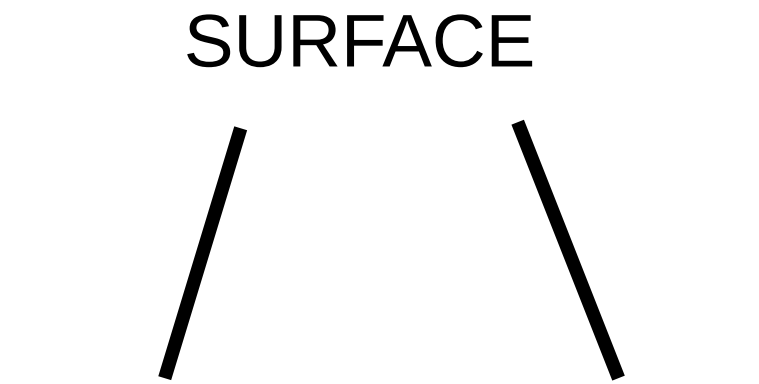
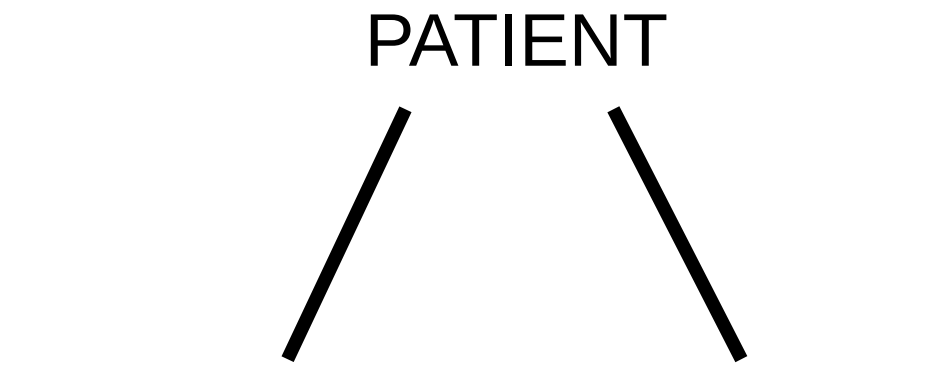
EARLY INFLAMMATORY RESPONSES TO VASCULAR DEVICES

JAMES M. ANDERSON, MD, PhD
DISTINGUISHED UNIVERSITY PROFESSOR
DEPARTMENTS OF PATHOLOGY, MACROMOLECULAR SCIENCE,
AND BIOMEDICAL ENGINEERING
CASE WESTERN RESERVE UNIVERSITY

INTERACTIONS IN PIS



VIRCHOWS TRIAD



POSTIMPLANTATION SYNDROME - PIS

INFLAMMATORY RESPONSE FOLLOWING ENDOVASCULAR REPAIR OF AN AORTIC ANEURYSM – EVAR

CLINICAL INDICATIONS:

FEVER: >38℃
LEUKOCYTES: >12,000/µL, >10,000/µL, >9,800/µL
CRP: >10mg/L

- RELEASE OF INFLAMMATORY MEDIATORS
- ENDOTHELIAL DYSFUNCTION
- GRAFT MATERIAL: WOVEN DACRON, ePTFE, NITINOL
- ENDOVASCULAR SURGICAL/DEPLOYMENT TECHNIQUE
- CO-MORBIDITIES

EARLY AND LATE RESPONSES IN BLOOD/TISSUE/MATERIAL INTERACTIONS

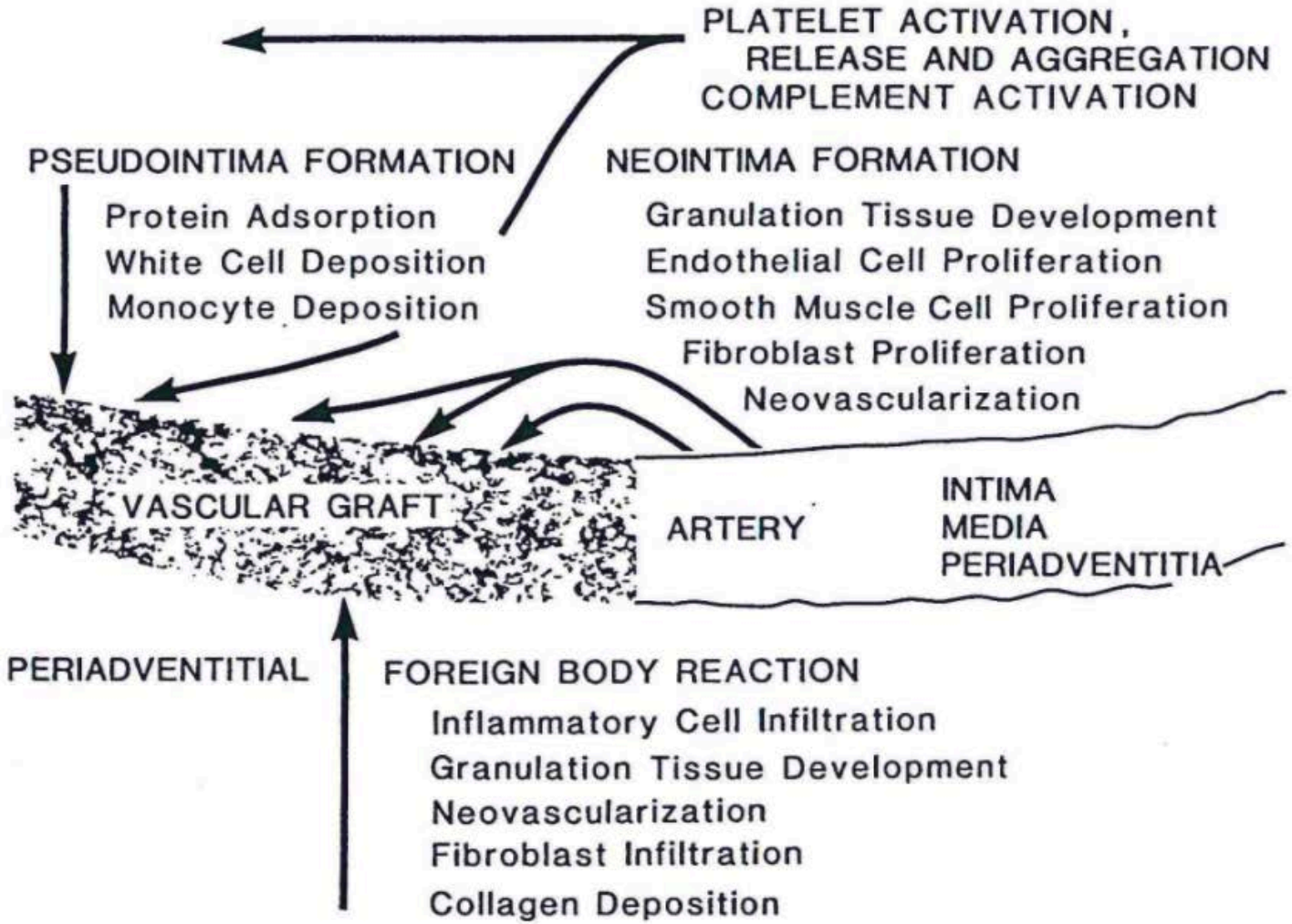


Fig. 1. Interactions controlling the success or failure of vascular grafts.

DISEASED ABDOMINAL AORTIC ANEURYSM

ATHEROSCLEROSIS

CELL TYPES:	MARKERS:
ENDOTHELIUM	IL-1, IL-6, TNF-α, CRP
NEUTROPHILS	IL-8, FGF, IL-10,
MACROPHAGES	MMPs, TIMPs
DENDRITIC CELLS	Proteases
MAST CELLS	
T and B LYMPHOCYTES	INF-ɣ, IL-2
STEM/PROGENITOR CELLS	
PLATELETS	PF-4, β-TG

ENDOVASCULAR DEVICES DEPLOYMENT INDUCED EFFECTS

MARKED ALTERATIONS IN BLOOD FLOW
- TURBULENCE, STASIS

FOCAL THROMBOSIS – PROVISIONAL MATRIX
- PRIMARY AND SECONDARY COAGULATION
- PLATELET ADHESION, AGGREGATION, AND ACTIVATION
- INFLAMMATORY CELL ADHESION AND ACTIVATION

ENDOTHELIAL DENUDATION, DYSFUNCTION

ATHEROSCLEROTIC PLAQUE DISRUPTION

INCOMPLETE DEPLOYMENT OF ENDOVASCULAR DEVICE

THROMBOSIS

SURGICAL INJURY

ENDOTHELIAL INJURY
- DEPLOYMENT– EXTENT
- EXTENT OF ATHEROSCLEROSIS
- PLAQUE VULNERABILITY

FLOW DISTURBANCE
- TURBULENCE, STASIS

COAGULATION – PRIMARY, SECONDARY

PLATELET ADHERENCE, AGGREGATION

PROVISIONAL MATRIX - THROMBUS

THROMBUS – PROVISIONAL MATRIX

ACUTE PHASE RESPONSE

FIBRIN NETWORK CONTAINING:

- COAGULATION PRODUCTS
- PLATELET PRODUCTS
- CELLULAR PRODUCTS

“A SLOW RELEASE MATRIX” FOR:

- CHEMOKINES
- CHEMOTACTIC AGENTS
- PROTEASES
- INHIBITORS
- CYTOKINES
- GROWTH FACTORS
- ROS

EARLY CELLULAR ADHESION TO VASCULAR MATERIALS

EFFECT OF IMPLANT SURFACE CHEMISTRY UPON ARTERIAL THROMBOSIS

C.L. VAN KAMPEN AND D.F.GIBBONS.

JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, VOL. 13, 517-541 (1979)

- Canines
- 30 seconds to 2 weeks
- *In situ* perfusion fixation under physiological pressure
- Light microscopic evaluation
- Scanning Electron Microscopy evaluation

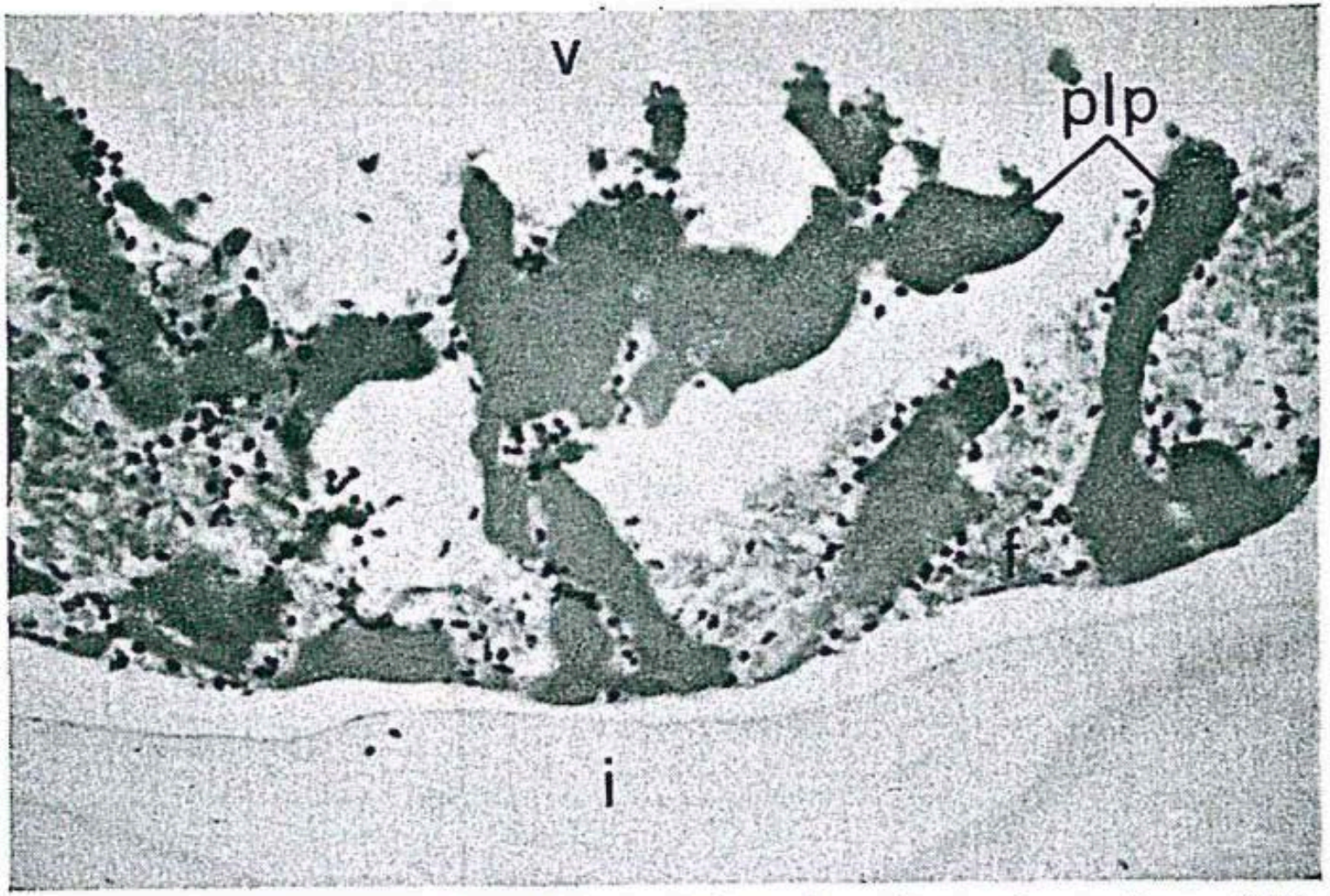


Fig. 3. Optical micrograph of the thrombus deposit on the surface of Glu(OH): Leu-1:1 after 10 min of implantation. Massive platelet–leukocyte pillars (plp) extend up from the surface of the implant (i) into the vessel lumen (v). Fibrin (f) and entrapped red blood cells fill the spaces between pillars. Original magnification = 100×.

