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doi:10.1093/qjmed/hcg129

Review

QJM

Fibrinogen: biochemistry, epidemiology and determinants

S. KAMATH and G.Y.H. LIP

From the Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

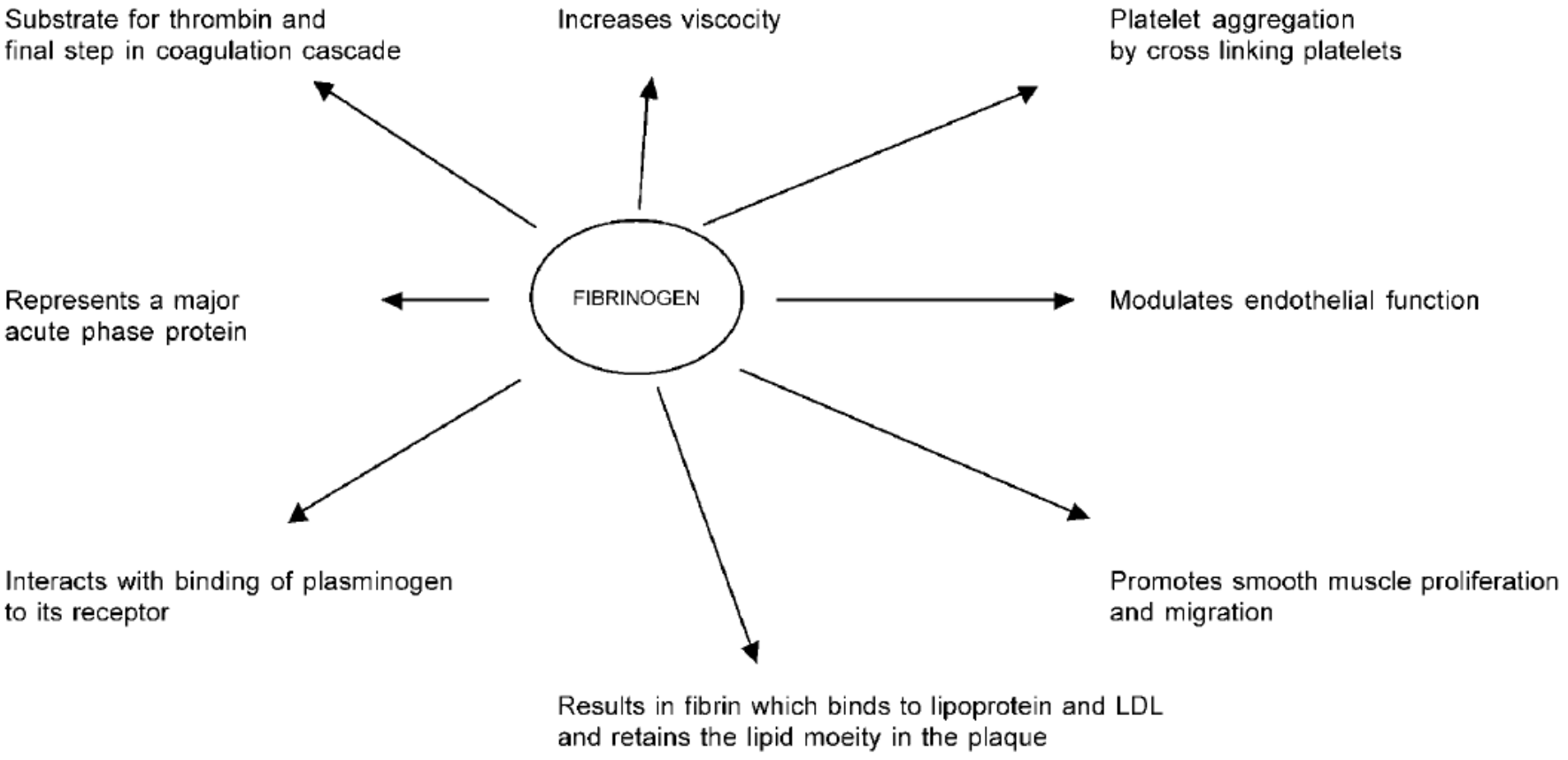
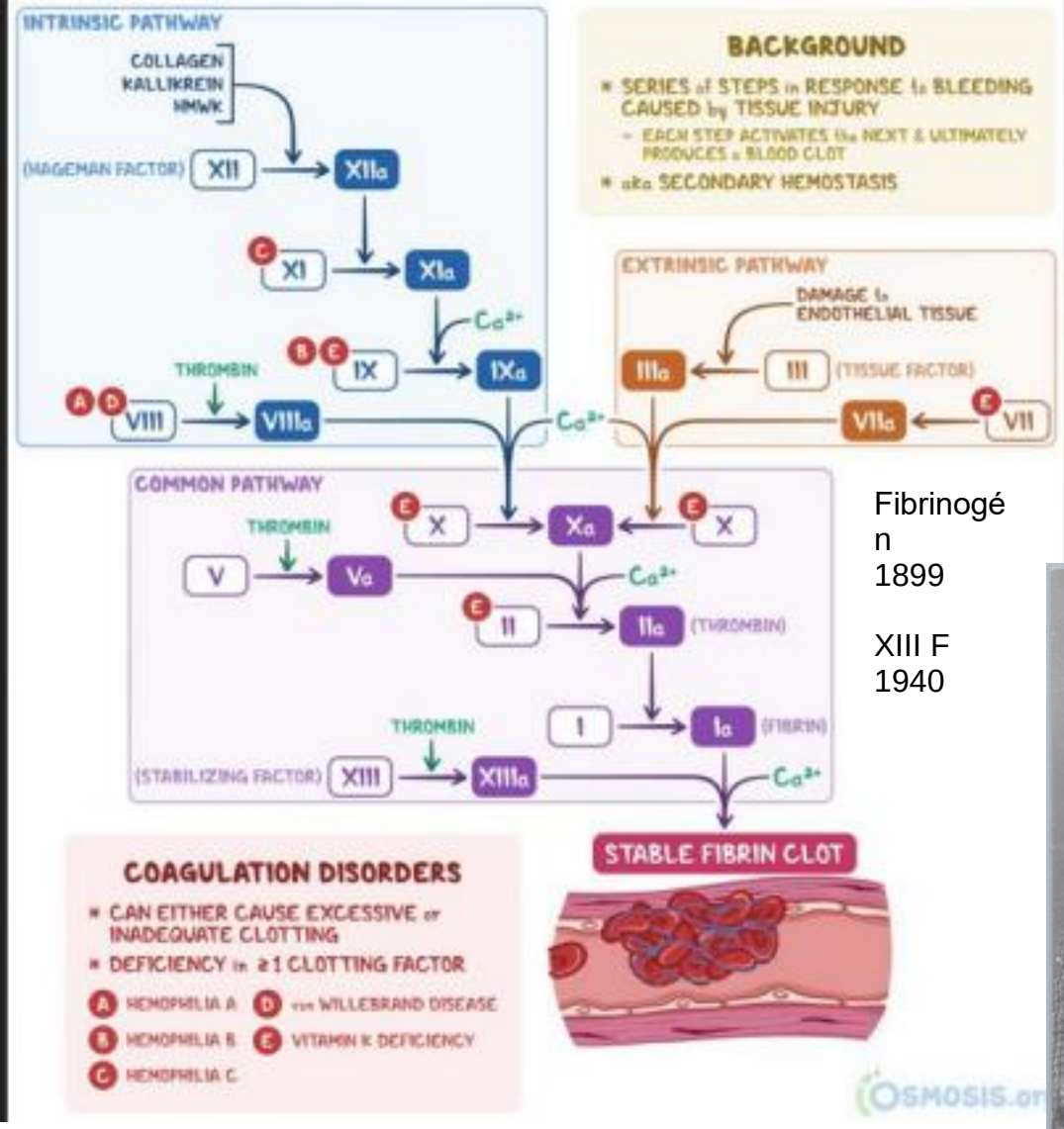
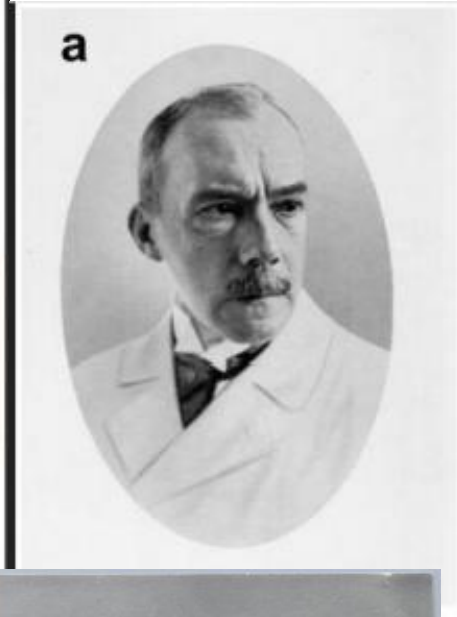


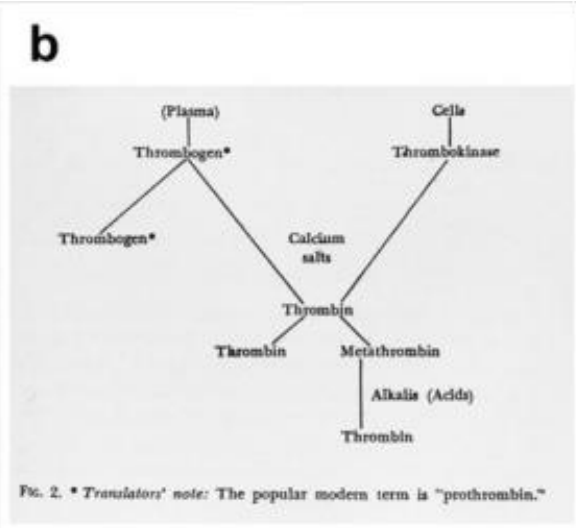
Figure 1. Plasma fibrinogen, thrombogenesis and atherogenesis.



