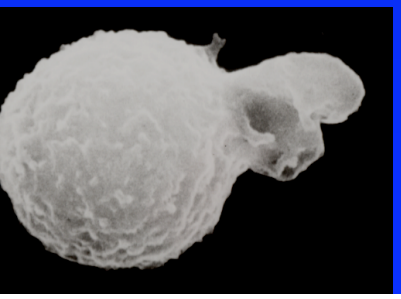
The Inflammatory Cascade:

Shock and Multi-organ Failure



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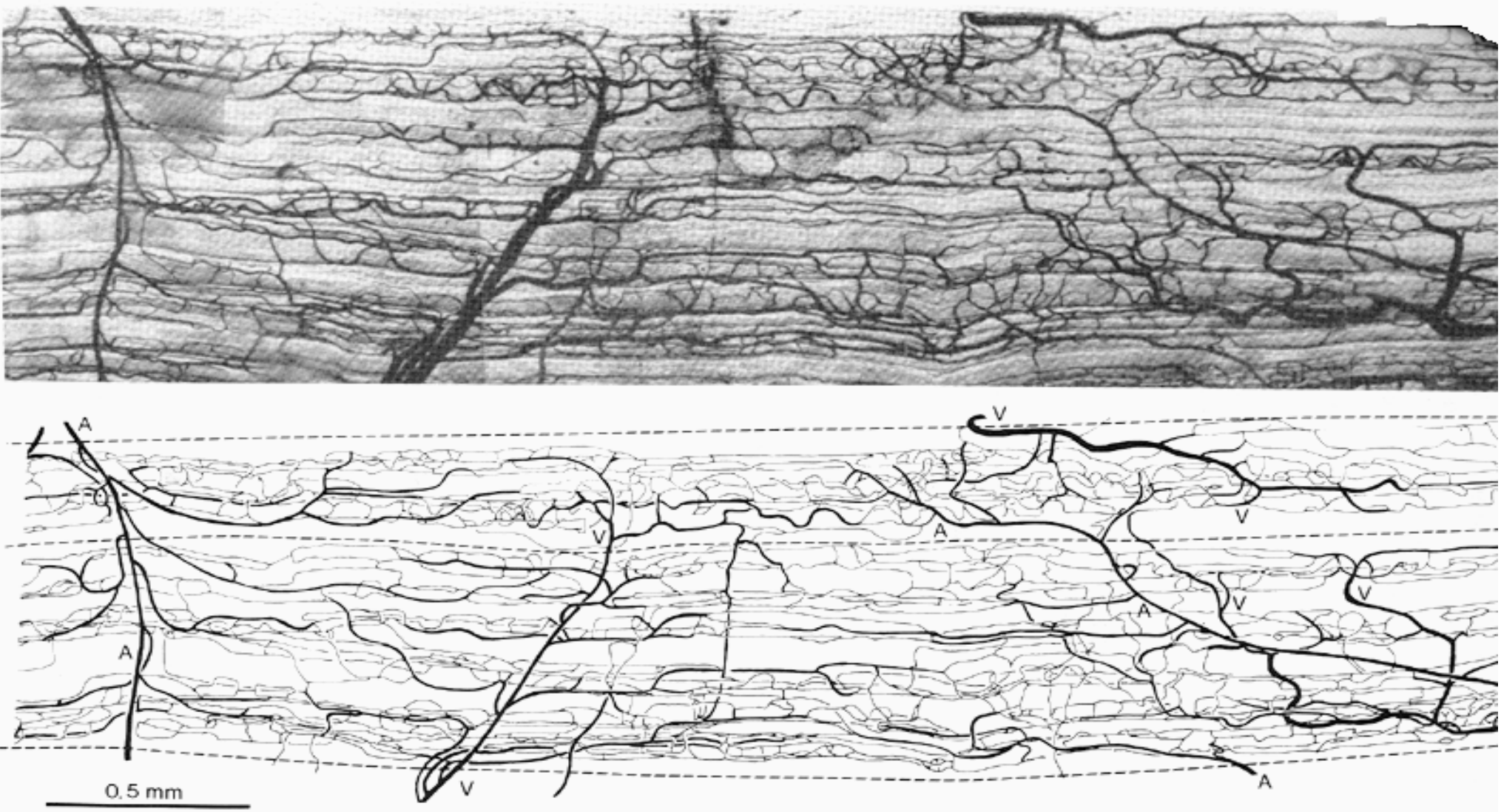
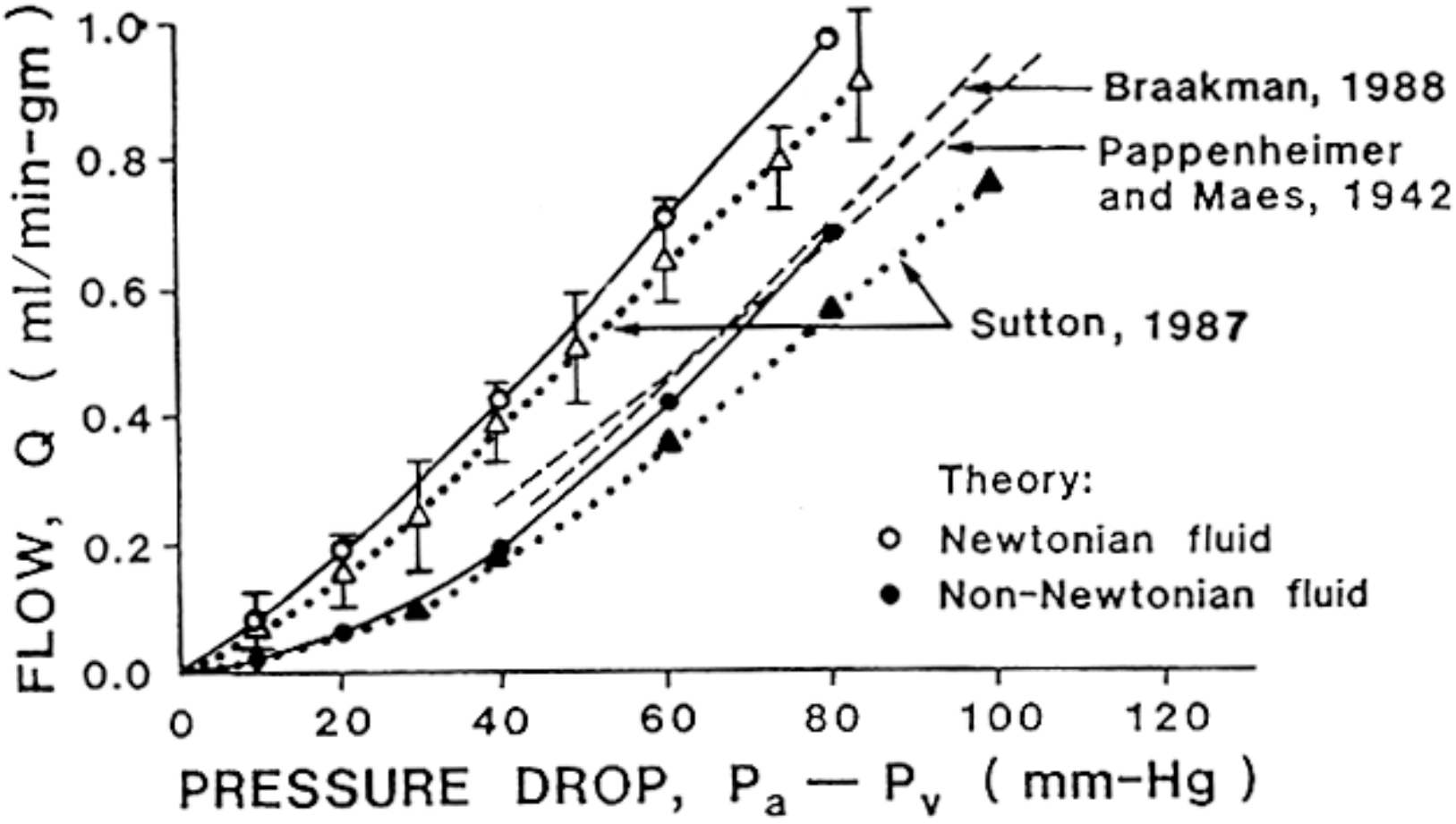