EFFECT OF IMPLANT SURFACE CHEMISTRY UPON ARTERIAL THROMBOSIS, C.L. VAN KAMPEN AND D.F.GIBBONS. JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, VOL. 13, 517-541 (1979)

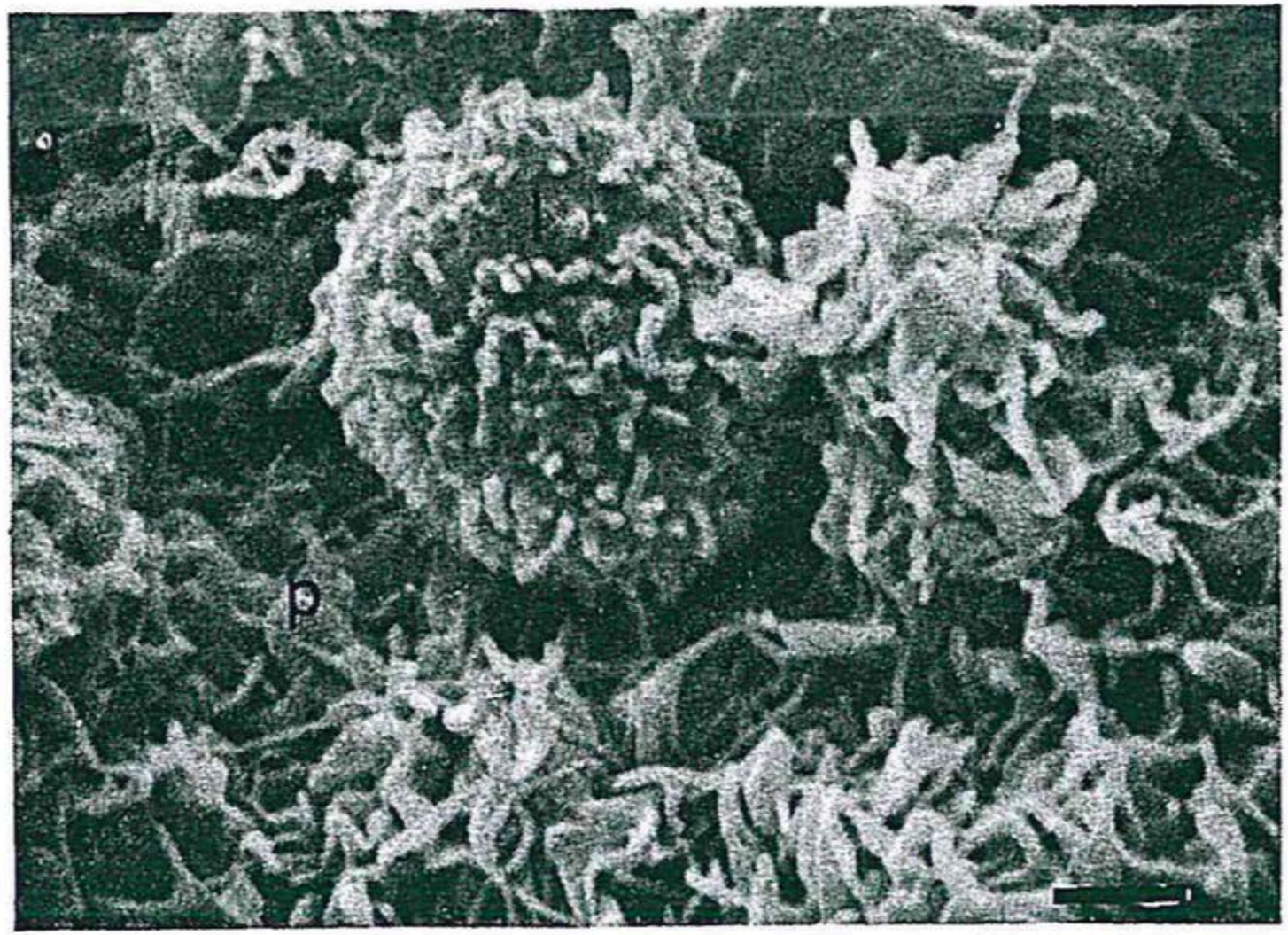


Fig. 4. Scanning electron micrograph of the surface of a platelet–leukocyte pillar present on the surface of Glu(OH):Leu-1:1 after 10 min of implantation. A leukocyte (l) is shown on a background of aggregated platelets (p). The particular surface morphology of the leukocyte shown is characteristic of polymorphonuclear leukocytes, which predominated corresponding histological sections. Bar = 2 μm.

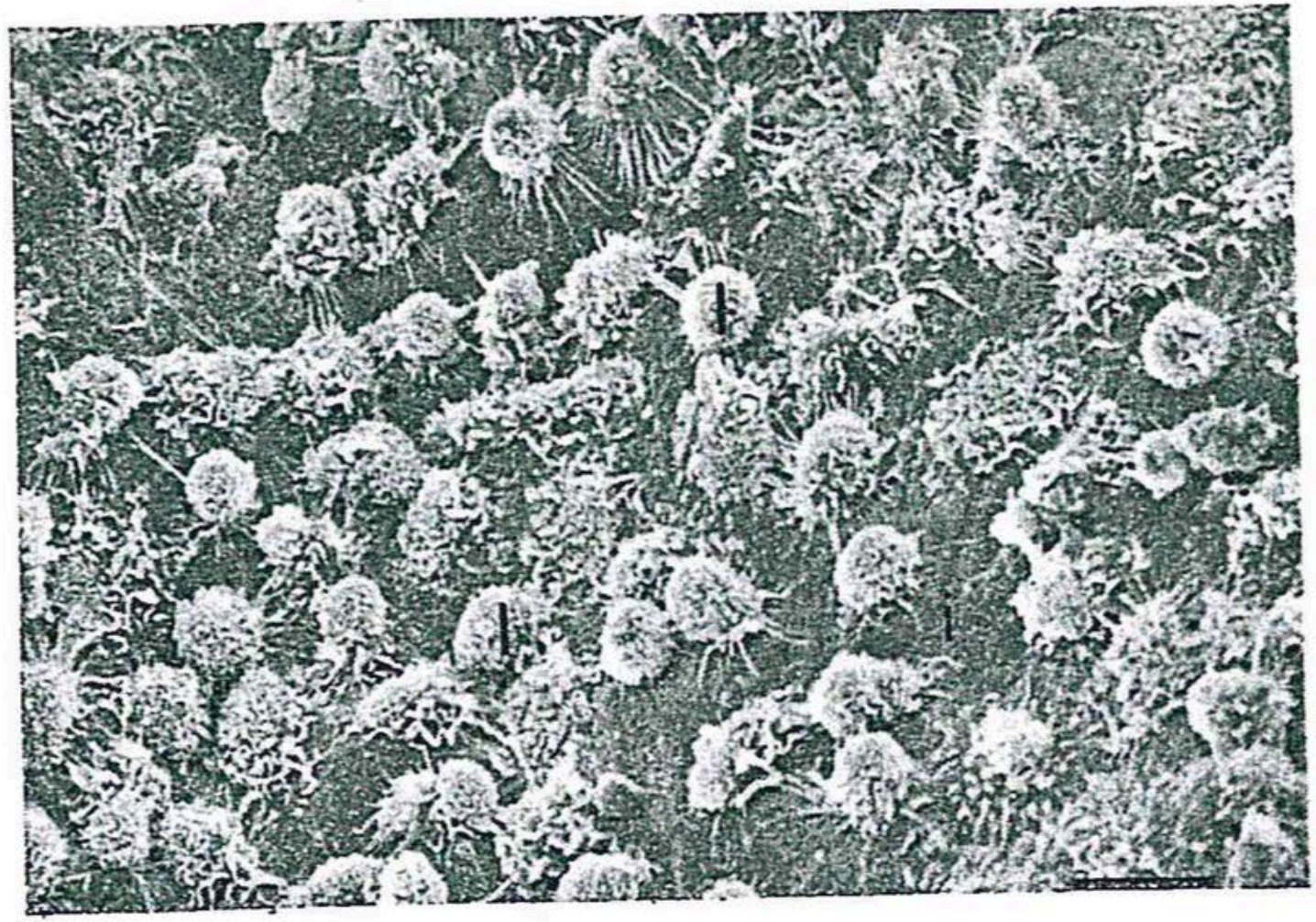


Fig. 7. Scanning electron micrograph of the surface of Glu(ONa):Leu-1:1 after 15 min of implantation showing close-up view between pillars. Numerous leukocytes (l) are adhered directly to the implant surface (i). The leukocytes demonstrate pseudopod extension and various stages of spreading on the implant surface. Bar = 10 μm.