Fibrinogén
1899

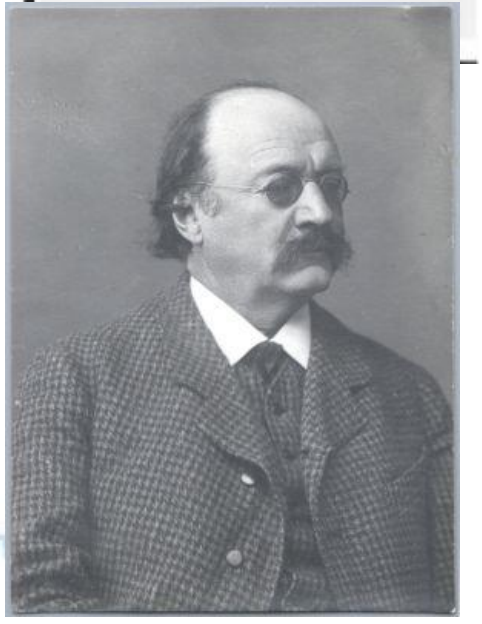
XIII F
1940





Paul Morawitz
1879 - 1936

Ami hiányzik:
AT, HCFII, TFPI
PF4



Alexander Schmidt
1831-1894

Ennek a megjözelítésnek a relevanciája elsősorban in-vitro

Mit nem magyaráz meg (in-vitro szinten!) a Schmidt Morawitz kaszkád ?

X. Y . mintája , Prothrombin Idő

Siemens : 9,5 sec.

IL: 10,8 sec

Stago: 12 sec

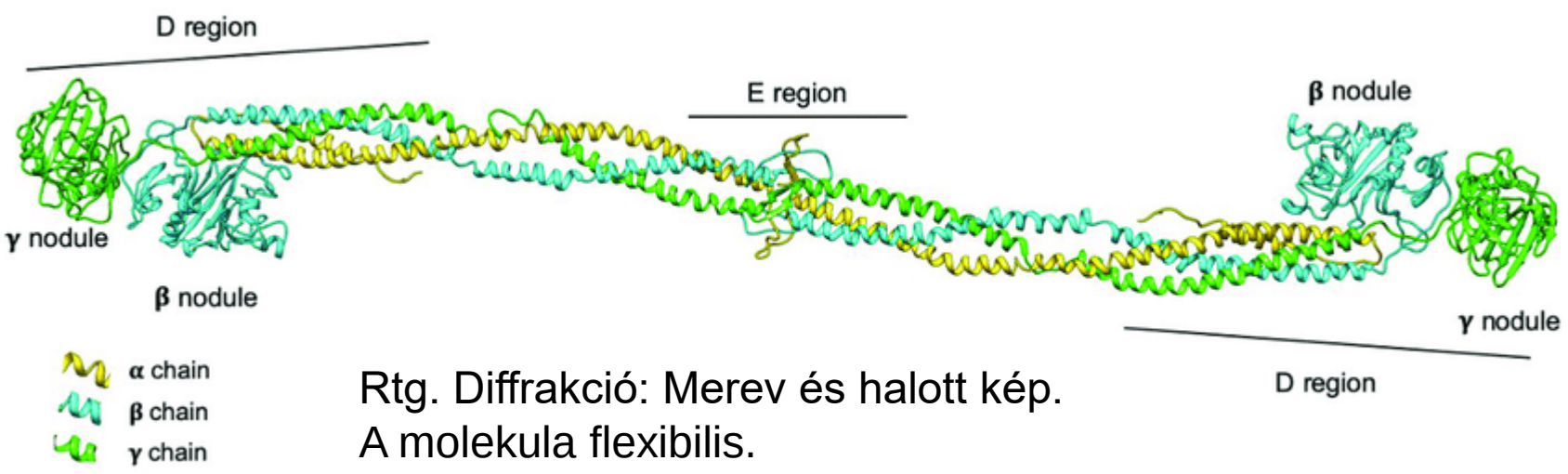
Diagon: 13 sec

Manuális: 17 secundum

XY beteg mintája APTT

3 éves 20 éves 50 éves 80 éves

40 sec. 36 sec. 32 sec. 28 sec.



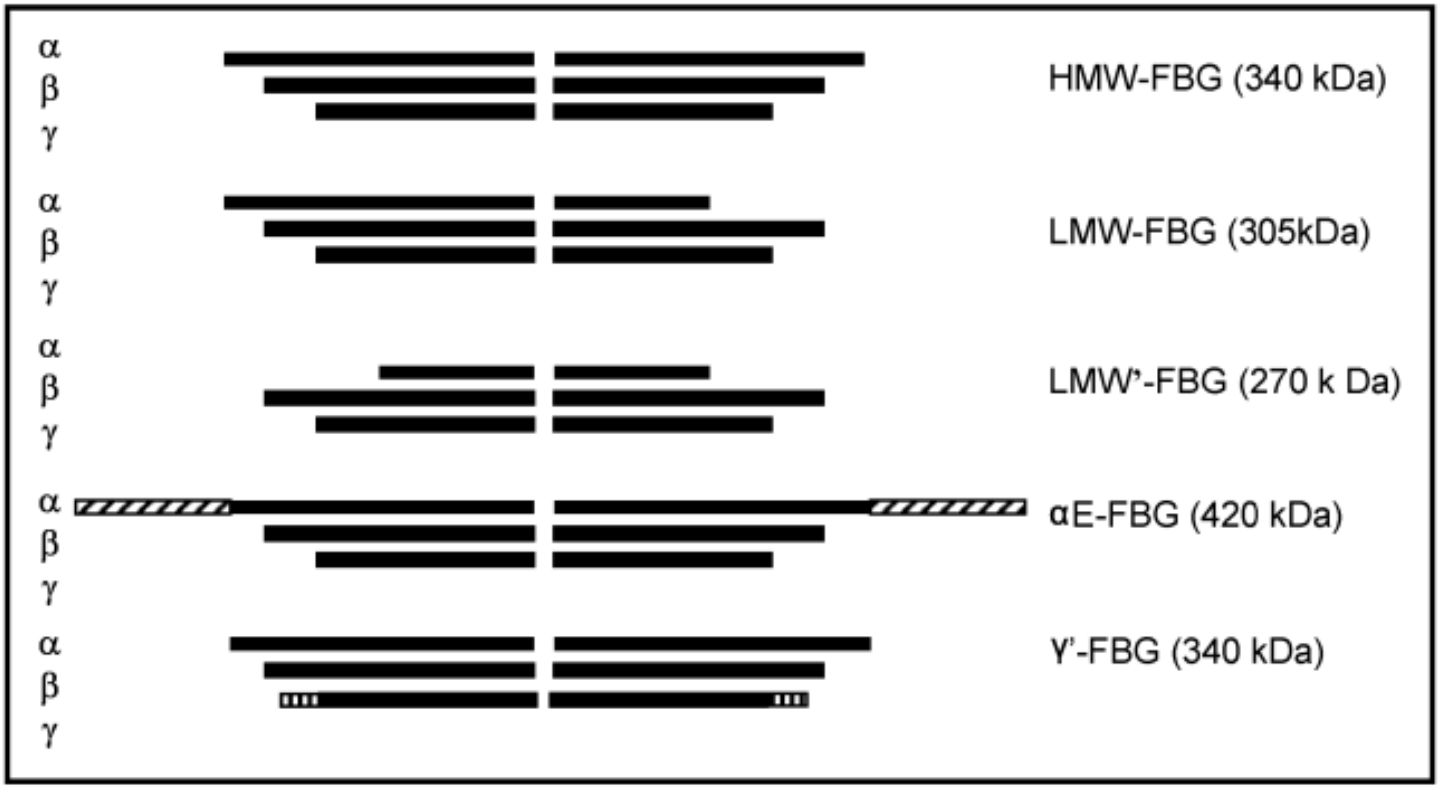
Rtg. Diffrakció: Merev és halott kép.
A molekula flexibilis.

3 láncpár (2 alfa, 2 béta, 2 gamma)

Jelentős genetikai polimorfizmusok : gamma ’ és béta

A harmadlagos szerkezet döntően befolyásolja a thrombinhoz való affinitását és ezen keresztül az alvadási képességét

Figure 3. Main plasma forms of fibrinogen



Bars indicate relative size of fibrinogen Aα, Bβ and γ chains; hatched bars indicate elongated sequences.

A Fbg. Szintézise után poszttranszlációsan módosul méreteiben. Egy minta ezen molekulaformák keveréke. Az arányok egyénenként változók . A nagyobb molekulák gyorsabban alvadnak. Az öregedéssel az eloszlás a nagy molekulák fele tolódik el.