FIGURE 6.4. A capillary network in the rat spinotrapezius muscle. *Top*: The carbon-filled specimen. *Bottom*: A detailed tracing of the network. The *dashed lines* delineate the lateral boundaries of the individual capillary bundles. The capillaries are interconnected over s millimeters along the muscle fibers. Note the repeated polarity of transverse arterioles (A) and collecting venules (V) along the individual cap bundles. (From *Microvascular Networks: Theoretical and Experimental Studies*, Schmid-Schönbein et al., 1986a. Figure 4, pg. 44, S. Karger

Pressure-Flow Relationship in Skeletal Muscle Microcirculation



Cardiovascular Disease is Accompanied By Cell Activation and Inflammation

- ✓ Infectious Diseases
- ✓ Chronic Degenerative Diseases
  (arthritis, retinopathy, dementia,
  venous disease, coeliac disease, …)
- ✓ Diabetes
- ✓ Cardiovascular Risks (smoking, obesity)
- ✓ Myocardial ischemia
- ✓ Stroke
- ✓ Atherosclerosis
- ✓ Arterial Hypertension
- ✓ Cancer
- ✓ Physiological Shock

{NEW TREATMENTS}

Researchers are linking inflammation to an ever-wider array of chronic illnesses. But treatments that block the inflammatory response can backfire. BY ANNE UNDERWOOD

Quieting A Body's Defenses

A DECADE AGO, THE CAUSE OF META Kiss's heart attack might have been written off as a medical mystery. The 59-year-old homemaker had never smoked, weighed in at a slender 119 pounds and had fabulous cholesterol readings, with her good cholesterol actually surpassing the bad. And there was no history of heart disease in her family. So what put her at risk for the heart attack she suffered in 2000? To Eric Matteson, one of her doctors at the Mayo Clinic, the answer leapt right out. "She had rheumatoid arthritis," he says.

If the two conditions sound unrelated, that's because most of us are just now awakening to the risks of chronic inflammation. A decade ago, researchers were blaming oxidative damage for everything from cancer to heart disease. Now chronic, low-grade inflammation is seizing the spotlight. "Inflammation is the evil twin of oxidation," says neuroscientist James Joseph of Tufts University. "Where you find one, you find the other." That would include not only such obvious inflammatory conditions as asthma and rheumatoid arthritis, but also ailments never previously associated with inflammation—such as atherosclerosis, Alzheimer's disease, colon cancer and diabetes. Suddenly medical puzzles seem to be fitting together, such as why hypertension puts patients at increased risk of Alzheimer's, or why rheumatoid-arthritis sufferers have higher rates of sudden cardiac death. They're all connected on some fundamental level—which raises a tantalizing question. If there are common threads in the development of all these diseases, are there common treatments? Drug companies are eager to find out. But it's not as simple as it seems.

If you can't live with inflammation, you can't live without it, either. Inflammation is a key component of the immune system's defenses. If you cut yourself, the body sends in a barrage of microbe-fighting molecules (including oxidants), and the wound becomes red, hot and swollen. When the threat of infection recedes, so does the inflammation. But persistent insults like cigarette smoke, excess

The Inflammatory Cascade

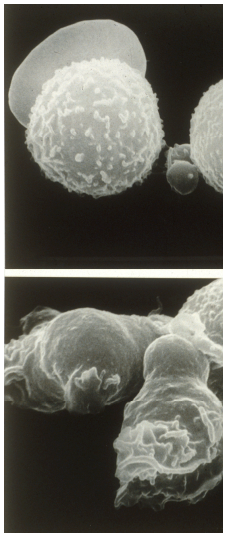
Trigger mechanism

Early Cell Responses:
- Ion exchange
- Pseudopod formation by actin polymerization/depolymerization
- Degranulation
- Production and release of inflammatory mediators
- Enhancement of endothelial permeability
- Upregulation of membrane adhesion molecules