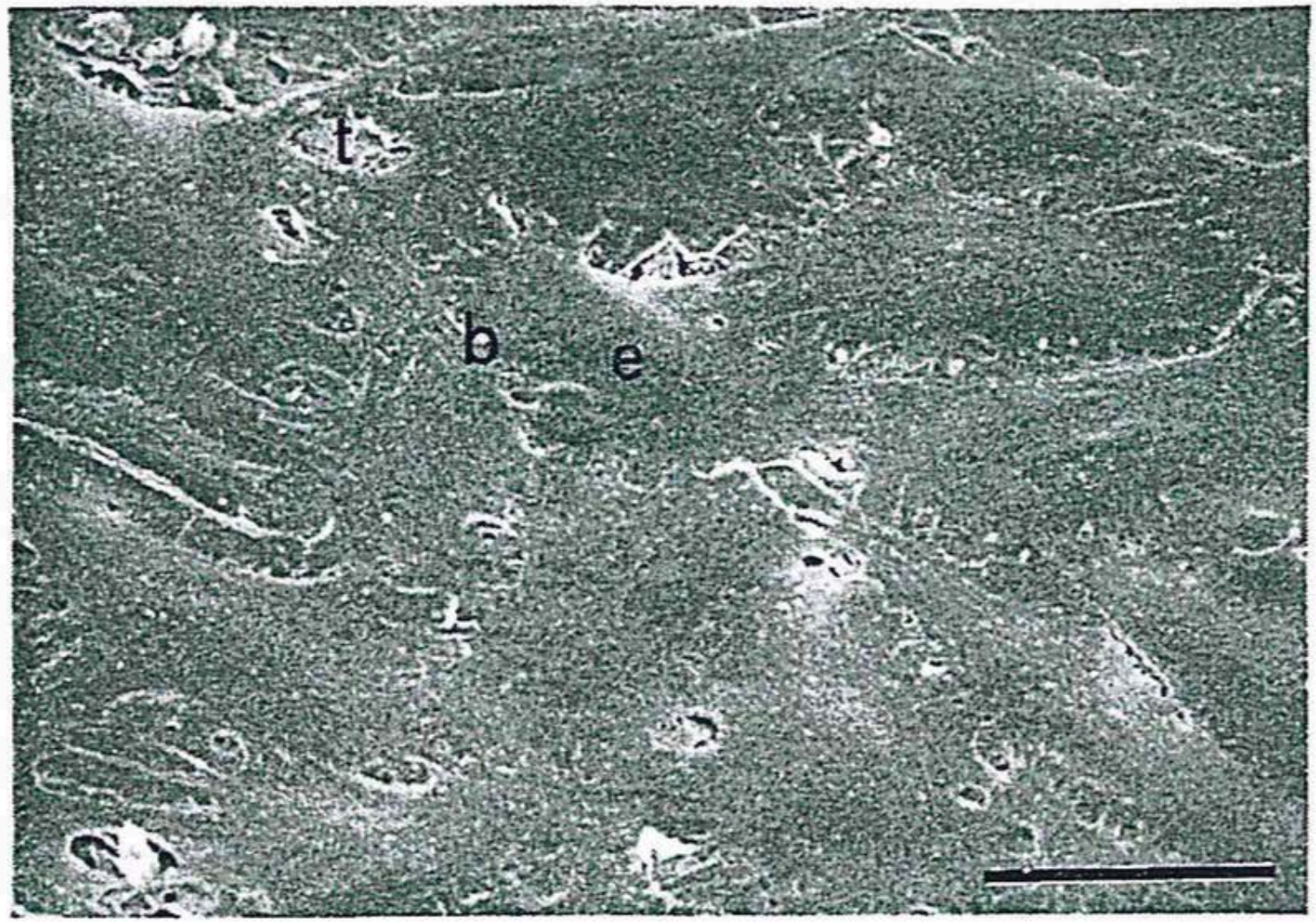


Fig. 10. Scanning electron micrograph of endothelial cells (e) covering the thrombus surface on Glu(ONa):Leu-1:1 after 1 week of implantation. Endothelial cell borders (b) are readily discernible and the underlying thrombus (t) is visible in small gaps between some endothelial cells. Bar = 10 μm.

ENDOTHELIALIZATION OF VASCULAR PROSTHESES – EARLY CELL ADHESION

METABOLISM AND ULTRASTRUCTURE OF THE ARTERIAL WALL IN ATHEROSCLEROSIS, ABEL L. ROBERTSON, JR., CLEVELAND CLINIC QUARTERLY, VOL. 32, 99-117 (1965)

- Barr Body identification within the nucleus of cross-transfused adherent female cells on Dacron vascular grafts in male canines

ORIGIN OF ARTERIAL PROSTHESIS LINING FROM CIRCULATING BLOOD CELLS, JR MACKENZIE, M HACKEET, C. TOPUZLU, DJ TIBBS, ARCHIVES OF SURGERY, VOL. 97, DEC., 879-885 (1968)

- Monocyte tagging with carbon particles
- 1 week – mononuclear (stem) cell adhesion
- 4 weeks – “endothelial” patches
- 16 weeks – “mature” endothelium

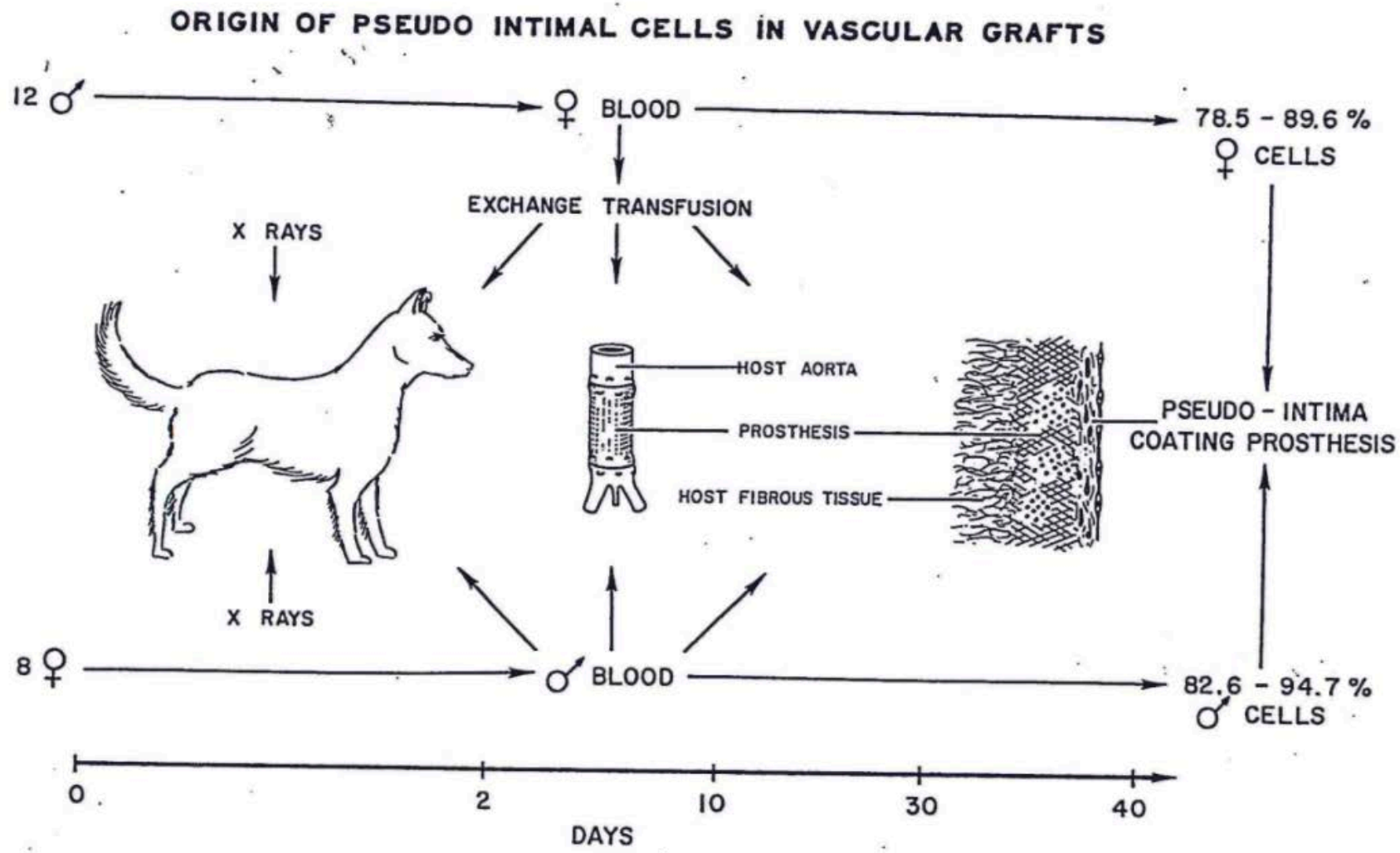


Fig. 1. Origin of pseudointimal cells coating vascular prosthesis. Dogs received total body irradiation preceding exchange transfusion with blood from opposite sex and replacement of a segment of abdominal aorta with a dacron prosthesis. The origin of the pseudointimal cells up to 40 days following transplantation was determined by their chromosomal characteristics. In both male and female hosts, the majority of intimacytes originated from blood cells.

CHALLENGES IN PIS DIAGNOSIS

PIS (TRANSIENT) VS SIRS (CHRONIC)
- NON-INFECTIOUS VS INFECTIOUS (SEPSIS)

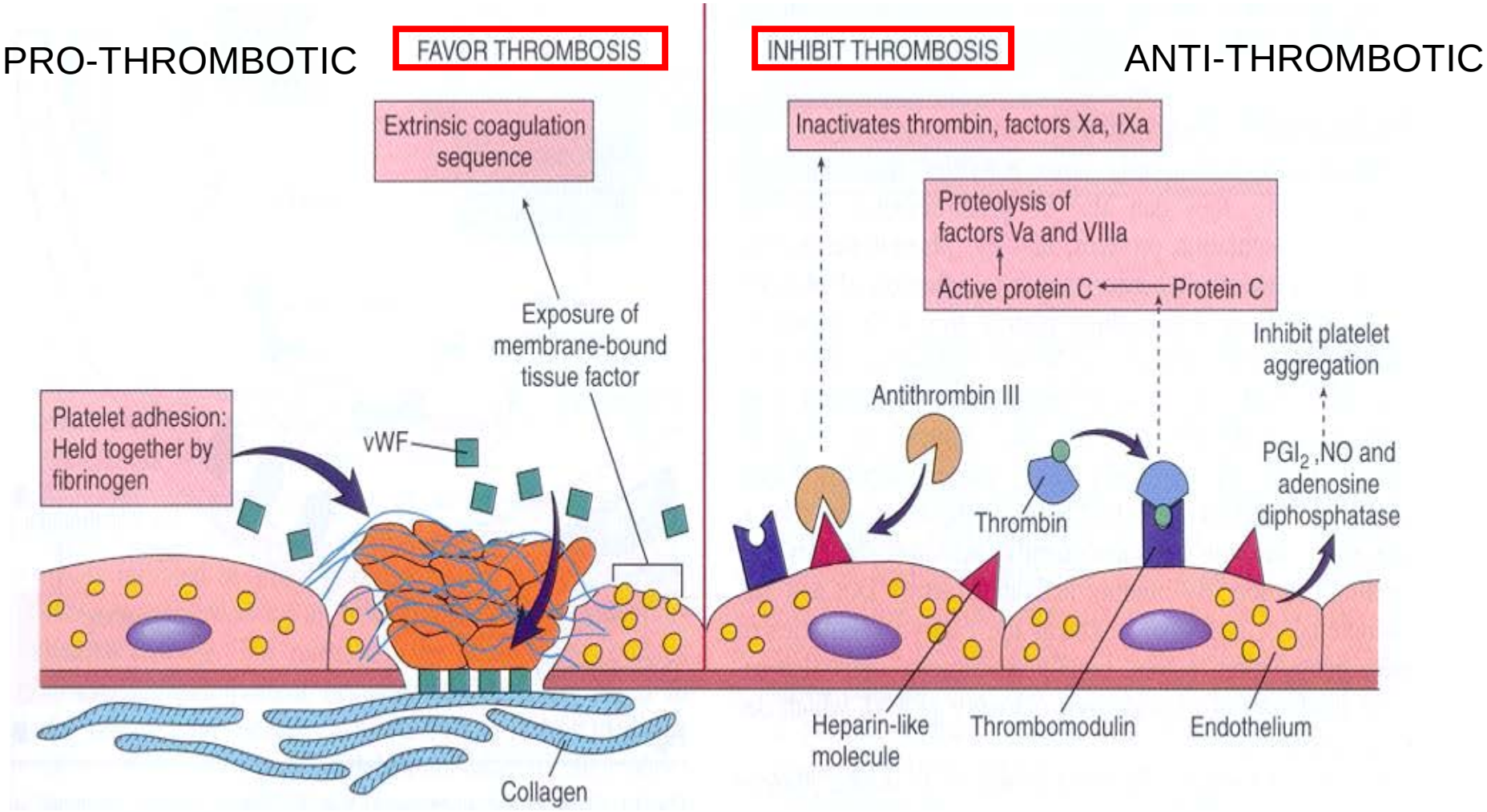
STANDARDIZED DIAGNOSTIC CRITERIA
- RAPID – POC – POINT OF CARE

BIOMARKERS – ACCURATE, SELECTIVE, SPECIFIC
- CRP – C-REACTIVE PROTEIN, LIVER
- PCT – PROCALCITONIN, LUNG AND INTESTINE CELLS
  - SEPSIS MARKER
- sCD25 – SOLUBLE IL-2 RECEPTOR ALPHA CHAIN
  - T-CELL ACTIVATION
- sCD14 – LPS RECEPTOR FRAGMENT
  - MONOCYTES, MACROPHAGES
- OTHERS IN DEVELOPMENT

