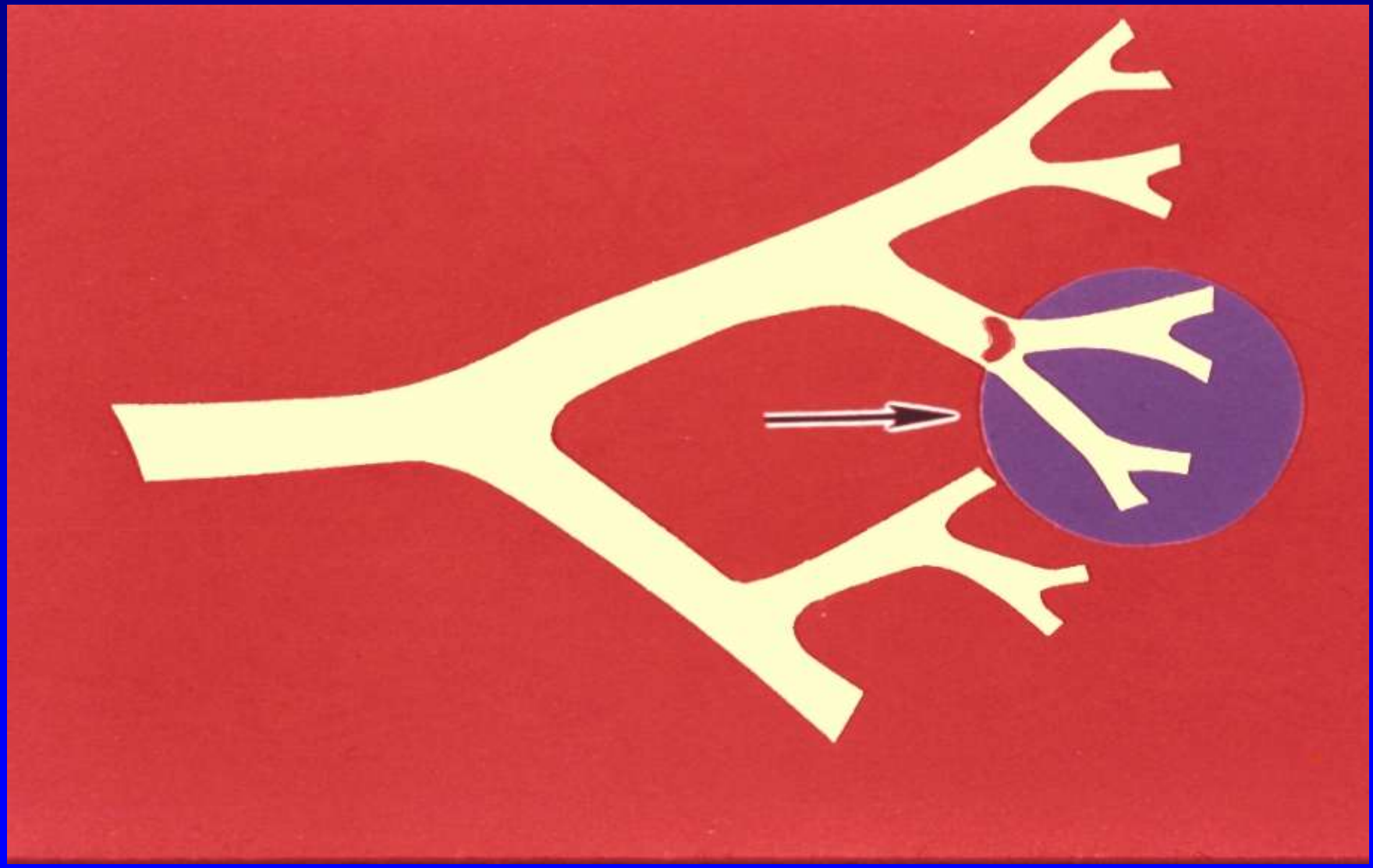
TINZAPARIN SHORTENS PAIN EPISODES

	Study group N=127 Mean ± SEM	Control group N=126 Mean ± SEM
Days in severe pain	1.28 ± 0.06*	1.72 ± 0.06
Duration of crisis	2.57 ± 0.12*	4.35 ± 0.11
Duration of Hospitalization	7.08 ± 0.36*	12.06 ± 0.76