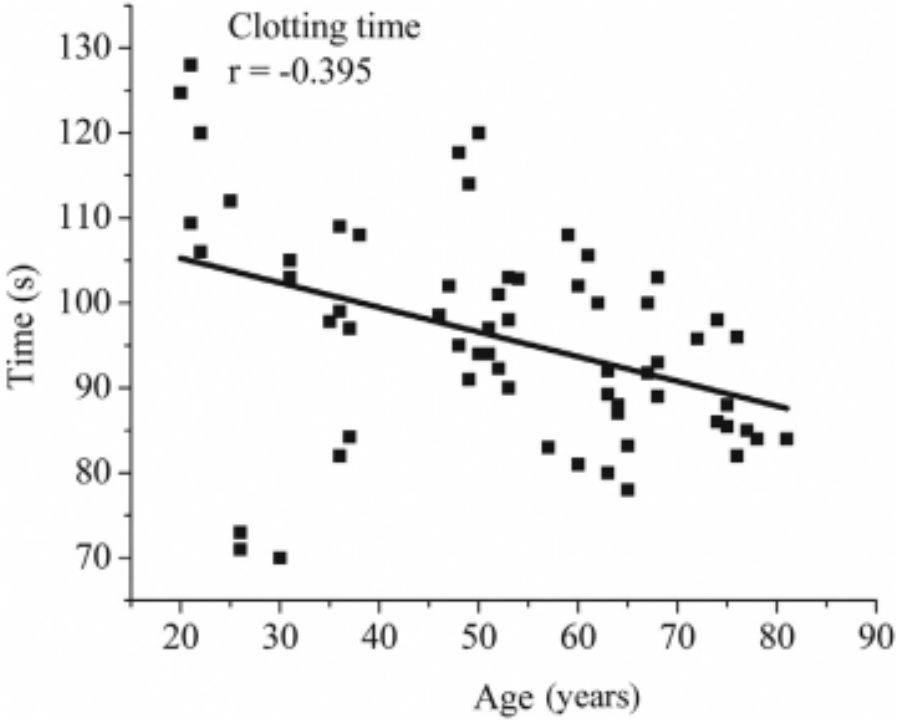


Fig. 3. Clotting time analysis in relation to aging. Turbidimetric analysis of fibrin clot formation was performed in a microplate using isolated fibrinogen at a final concentration of 0.8 mg/ml. After thrombin addition, microplate was immediately placed in a Victor^{3}V multilabel reader. Optical density was measured at 350 nm, every 10 s. Clotting time for each sample was calculated as the time required to reach a midpoint between the minimum and maximum optical density. r- Pearson correlation coefficient.

A fibrinogén molekula eloszlása az atheroszklerózis egyik rizikófaktora. Sajnos ez a mért alvadási sebességgel csak gyengén korrelál, mert a laboratóriumban alkalmazott ún. Clauss módszer sem az eloszlást nem tükrözi vissza, sem a valódi koncentrációt.

A konformációt befolyásoló szubsztitúciók normál körülmények között;
Glikoziláció, foszforiláció, tirozíniláció

Patológiás módosulatok:

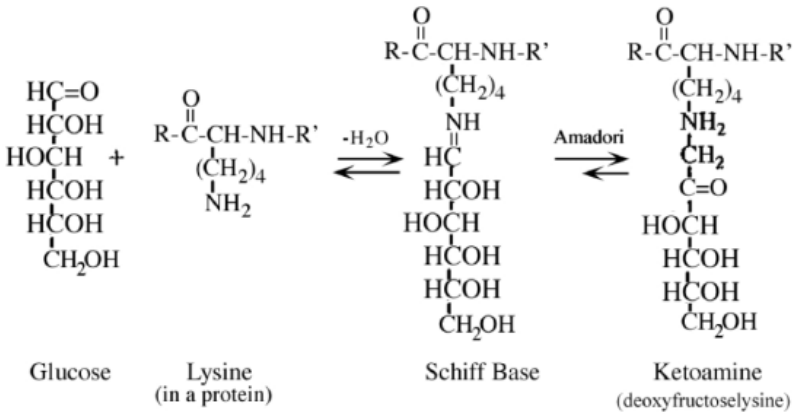


Fig. (2). Non-enzymatic condensation of glucose with a lysine residue in a protein - the first step in the Maillard reaction.

[66].

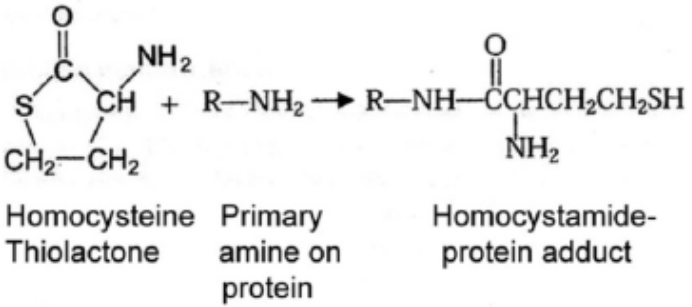


Fig. (1). The reaction of homocysteine thiolactone with a primary amine. The most favored such reaction under physiologic conditions is with the ε-amino group of lysine residues.