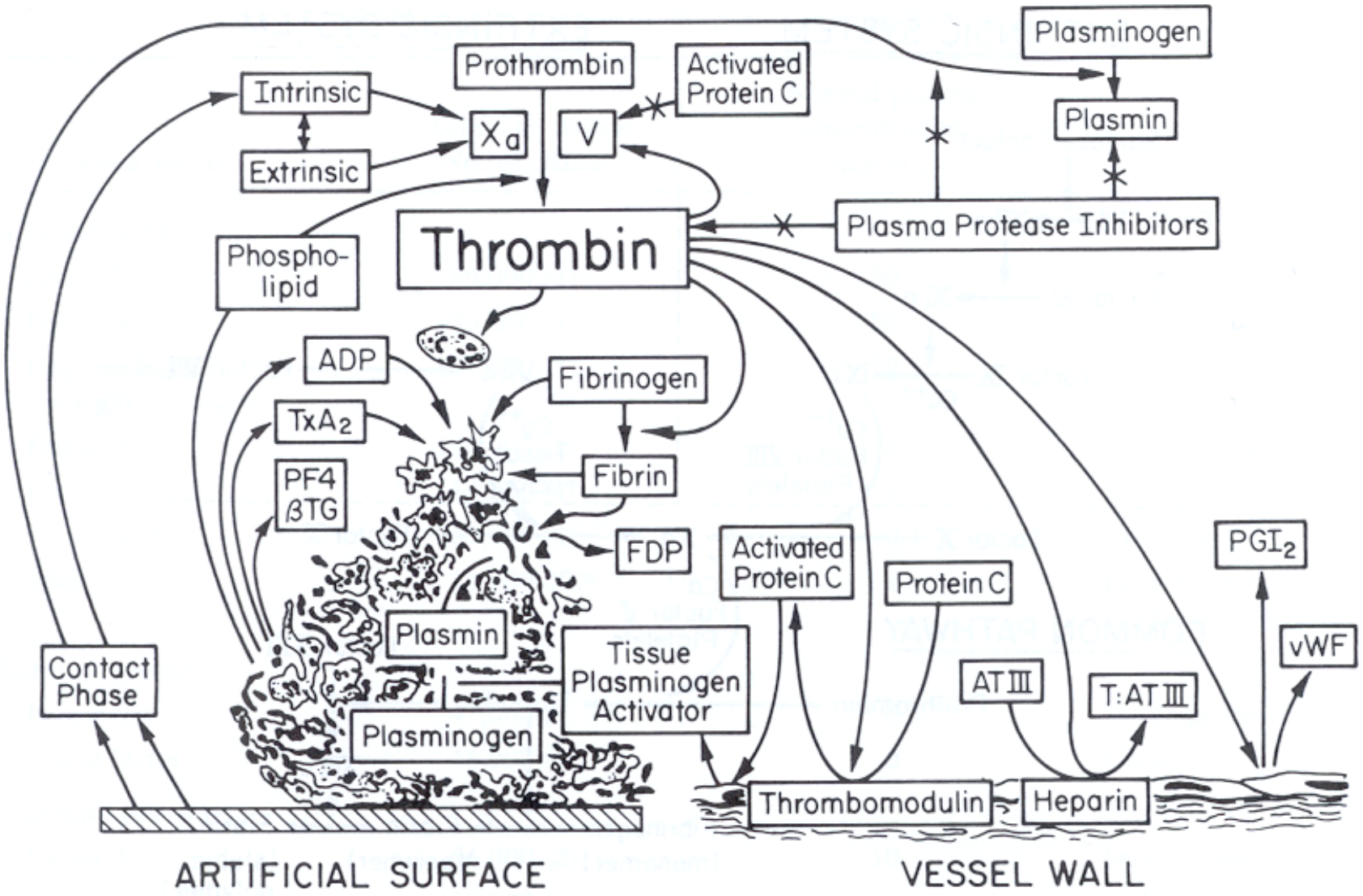
OVERLAP BETWEEN COAGULATION, THROMBOSIS, AND INFLAMMATION


HELP!

Hemostasis & Thrombosis



Blood Surface Interactions



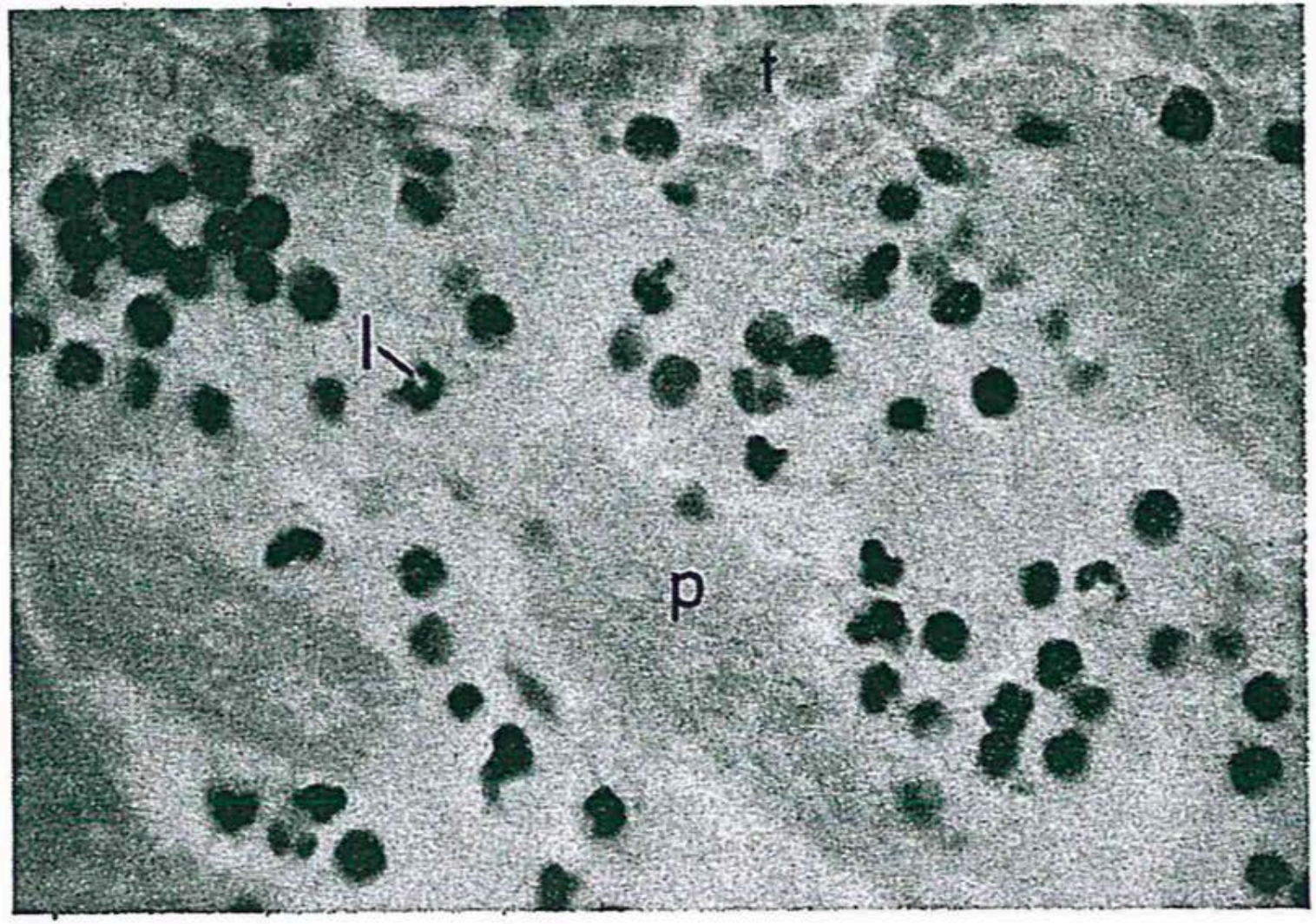
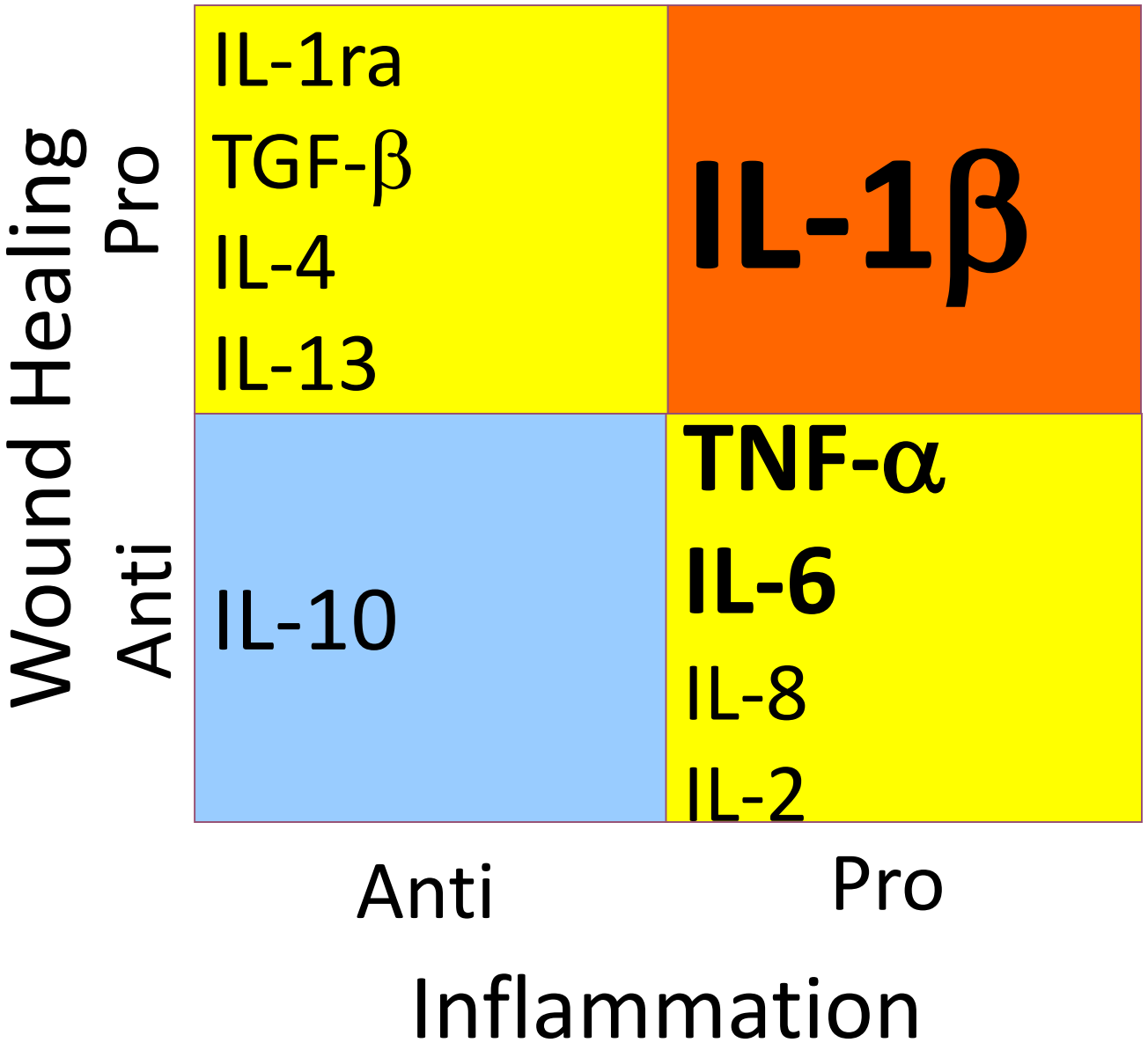
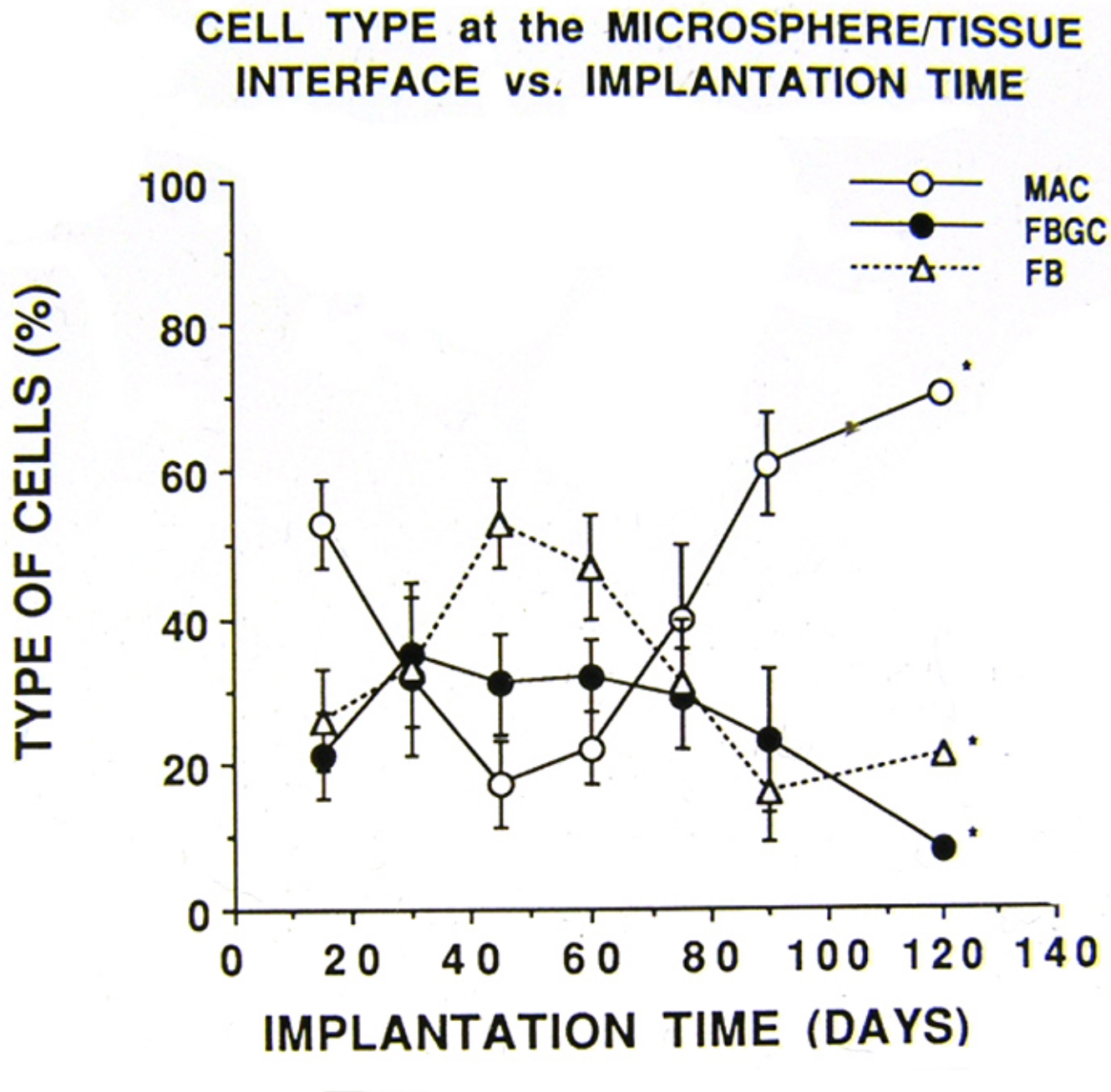
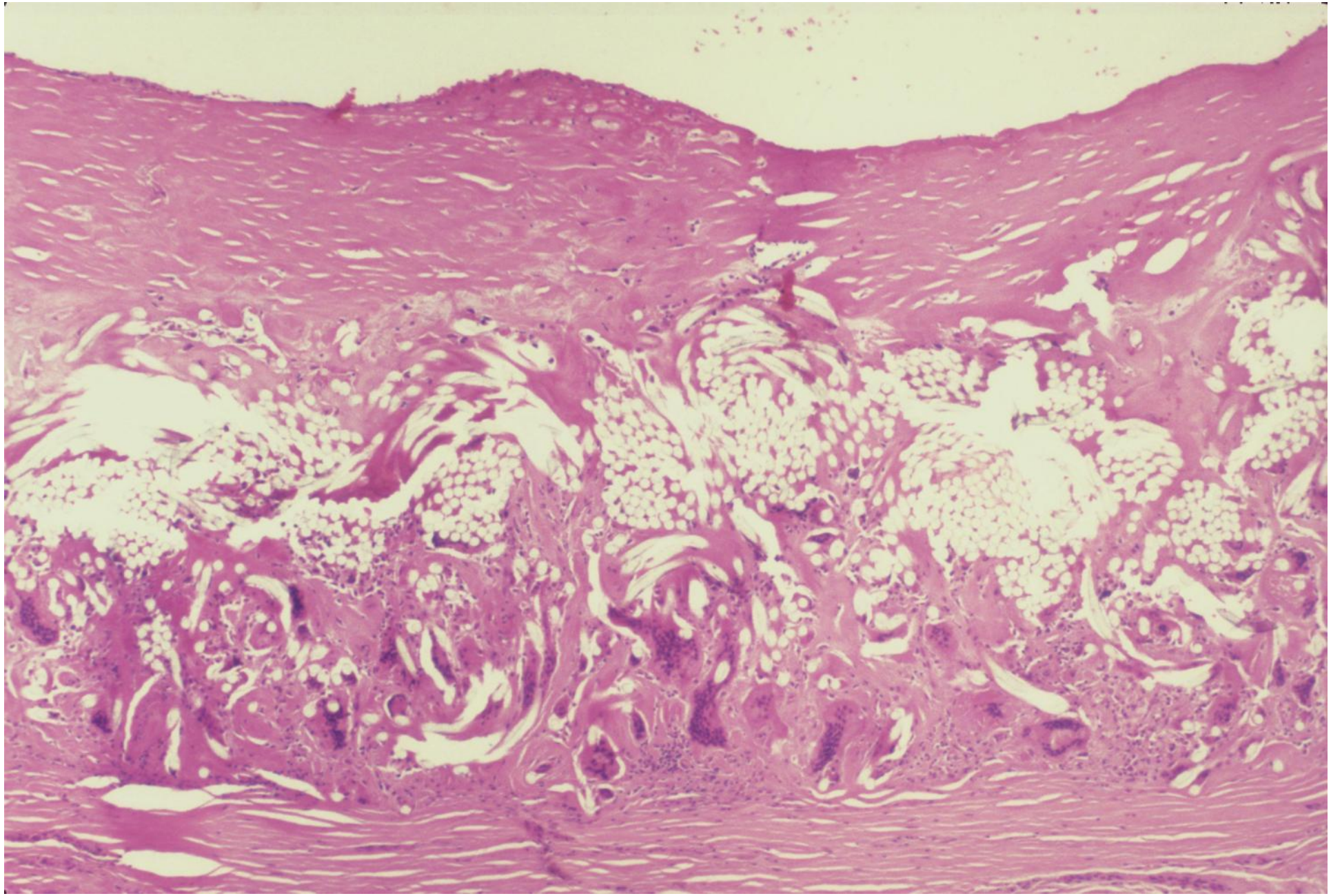