*P< 0.05 Qari et al Blood 2005;106:2340a

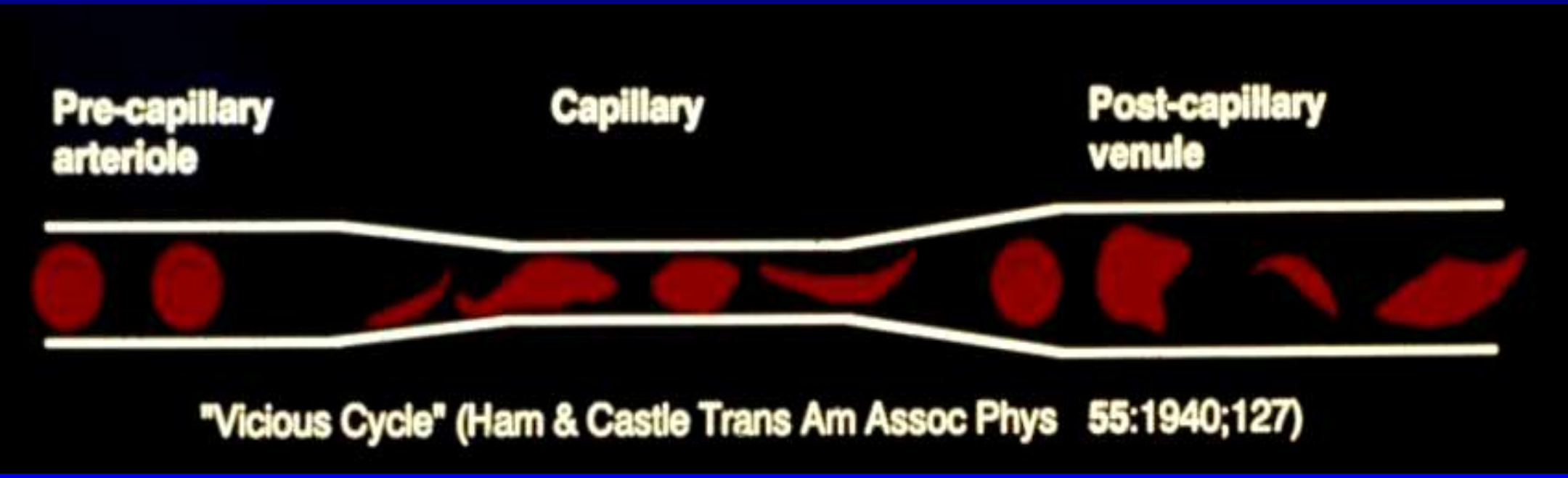
Why is there simultaneous onset of pain in so many parts of the body ?