Diabétesz

Homociszteinemia

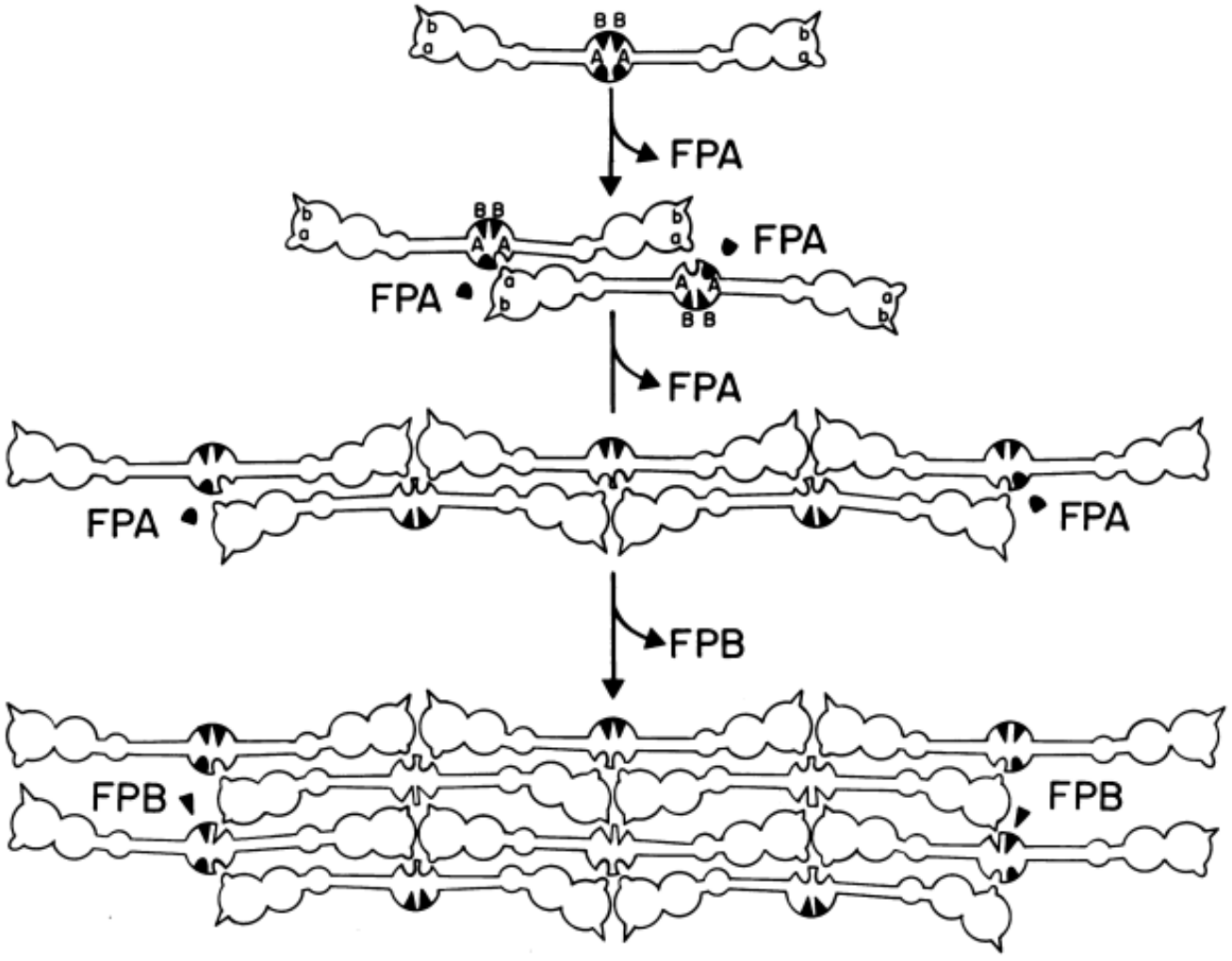
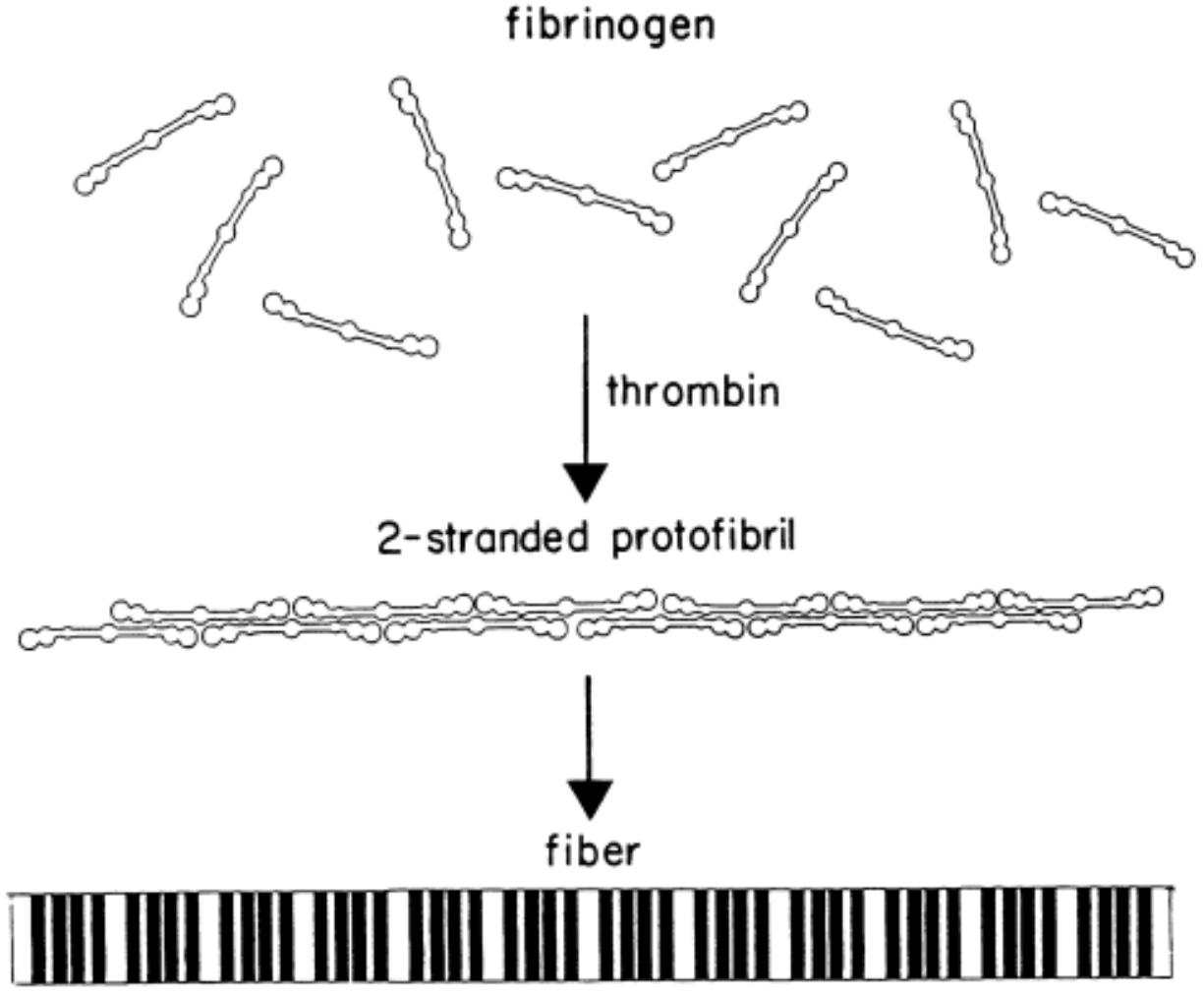
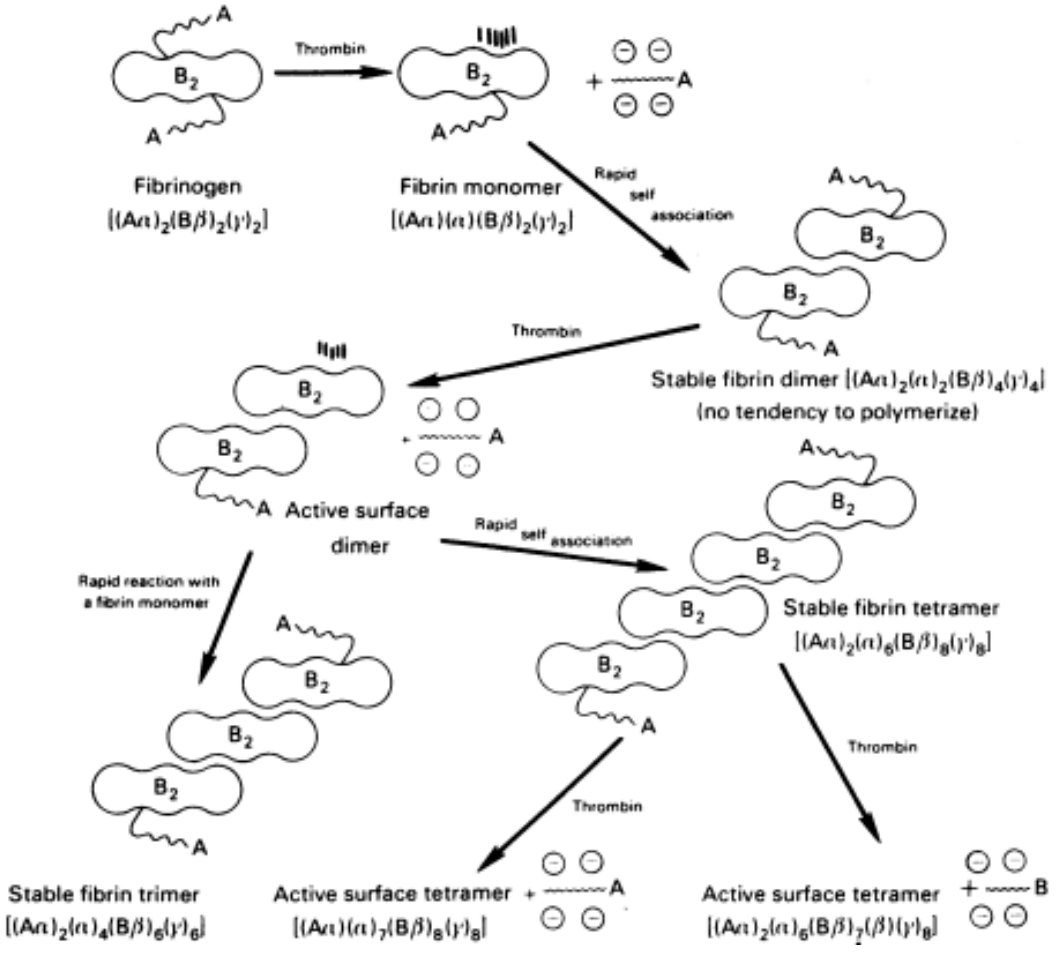
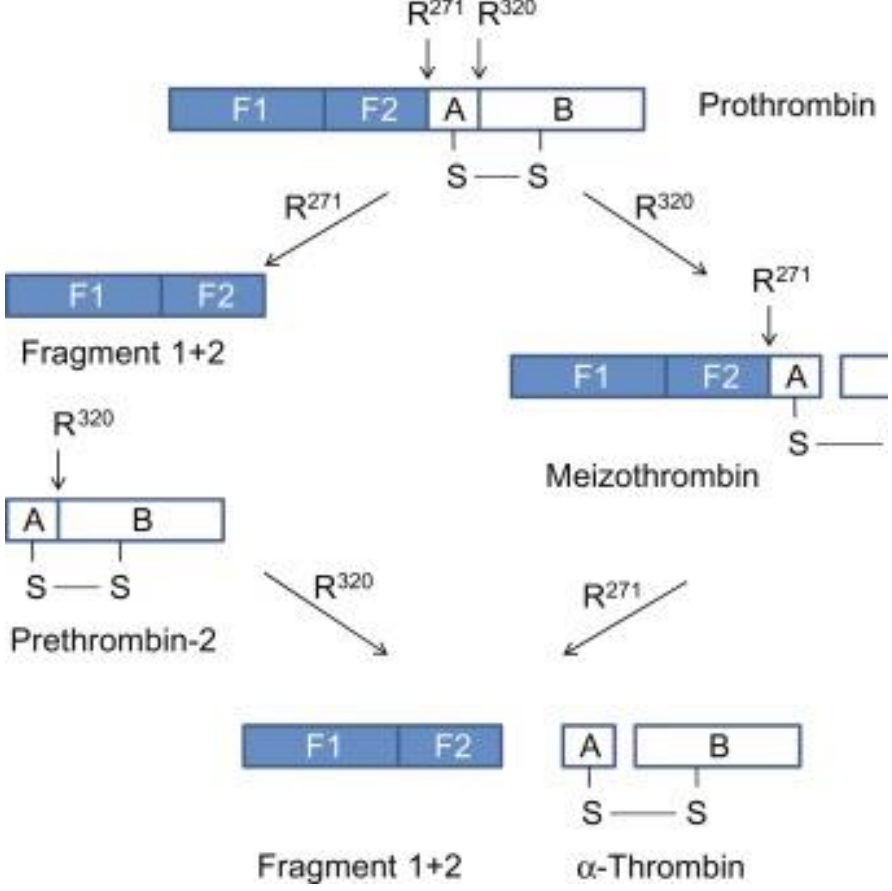


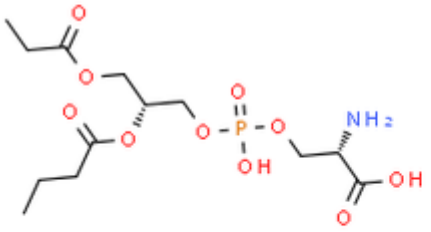
FIGURE 1 A model for fibrin assembly involving two sets of complementary binding sites: one for protofibril formation and another for


fibrinogen
thrombin
2-stranded protofibril
fiber

MECHANISM OF FIBRIN POLYMERIZATION



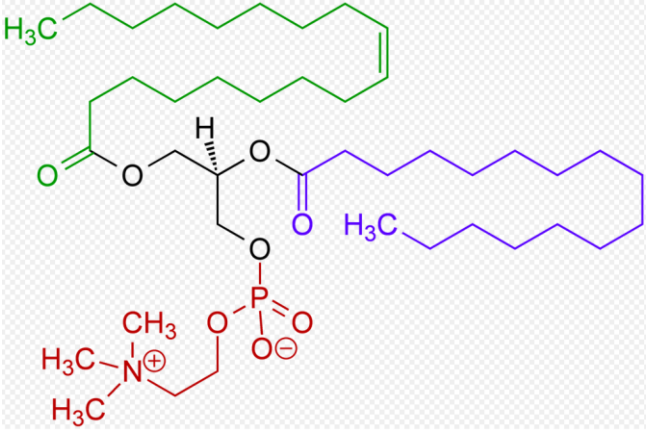




Phosphatidylserine

Molecular Formula	$C_{13}H_{24}NO_{10}P$
Average mass	385.304 Da
Monoisotopic mass	385.113770 Da
ChemSpider ID	13628254

- 2 of 2 defined stereocentres



phosphatidylcholine

1, Az intermedierek vagy a FPA v. a FPB lehasítására képesek csak.