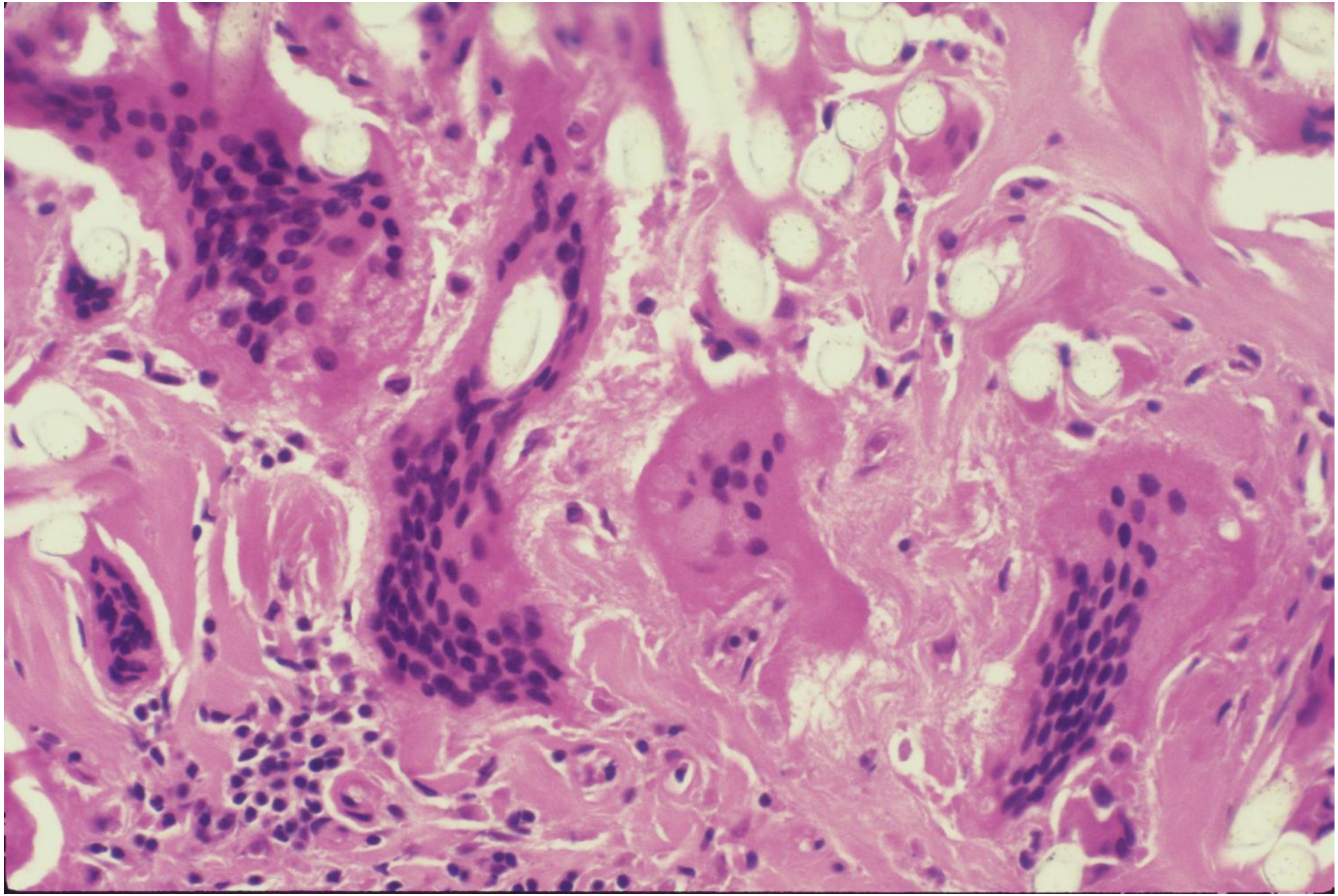
Fig. 5. Optical micrograph of the thrombus deposit on Glu(OH):Leu-1:1 after 15 min of implantation. Platelet-rich areas (p) are generally distinct from fibrin and red blood cell areas (f). Polymorphonuclear leukocytes (l) are the predominant cell type. Original magnification = 400×.