VASO - OCCLUSION



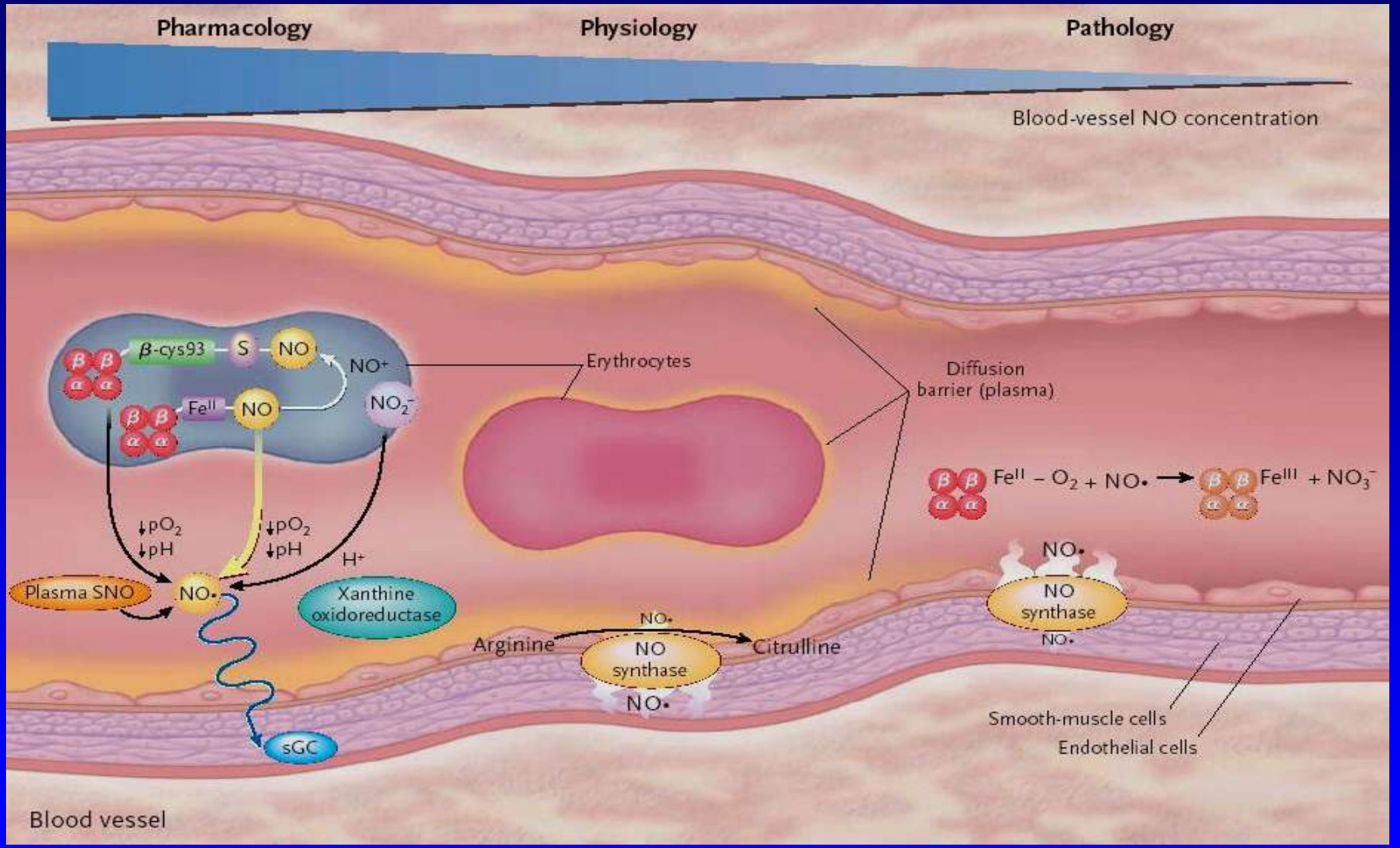
VASO – OCCLUSION

Wick et al



Poiseuille's Formula

$$F = \triangle P \times \frac{\Pi \ r^4}{8 \ \eta \ L}$$

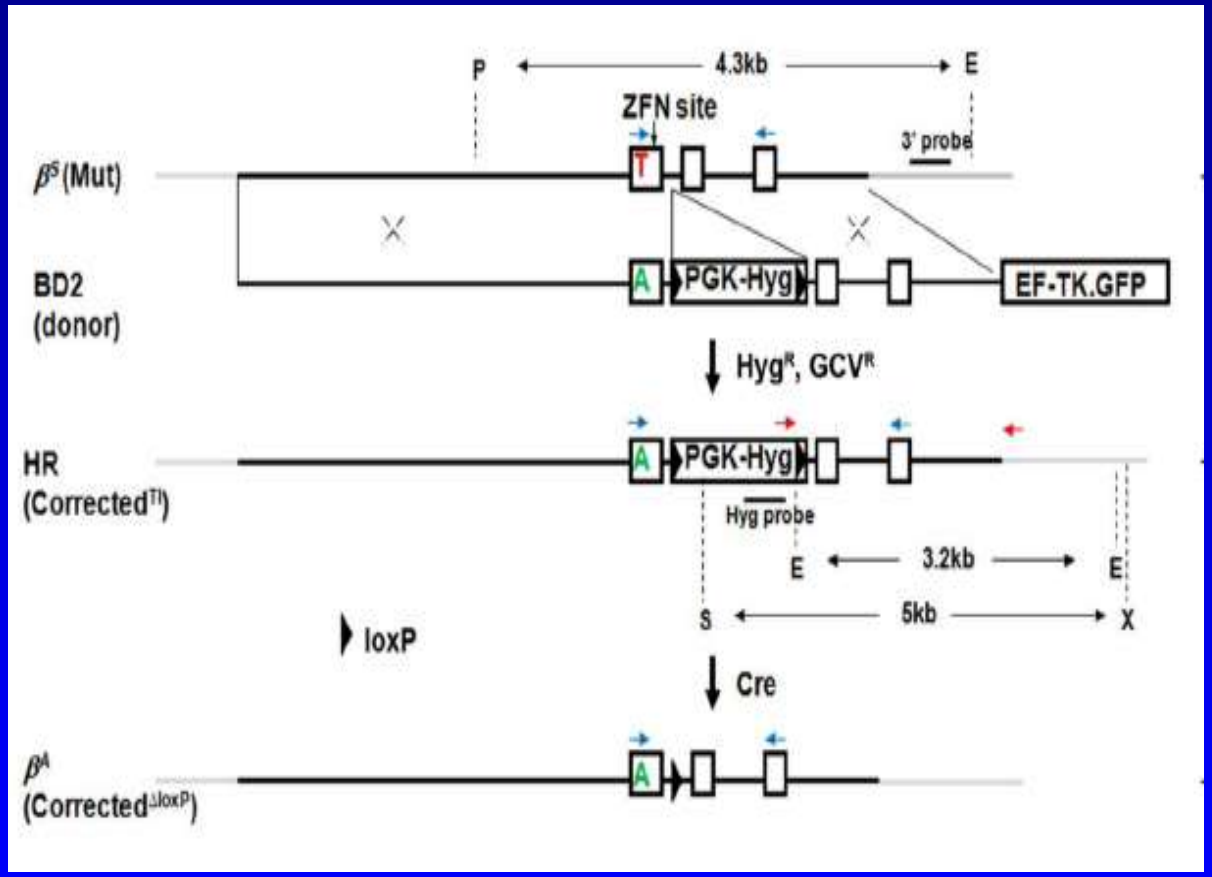


Schechter & Gladwin N Engl J Med 348(15):1483-5, 2003

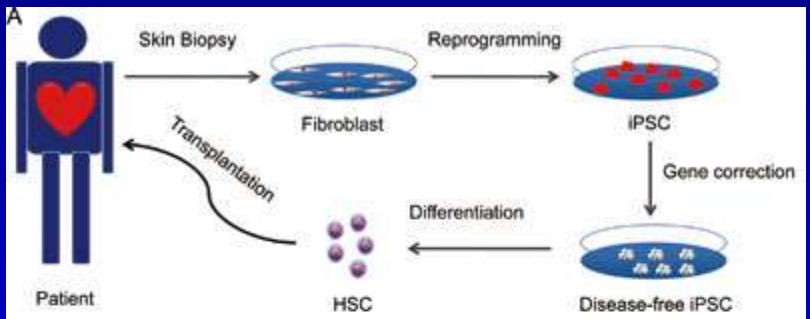
SICKLE PAIN EPISODES

- Increased hemolysis
- Release of arginase reduces NO production and free hemoglobin scavenging of nitric oxide
- Diffuse vasoconstriction with ischemia
- More sickling and hemolysis
- Positive feedback loop intensifying vasoconstriction and diffuse ischemia
- Diffuse Pain

Molecular Genetic Therapy



Zou et al Blood 211;118:4599-4608



B

Diseases	Mutated genes	Reprogramming Factors	Gene Delivery	Ref
Sickle cell	*HBB*	KOSM	Retrovirus	[9]
Sickle cell	*HBB*	KOSL+Lin28 +p53 shRNA	Episomal Vector	[9]
Sickle cell	*HBB*	KOSM+Lin28	*PiggyBac* Transposon	[6, 7]
Sickle cell	*HBB*	KOSM	Lentivirus	[8]
Thalassemia	*HBB*	KOSM	Retrovirus	[4]
Thalassemia	*HBB*	KOS	Retrovirus	[5]
Thalassemia	*HBB*	KOSM or KOS	Retrovirus	[3]
Thalassemia	*HBB*	KOSM	Lentivirus	[14]
Fanconi	*FANCA, D2*	KOSM or KOS	Retrovirus	[11, 12]
Fanconi	*FANCA, C, G, D2*	KOSM	Lentivirus	[13]

Zou et al Cell Research 2012;22:491-494

WWW . SCINFO . ORG

Thank You