2,Az a tény, hogy melyik út a domináló a PS/PC aránytól függ (a reagensben; in vivo a thrombocyta membrán aktivációs állapotától.

FIG 1 - uploaded by Danilo S. Boskovic

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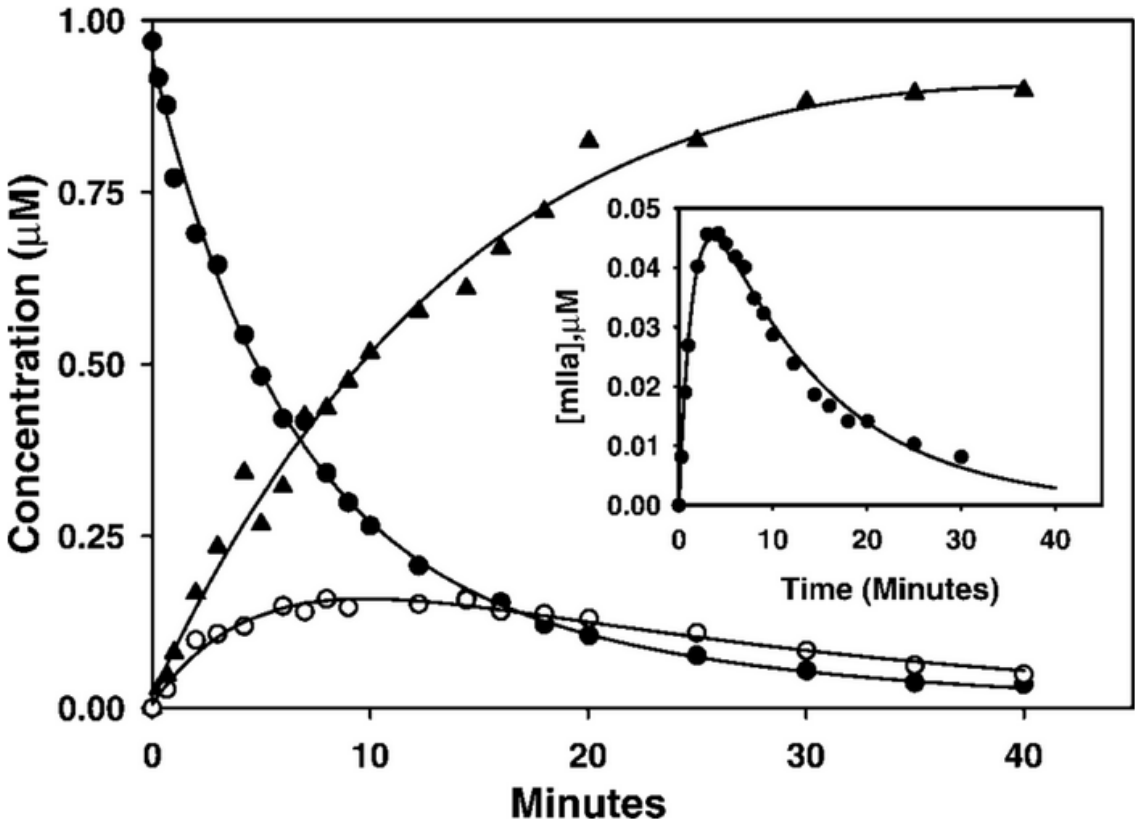
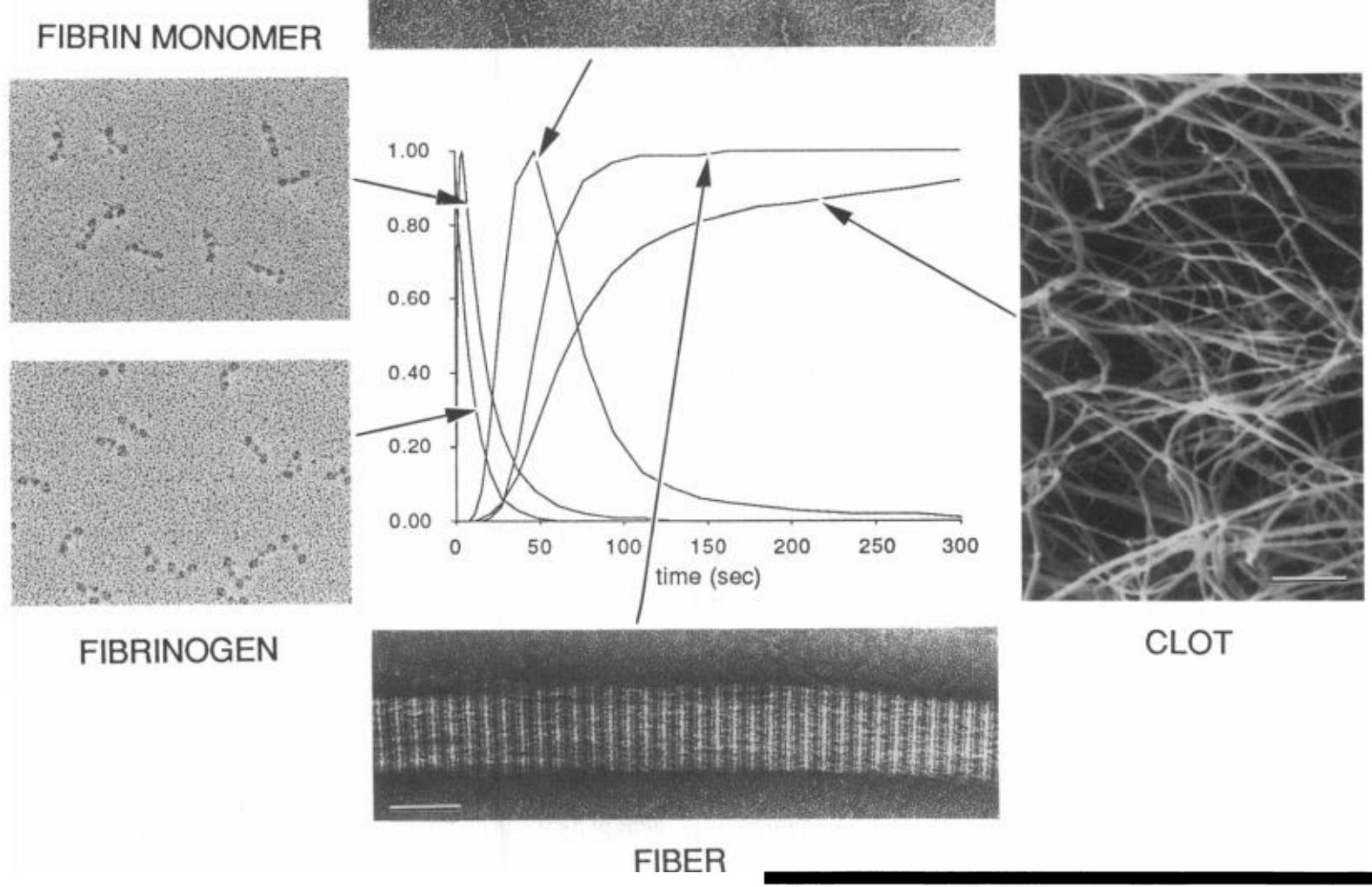


Time courses of prothrombin, meizothrombin, pre- thrombin-2, and thrombin during prothrombin activation. The concentrations of prothrombin (closed circles), meizothrombin (closed circles, inset), prethrombin-2 (open circles), and thrombin (closed triangles) were measured as described under " Experimental Procedures. " The thrombin time course does not show the initial lag expected for a reaction that has free meizothrombin and

A kis kockában az össz thrombin mennyiség időbeli lefutása látható.