Macrophage and Lymphocyte Derived Cytokines




CELL TYPE at the MICROSPHERE/TISSUE INTERFACE vs. IMPLANTATION TIME
MAC
FBGC
FB
TYPE OF CELLS (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
140
IMPLANTATION TIME (DAYS)
*
*
*

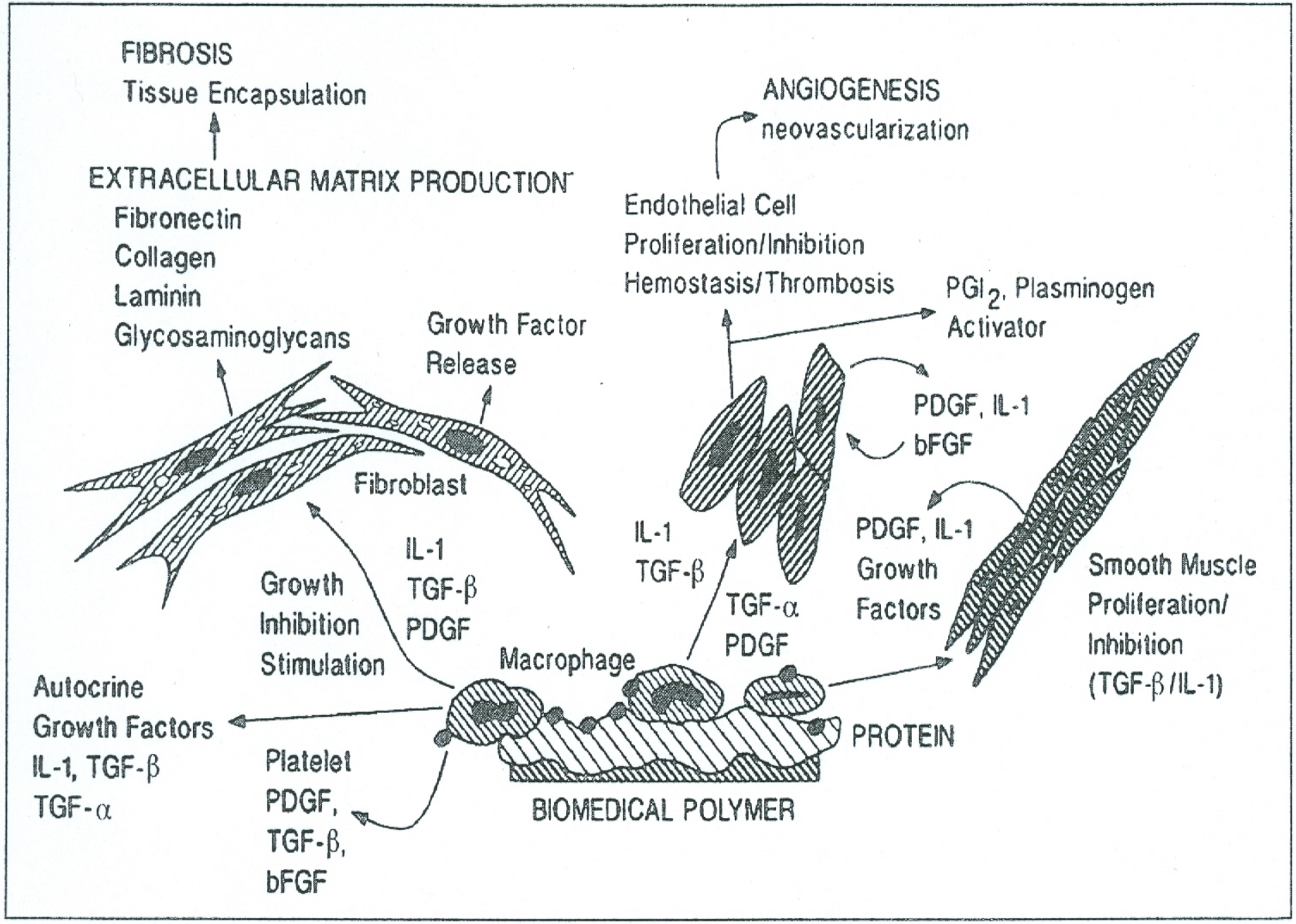


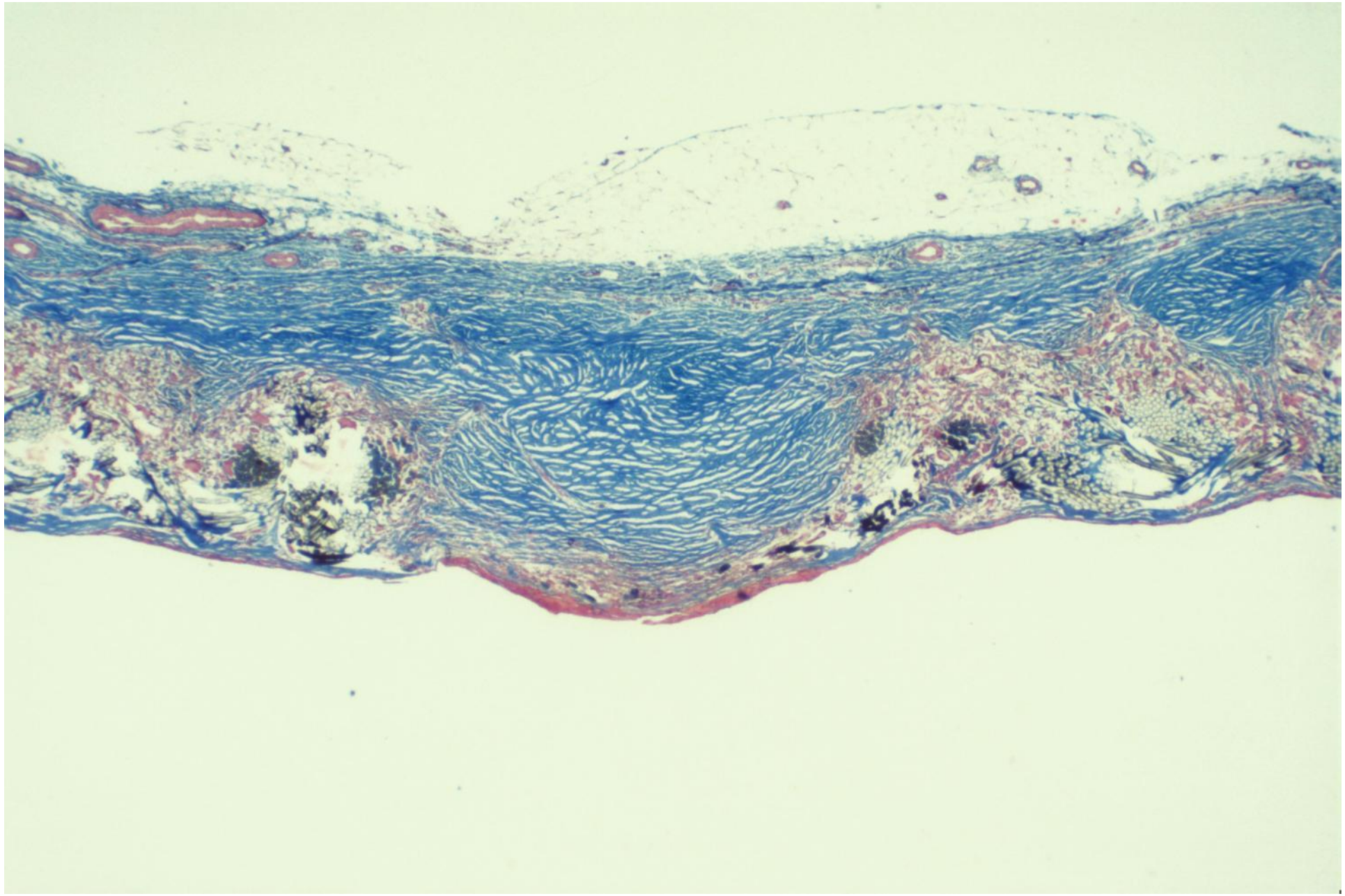


The obvious we see eventually,

The completely apparent takes longer.

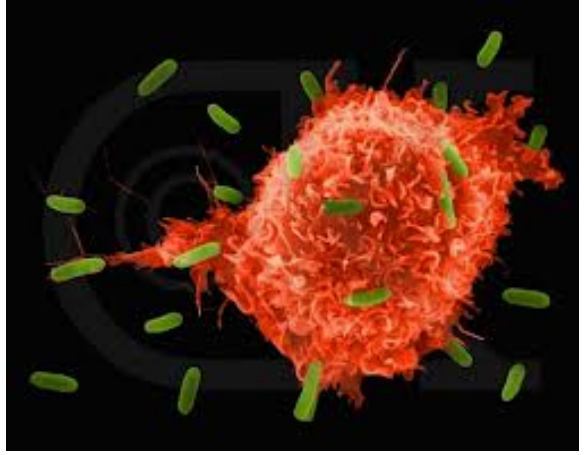
Edward R. Murrow


FIBROSIS
Tissue Encapsulation
EXTRACELLULAR MATRIX PRODUCTION
Fibronectin
Collagen
Laminin
Glycosaminoglycans
Growth Factor
Release
Fibroblast
ANGIOGENESIS
neovascularization
Endothelial Cell
Proliferation/Inhibition
Hemostasis/Thrombosis
PGI2, Plasminogen
Activator
PDGF, IL-1
bFGF
IL-1
TGF-β
TGF-α
PDGF
PDGF, IL-1
Growth
Factors
Smooth Muscle
Proliferation/
Inhibition
(TGF-β/IL-1)
IL-1
TGF-β
PDGF
Growth
Inhibition
Stimulation
Macrophage
Autocrine
Growth Factors
IL-1, TGF-β
TGF-α
PROTEIN
Platelet
PDGF,
TGF-β,
bFGF
BIOMEDICAL POLYMER



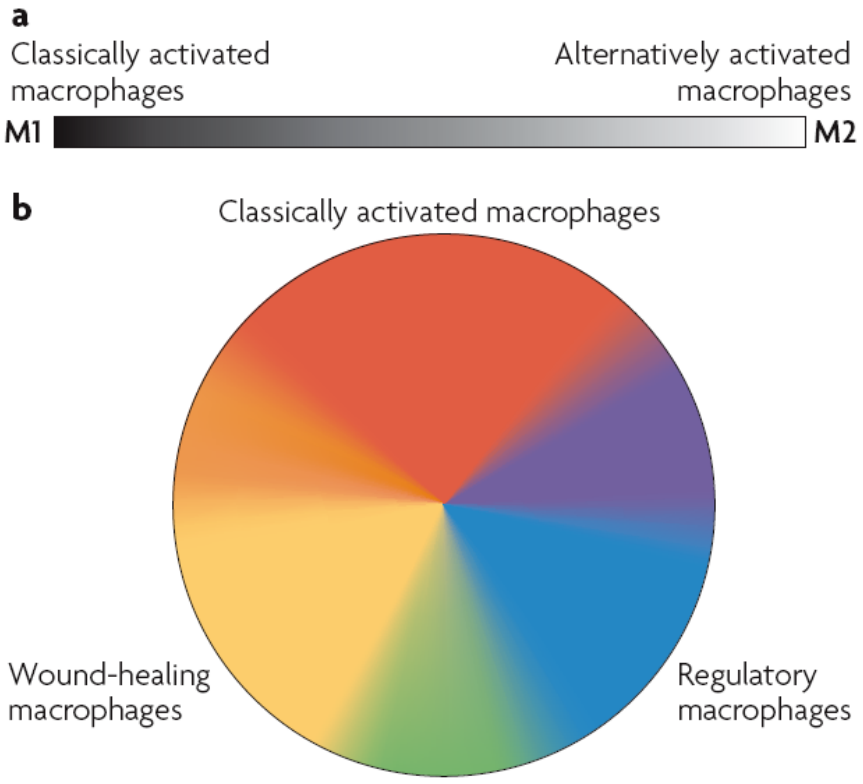
MYOFIBROBLASTS

- A NEW PLAYER IN THE FOREIGN BODY REACTION AND HEALING RESPONSE TO BIOMATERIALS
- SCAFFOLD AND FIBROUS CAPSULE CONTRACTION THROUGH SMA
- RESPONSIVE TO SUBSTRATE MECHANICAL RESISTANCE
- PERSISTENT FOR THE DURATION OF THE RESORPTION PROCESS



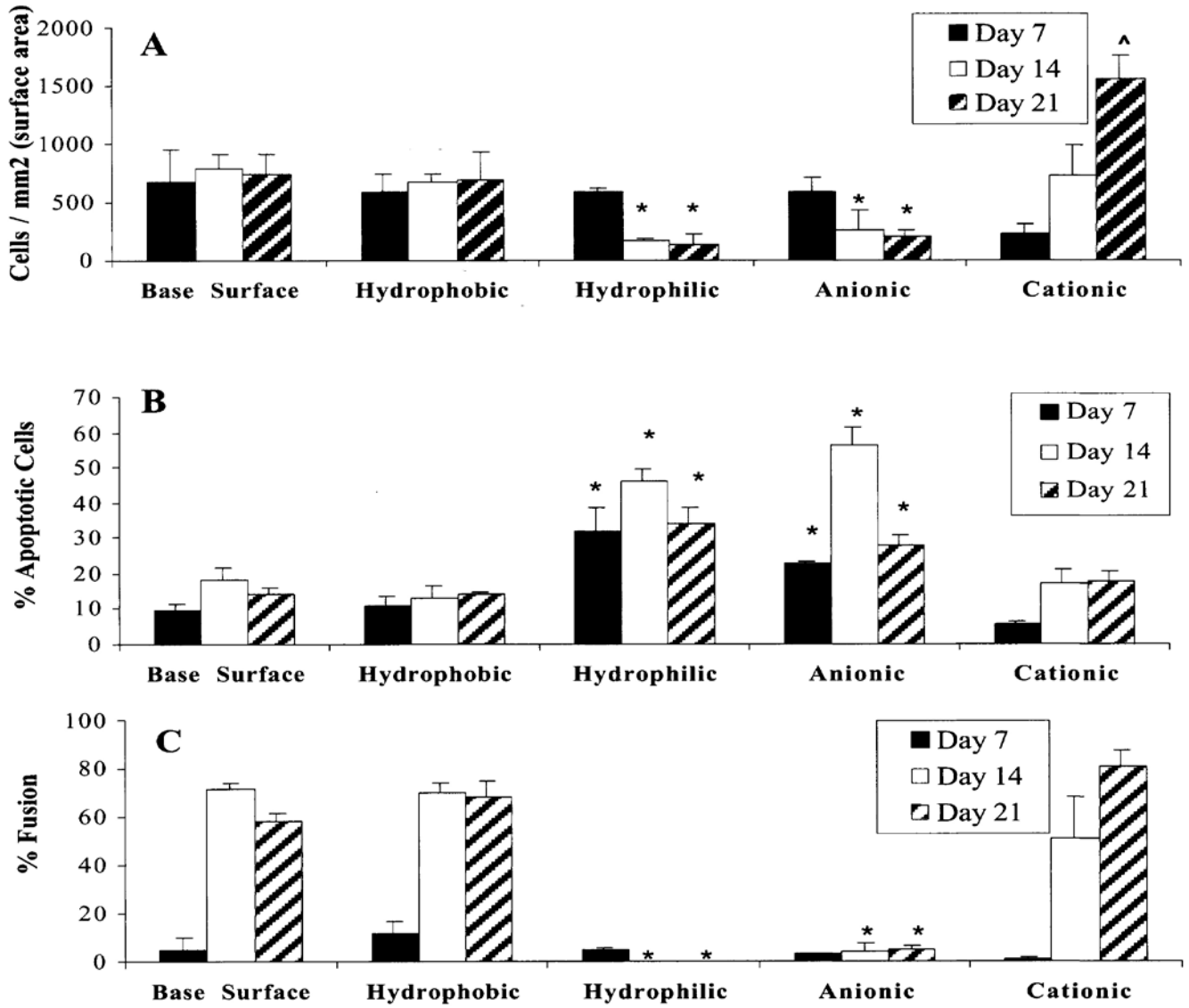
Macrophages as master conductors…

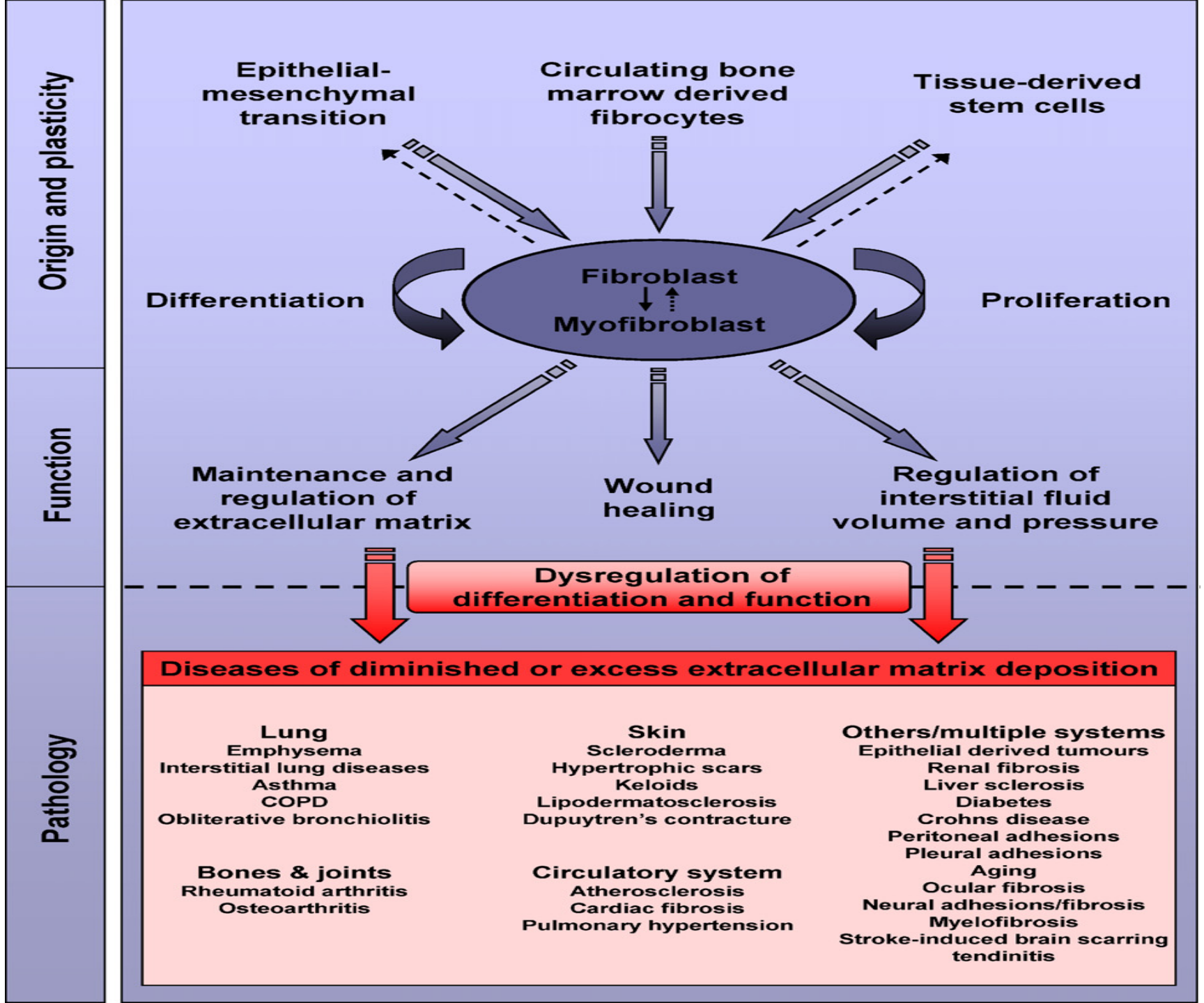
- Classically activated (**M1**):
  - inflammatory, microbicidal, and tumor destructive
- Alternatively activated (**M2**)
  - **M2a**: growth stimulation, tissue repair, collagen formation
  - **M2b**: Pro- and anti-inflammatory function. Regulatory
  - **M2c**: Debris scavenging, pro-healing function



David M. Mosser, J. Leukocyte Biology, 2003, 73, 209-212.
David M. Mosser et al., Nature Immunology, 2008, 8, 958-969.

IN VIVO MACROPHAGE ADHESION, APOPTOSIS, AND FUSION




Origin and plasticity
Function
Pathology
Epithelial-mesenchymal transition
Circulating bone marrow derived fibrocytes
Tissue-derived stem cells
Differentiation
Fibroblast
Myofibroblast
Proliferation
Maintenance and regulation of extracellular matrix
Wound healing
Regulation of interstitial fluid volume and pressure
Dysregulation of differentiation and function
Diseases of diminished or excess extracellular matrix deposition
Lung
Emphysema
Interstitial lung diseases
Asthma
COPD
Obliterative bronchiolitis
Bones & joints
Rheumatoid arthritis
Osteoarthritis
Skin
Scleroderma
Hypertrophic scars
Keloids
Lipodermatosclerosis
Dupuytren's contracture
Circulatory system
Atherosclerosis
Cardiac fibrosis
Pulmonary hypertension
Others/multiple systems
Epithelial derived tumours
Renal fibrosis
Liver sclerosis
Diabetes
Crohns disease
Peritoneal adhesions
Pleural adhesions
Aging
Ocular fibrosis
Neural adhesions/fibrosis
Myelofibrosis
Stroke-induced brain scarring
tendinitis

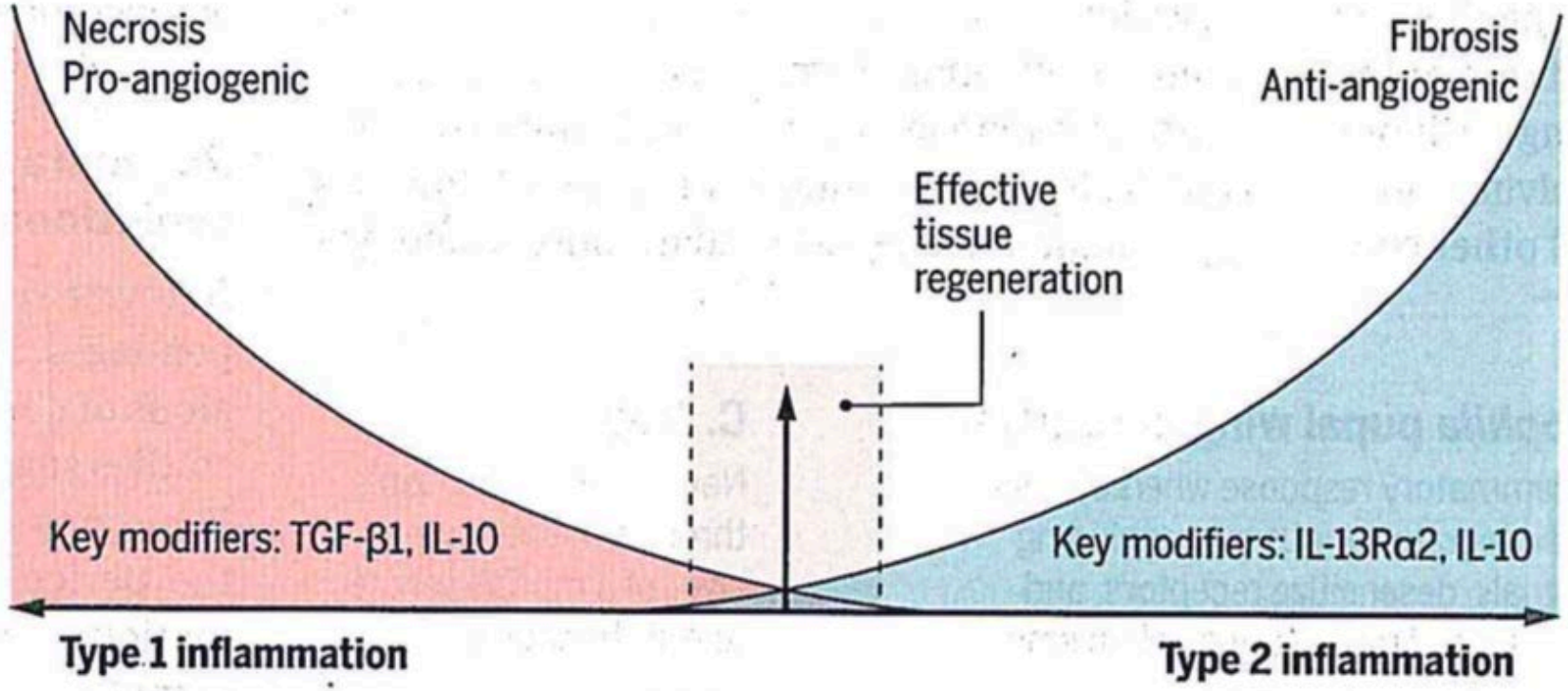


Fig. 2. Distinct mechanisms contribute to pathological tissue remodeling during highly polarized type 1 and type 2 responses. Sustained type 1 responses (IFN-γ and IL-17A) lead to substantial tissue damage. The injury, in turn, activates TGF-β, which suppresses the inflammatory response while activating extracellular matrix production by myofibroblasts that contribute to fibrosis. During a polarized type 2 response, IL-13 serves as an important driver of fibrosis, with the IL-13 decoy receptor (IL-13Rα2) and IL-10 exhibiting negative regulatory activity. Effective tissue regeneration is typically associated with less polarized immune responses.