A nagy kockában a prothrombin csökkenés, és a prethrombin ill. meizothrombin aktivációs kinetikája



Computer modeling of fibrin polymerization kinetics correlated with electron microscope and turbidity observations: clot structure and assembly are kinetically controlled

John W. Weisel and Chandrasekaran Nagaswami
Department of Anatomy, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6058 USA

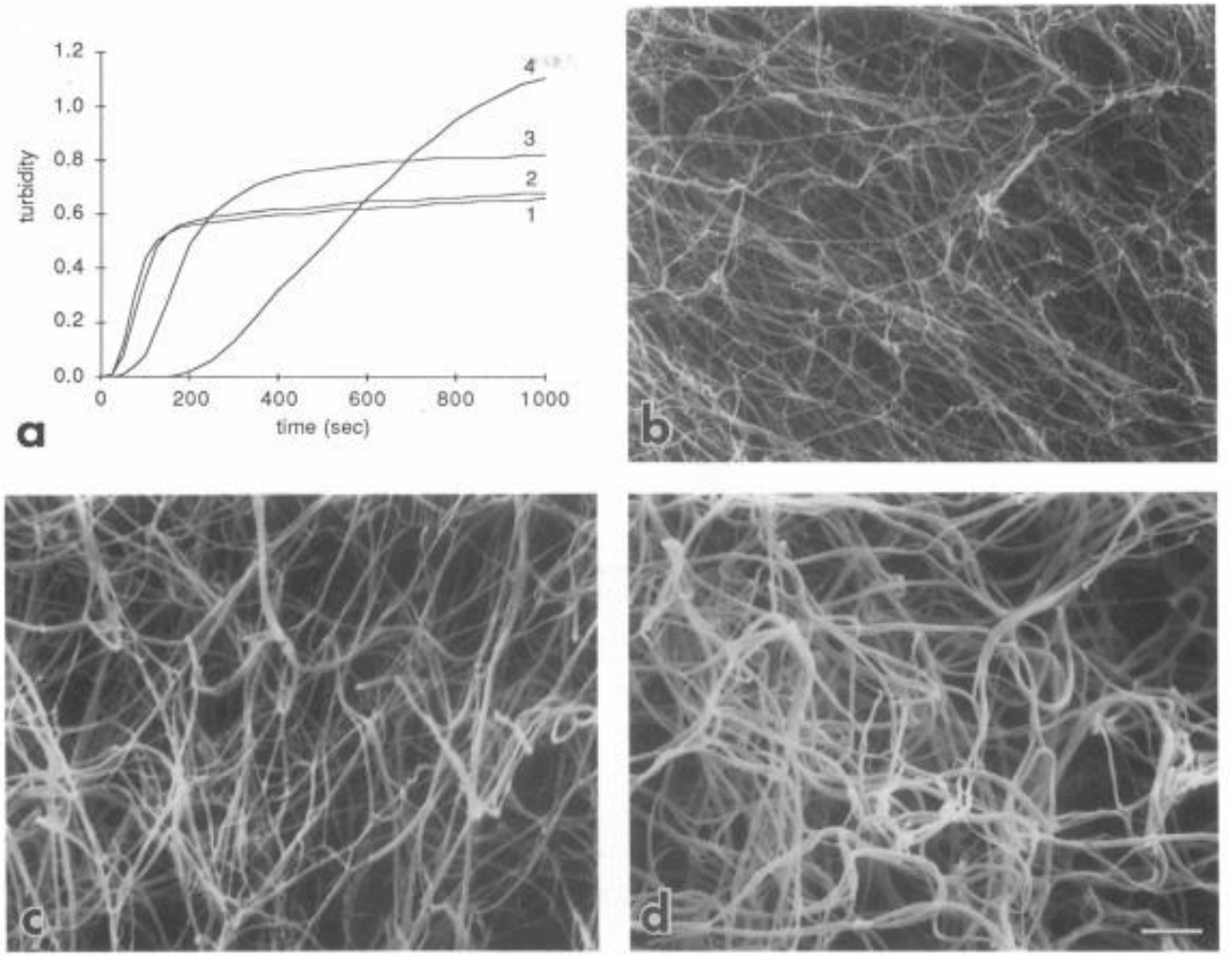


FIGURE 4 Effects of thrombin concentration on clot structure and turbidity curves. (*a*) Turbidity curves for clots formed using different thrombin concentrations: (1) 1 unit/mL; (2) 0.1 unit/mL; (3) 0.01 unit/mL; (4) 0.001 unit/mL. Compare these curves with the variation of k_A in Fig. 3. (*b*, *c*, and *d*) Scanning electron micrographs of clots formed using different concentrations of thrombin: (*b*) 1 unit/mL; (*c*) 0.01 unit/mL; (*d*) 0.001 unit/mL. The bar represents 1.0 μm.

Chronometric

Clauss diluted, optical and mechanical.
'Clauss Undiluted', optical and mechanical.

Immunological

RID
Intact[1]
Nephelometric
Turbidimetric

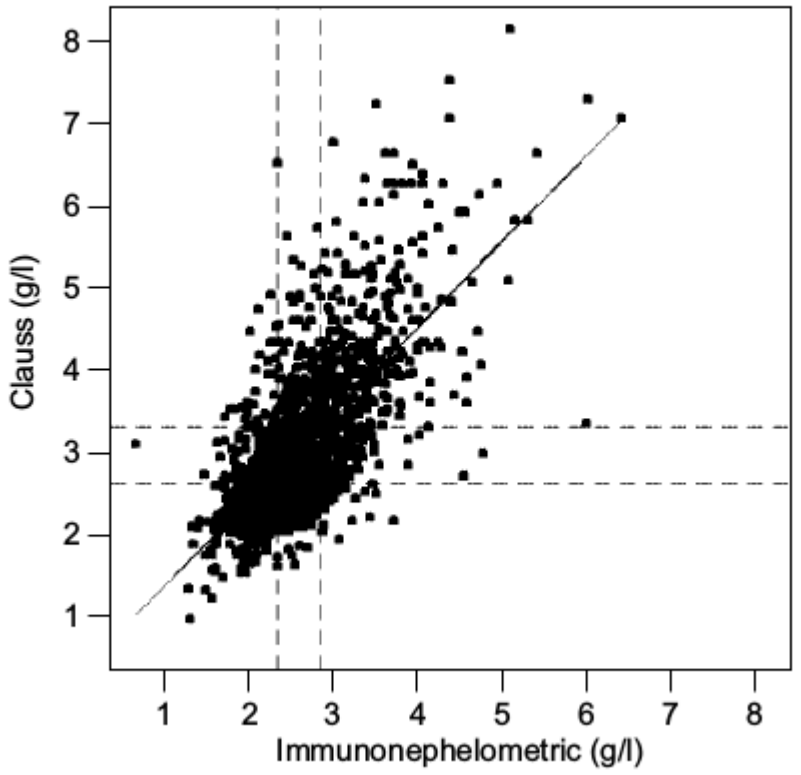
Derived[2]

Nephelometric
Turbidimetric

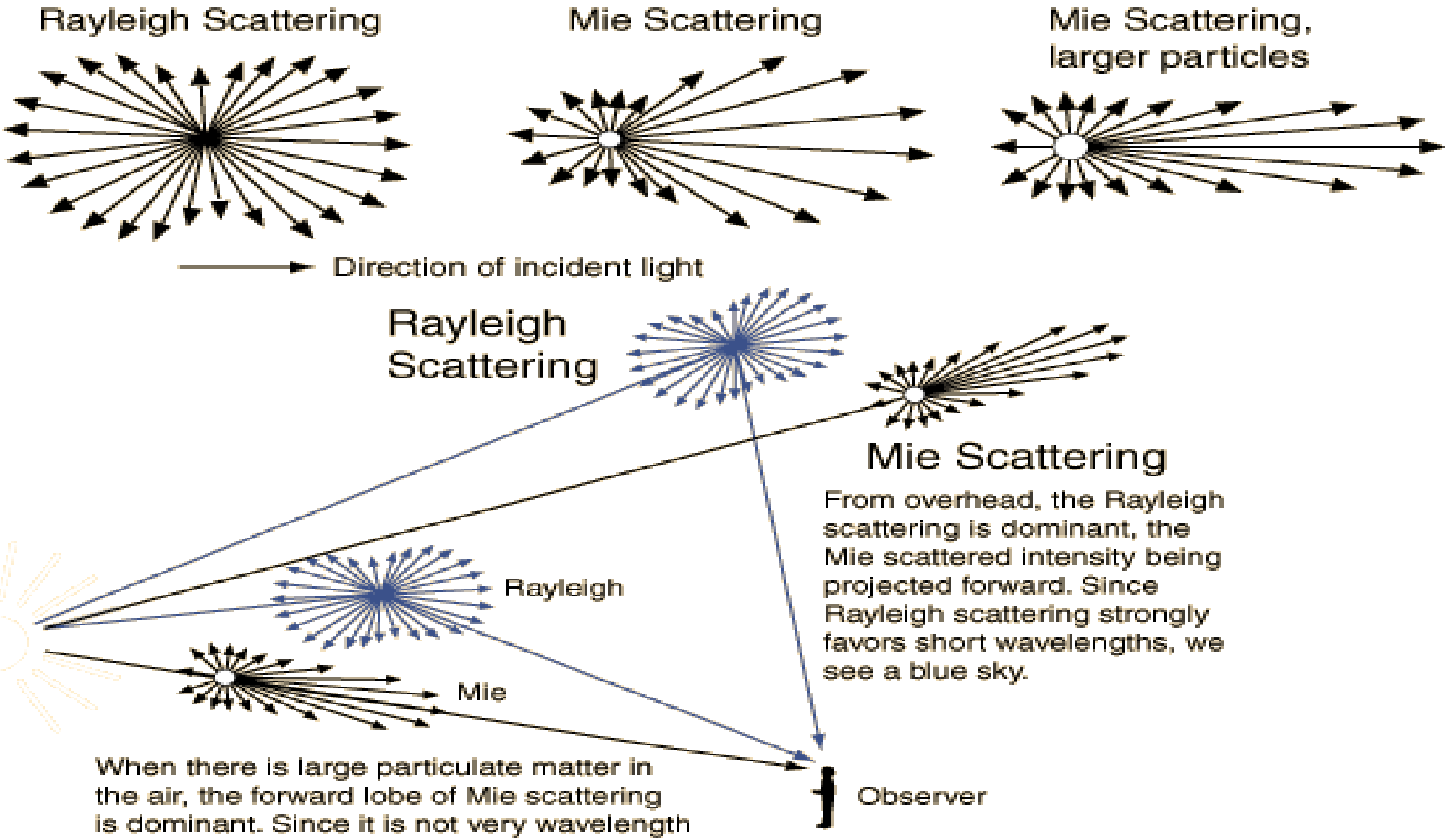
Clottable

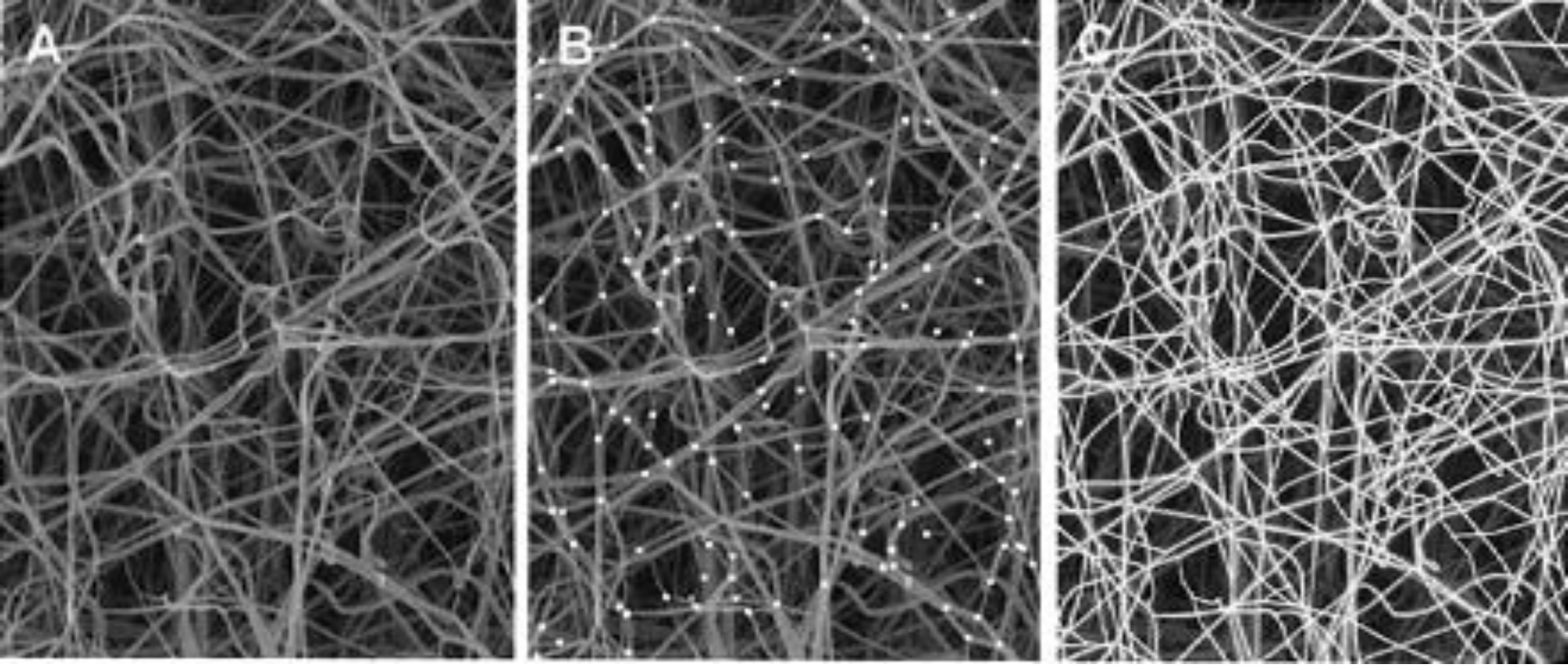
Clot dry weight (gravimetric).
Clot protein concentration (A_{280} Blombäck, Jacobsson).
Clot protein concentration (Biuret, Ratnoff Menzie).
Clot protein concentration (dye binding).
Clotting rate (kinetic).

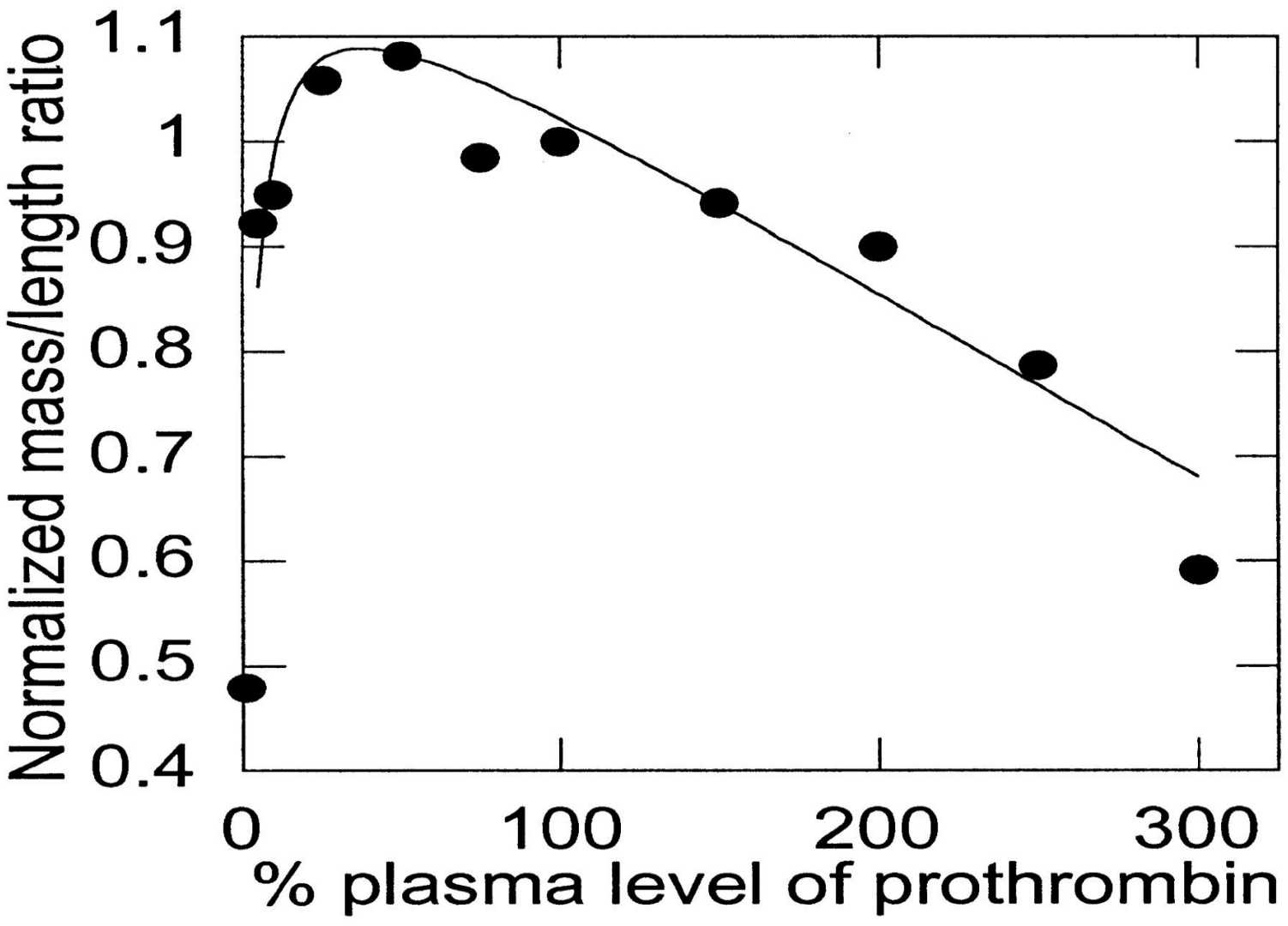
Fig. 3



Fibrinogén meghatározási módszerek


Rayleigh Scattering
Mie Scattering
Mie Scattering, larger particles
Direction of incident light
Rayleigh Scattering
Mie Scattering
From overhead, the Rayleigh scattering is dominant, the Mie scattered intensity being projected forward. Since Rayleigh scattering strongly favors short wavelengths, we see a blue sky.
Rayleigh
Mie
When there is large particulate matter in the air, the forward lobe of Mie scattering is dominant. Since it is not very wavelength dependent, we see a white glare around the sun.
Observer


A
B
C


Normalized mass/length ratio
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0
100
200
300
% plasma level of prothrombin

[63] Continuation-in-part of Ser. No. 846,992, June 13, 1969, Pat. No. 3,635,678, which is a continuation-in-part of Ser. No. 738,382, June 17, 1968, abandoned.