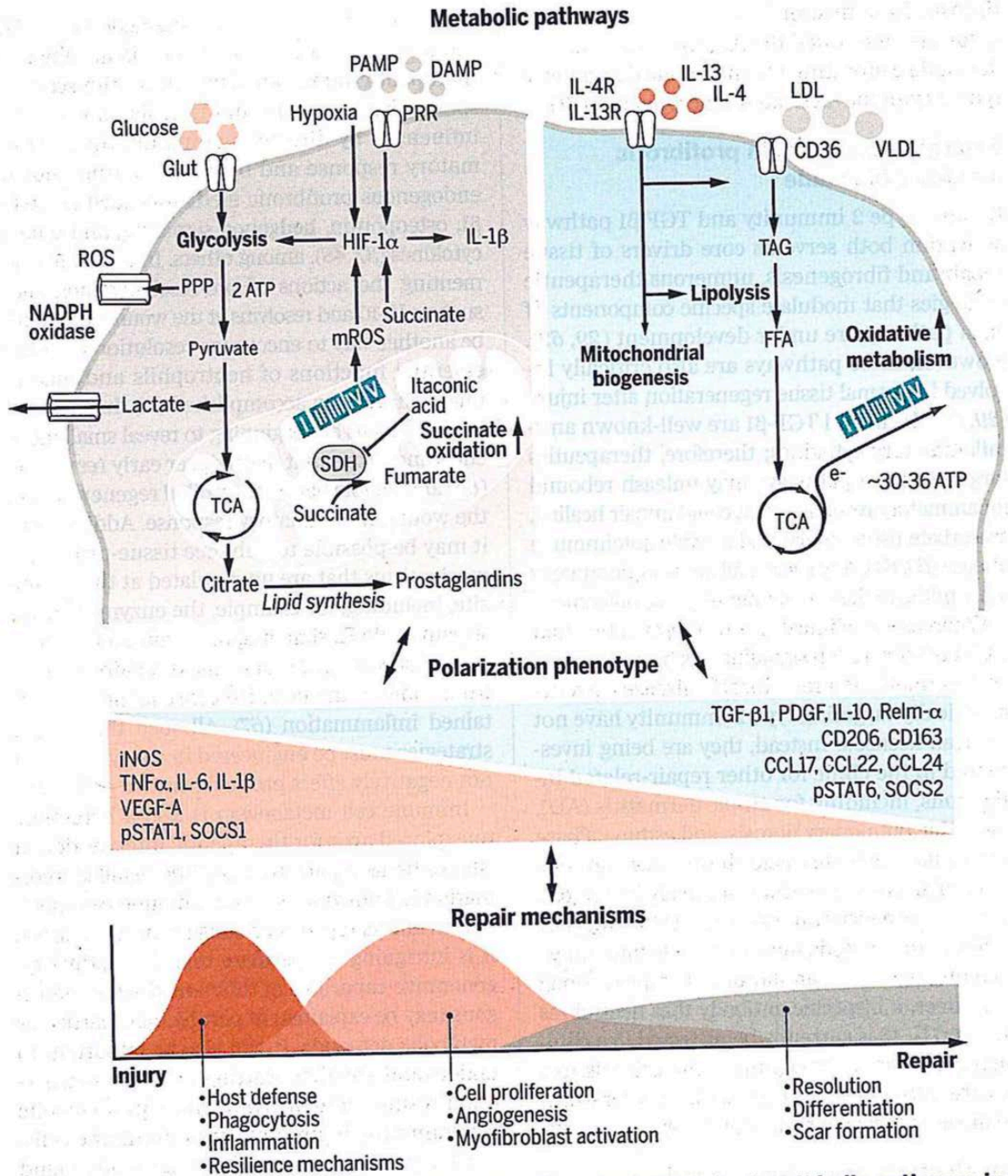


Fig. 3. Integrated perspective of potential activation phenotypes and metabolic pathways in wound macrophages.

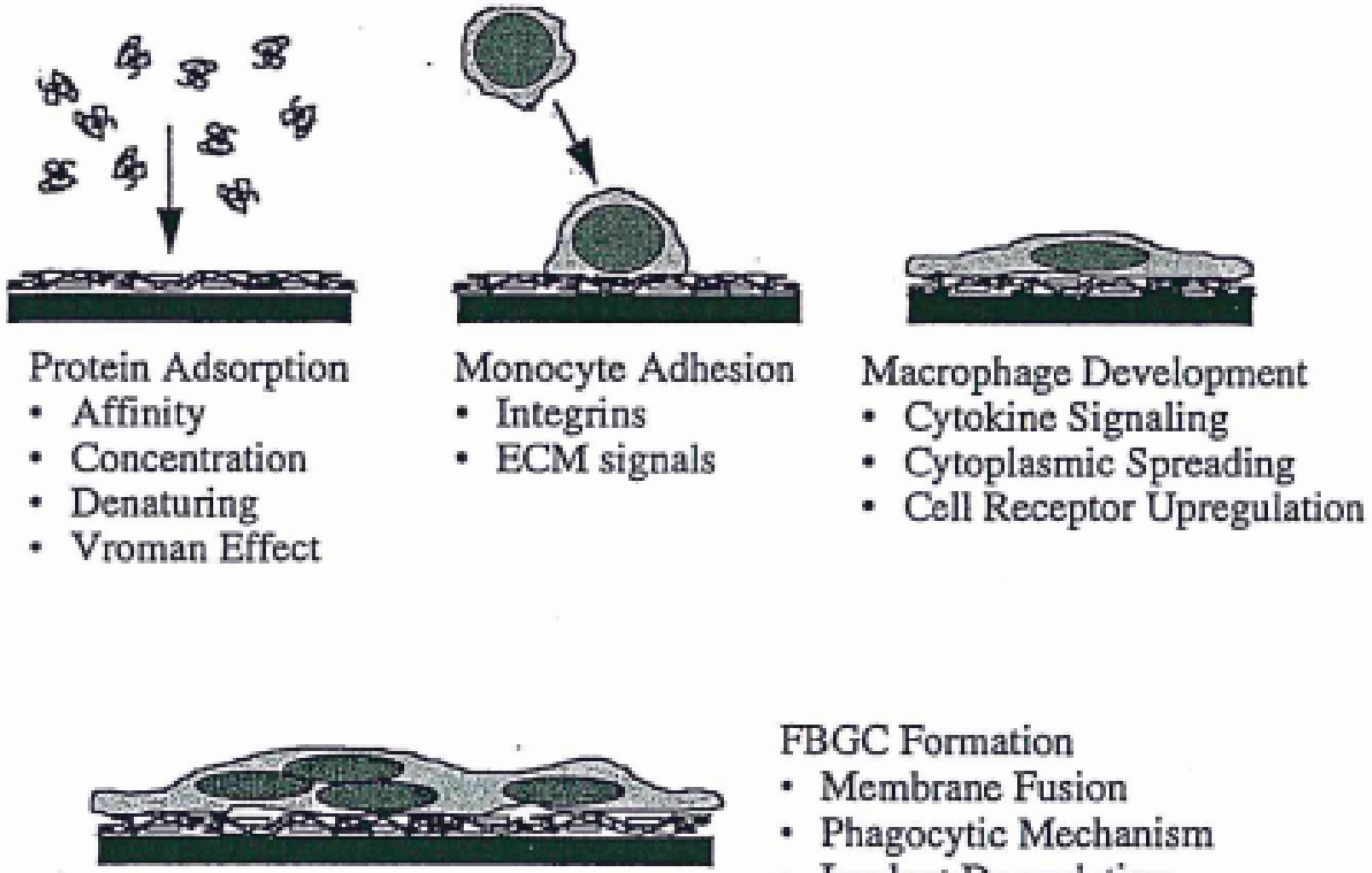
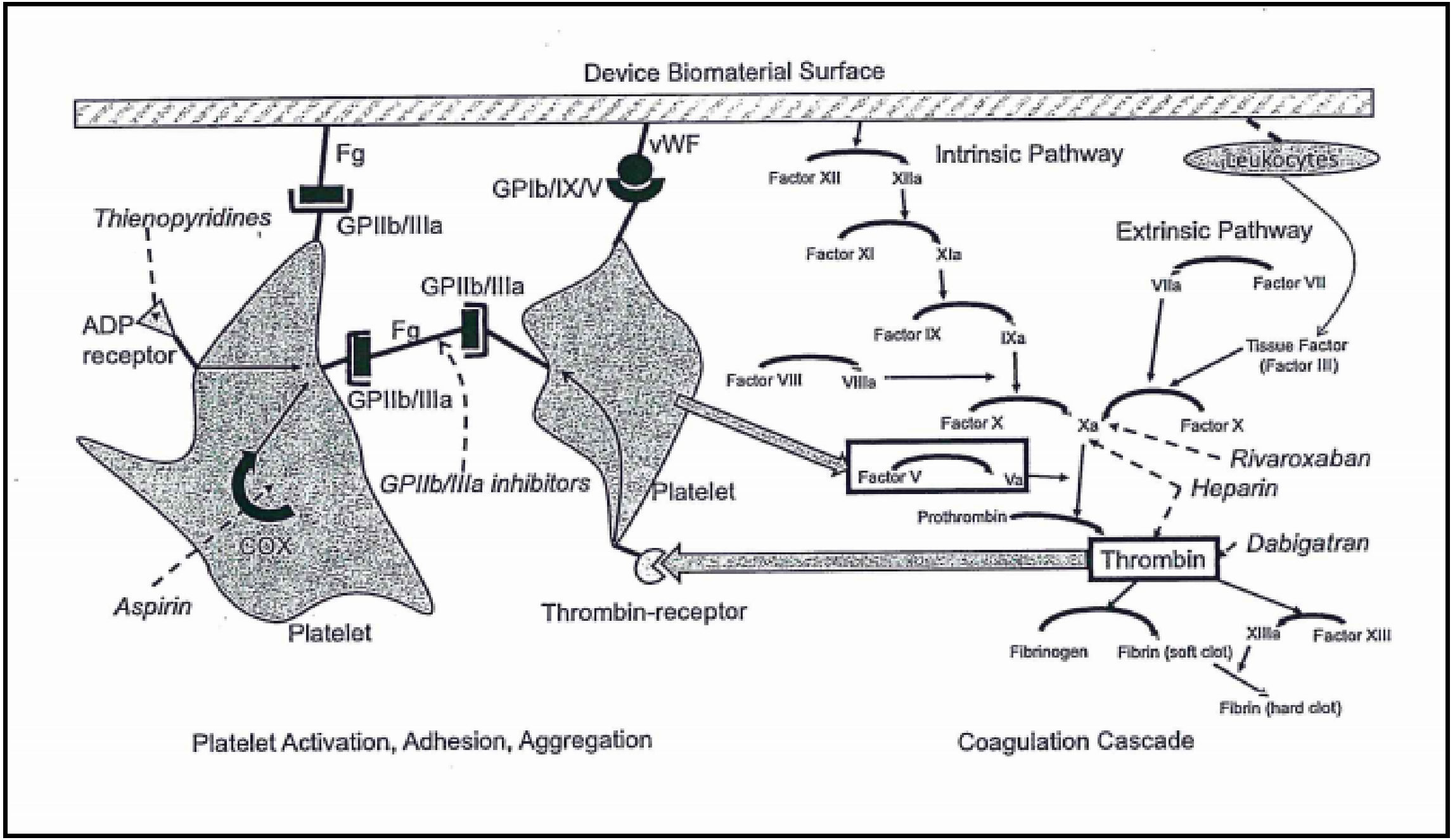


Figure 1. The inflammatory response at tissue/material interfaces.


Device Biomaterial Surface
Fg
vWF
GPIb/IX/V
Thienopyridines
GPIIb/IIIa
GPIIb/IIIa
Fg
ADP
receptor
GPIIb/IIIa
GPIIb/IIIa inhibitors
Platelet
COX
Aspirin
Platelet
Thrombin-receptor
Intrinsic Pathway
Factor XII
XIIa
Factor XI
XIa
Factor IX
IXa
Factor VIII
VIIIa
Factor X
Xa
Factor V
Va
Prothrombin
Thrombin
Fibrinogen
Fibrin (soft clot)
XIIIa
Factor XIII
Fibrin (hard clot)
Leukocytes
Extrinsic Pathway
VIIa
Factor VII
Tissue Factor
(Factor III)
Factor X
Rivaroxaban
Heparin
Dabigatran
Platelet Activation, Adhesion, Aggregation
Coagulation Cascade