[52] **U.S. Cl.** ..... **23/253 R;** 23/259; 73/57; 73/59; 73/64.1

[51] **Int. Cl.**[2] **G01N 11/10;** G01N 33/16

[58] **Field of Search** ..... 23/230 R, 230 B, 253 R, 23/259; 73/57, 59, 64.1

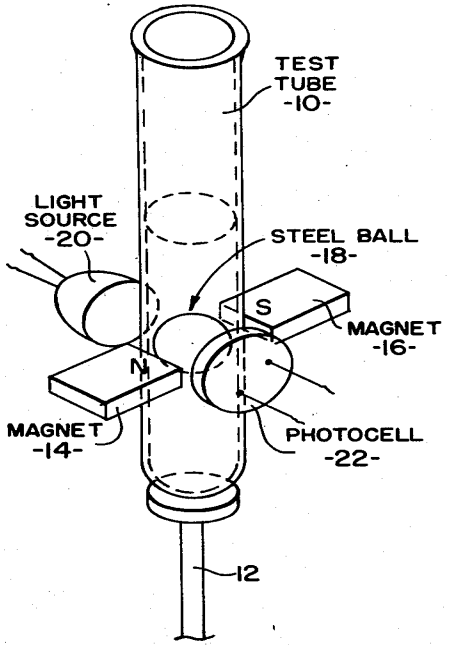
[56] **References Cited**

UNITED STATES PATENTS

2,957,338 10/1960 Kennedy et al. 73/54

cosity to a particular level. The system and method to be described is predicated on a viscosity principle, and it includes a movable magnetic member suspended in the fluid sample and which changes position when the sample achieves a predetermined degree of viscosity. The change in position of the aforesaid member is photoelectrically or electromagnetically detected, and the time at which the change occurs, is used in the determination of the time required, for example, for the sample to form a fibrin clot, in a blood or plasma sample or to effect a particular reaction causing solidification or congealing of the sample.

1 Claim, 8 Drawing Figures



Archives of Gerontology and Geriatrics
Volume 19, Supplement 1, 1994, Pages 99-106

Plasma fibrinogen — are there age-dependent changes?

K. Hager [a], G. Seefried [b], M. Felicetti [b], D. Platt [b]

Table II. The clinical utility of fibrinogen assays.

Investigation of a haemorrhagic state (afibrinogenaemia, hypofibrinogenaemia, acquired or congenital dysfibrinogenaemia)
Investigation of unexpected prolonged/abnormal coagulation tests
Detection of DIC
The establishment and monitoring of prolonged thrombolytic therapy
During Arvin therapy
Risk assessment profiling for arterial disease
Commercial use (diagnostics industry, pharmaceutical industry, blood transfusion service) for quality monitoring and potency assignment (e.g. factor VIII and fibrinogen concentrates)

Minden adat a referens tartományon belül van !

Table 1 Mean fibrinogen concentration in different epidemiological studies

Study (reference)	Method	*n*	Mean fibrinogen (g/l)		*p*
			Without CHD	With CHD	
Northwick Park Heart Study (Meade *et al.* 1986)	Gravimetry	1511	2.90	3.15	< 0.001
Framingham (Kannel *et al.* 1987)	Spectrophotometry	1315	2.91		
Goteborg (Wilhelmsen *et al.* 1984)	Spectrophotometry	792	3.30	3.56	< 0.001
Leigh (Stone *et al.* 1985)	Nephelometry	297	3.13	3.92	< 0.001
PROCAM (Heinrich *et al.* 1991)	Clauss	2187	2.62	2.86	< 0.01
Copenhagen (Moller *et al.* 1991)	Gravimetry	438	2.73		
Caerphilly (Yarnell *et al.* 1985)	Nephelometry	134	3.60		
Speedwell	Nephelometry	226	2.97	2.87	NS
(Baker *et al.* 1982)	Clauss	223	4.02	4.39	< 0.01

Adapted from Dippel K. Fibrinogen; a cardiovascular risk factor. Boehringer Mannheim GmbH 1992, 1st edition.

Table 2 Plasma fibrinogen levels according to endpoints in epidemiological studies

Study (reference)	Person-years	Number of events	Fibrinogen level according to end point	
			End point	Fibrinogen level (g/l)
Northwick Park Heart Study (Meade *et al.* 1986)	15 110	128	None	2.9
			IHD deaths	3.1
			IHD non-fatal	3.2
			All IHD end points	3.2
			Other deaths	3.0
Gothenburg Study (Wilhelmsen *et al. 1984)*	10 692	130	None	3.3
			MI	3.6
			Stroke	3.7
			Other deaths	3.3
Leigh Study (Stone *et al.* 1985)	2168	40	None	3.0
			MI	4.0
Framingham Study (Kannel *et al.* 1987)	15 780	404	16 events/1000/year	< 2.7
			18 events /1000/year	2.7–3.1
			26 events/1000/year	> 3.1
Caerphilly and Speedwell Studies (Yarnell *et al.* 1991)	20 325	251	None	3.7
			IHD	4.1
Munster Heart Study (Assmann *et al.* 1996)	4045	15	None	2.6
			Any event	3.3
GRIPS (Cremer *et al.* 1996)	26 195	107	None	3.7
			MI	4.0

GRIPS, Gottingen Risk, Incidence and Prevalence Study; IHD, Ischaemic Heart Disease; MI, myocardial infarction. Adapted from reference 39.

A Clauss módszer nem igazán alkalmas CHD rizikó mérésére

Főbb üzenetek

1, A fibrinogén méretében, szerkezetében egy egyénen belül is heterogén. Az eloszlás korfüggő.

2, Az atheroszklerózis előrehaladtával a nagyobb molekulaformák dominálnak.

2, A prothrombin és thrombin közötti intermedierek aránya döntően befolyásolják a fibrinháló szerkezetét.

3, A fibrinháló kialakulásának kinetikáját másképp követi a nefelometria (oxigén gerjesztés) mint a viszkozimetria (szál hossz/vastagság)

4, A fibrinháló szerkezete meghatározza a fibrinolitikus lehetőségeket.

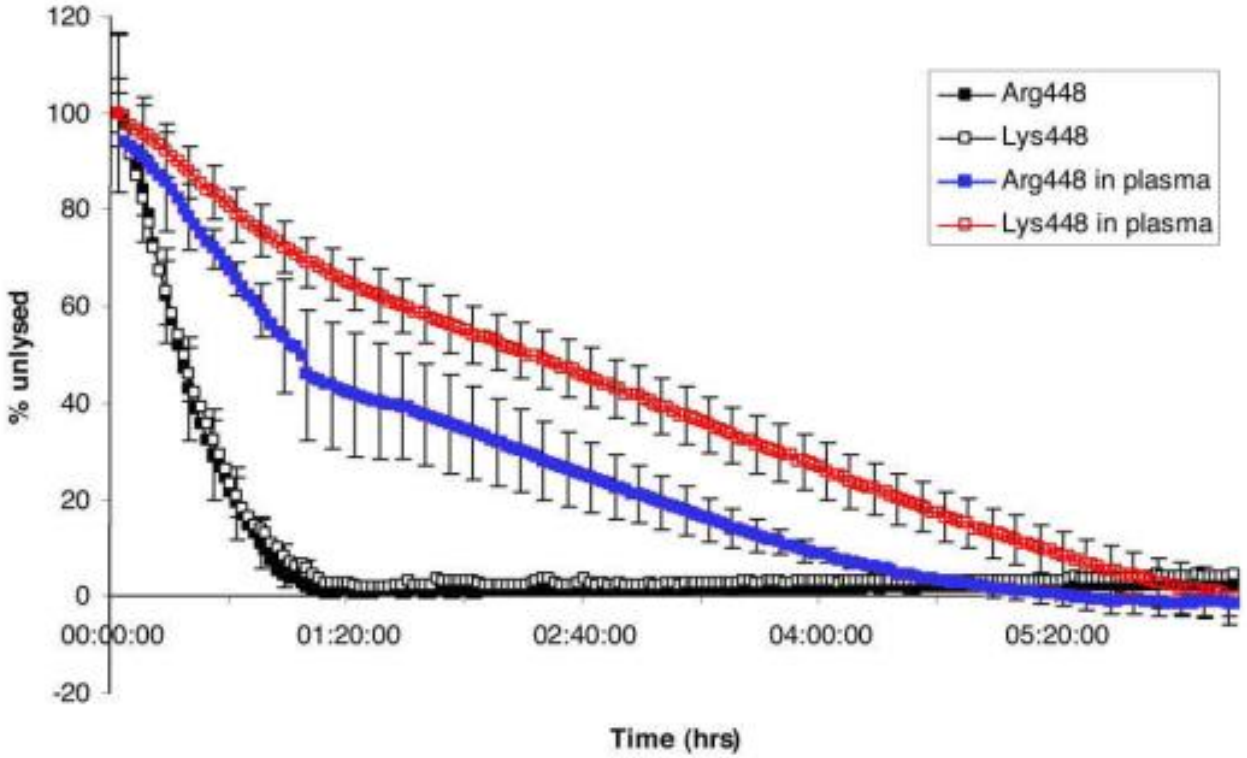


Figure 4. Macroscopic lysis velocity of fibrin clots formed from recombinant BβArg448 and BβLys448. Fibrinolysis was assessed directly after completion of polymerization (1.2 μmol/L fibrinogen, 2.5 mmol CaCl$_2$ and 0.5 U/mL thrombin) at

Dogmák és anekdoták

Sas Géza

"If a physician lives long enough, a few things he or she reported will turn out to be true."

R. C. Williams (New England Journal of Medicine, 2003)

Az hogy a laboratóriumban a fibrinogén koncentrációt határozzuk meg az egy (hamis) dogma

Az hogy (látszólag) alacsony fibrinogén aktivitásnál vérzés lép fel, csak anekdota.