Tissue Degradation:
- Neutrophil entrapment in microvessels, transvascular migration
- Platelet attachment, aggregation, thrombosis, red cell aggregation
- Protease release and activation
- Oxygen free radical formation
- Apoptosis
- Organ dysfunction

Initial Repair:
- Downregulation of anti-inflammatory genes
- Upregulation of pro-inflammatory genes (cytokines, etc.)
- Monocyte and T-Lymphocyte infiltration

Repair:
- Release of growth factors
- Connective tissue growth
- Revascularization
- “Resolution of Inflammation”



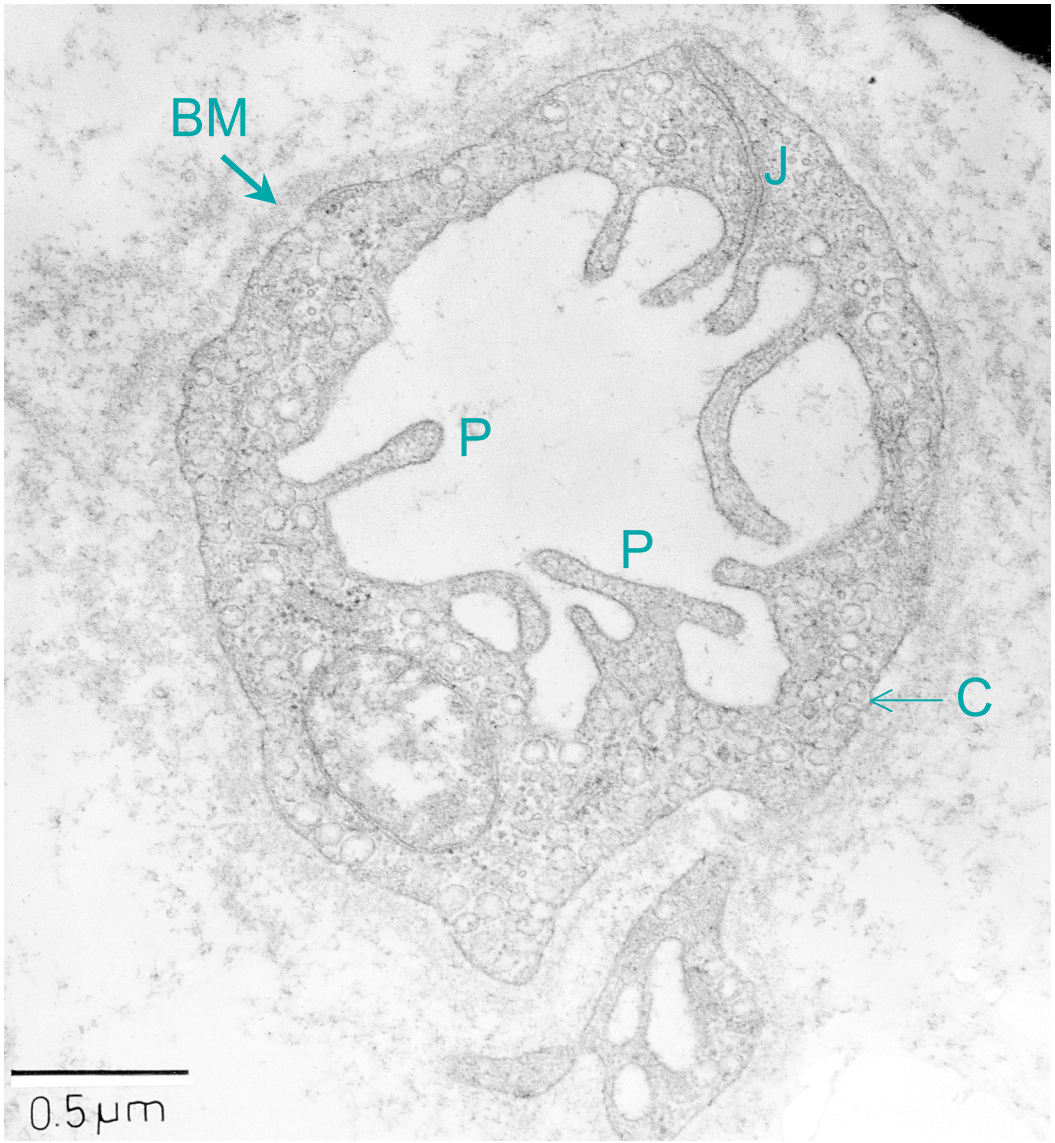


Figure 3

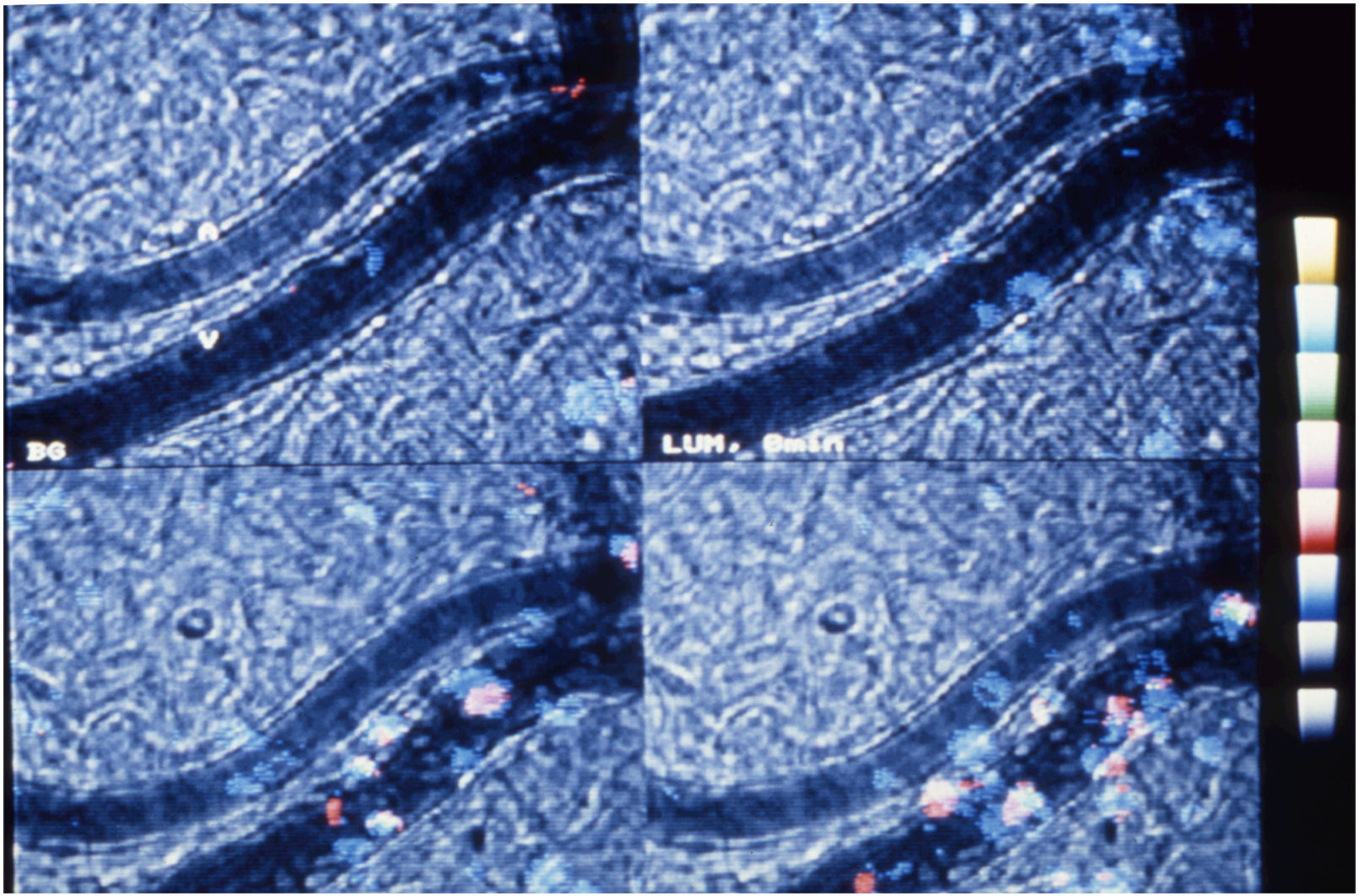


Figure 4

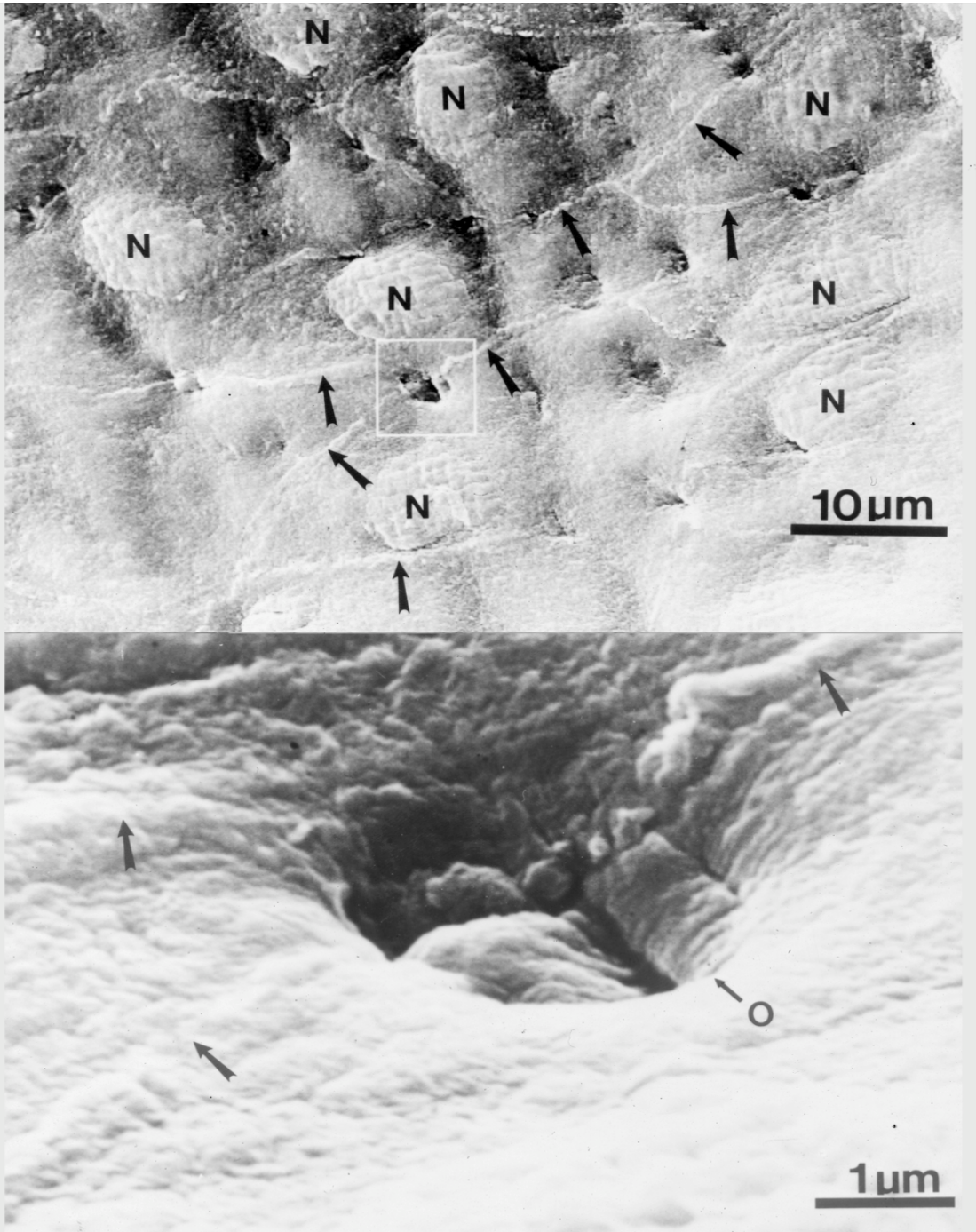


Figure 5

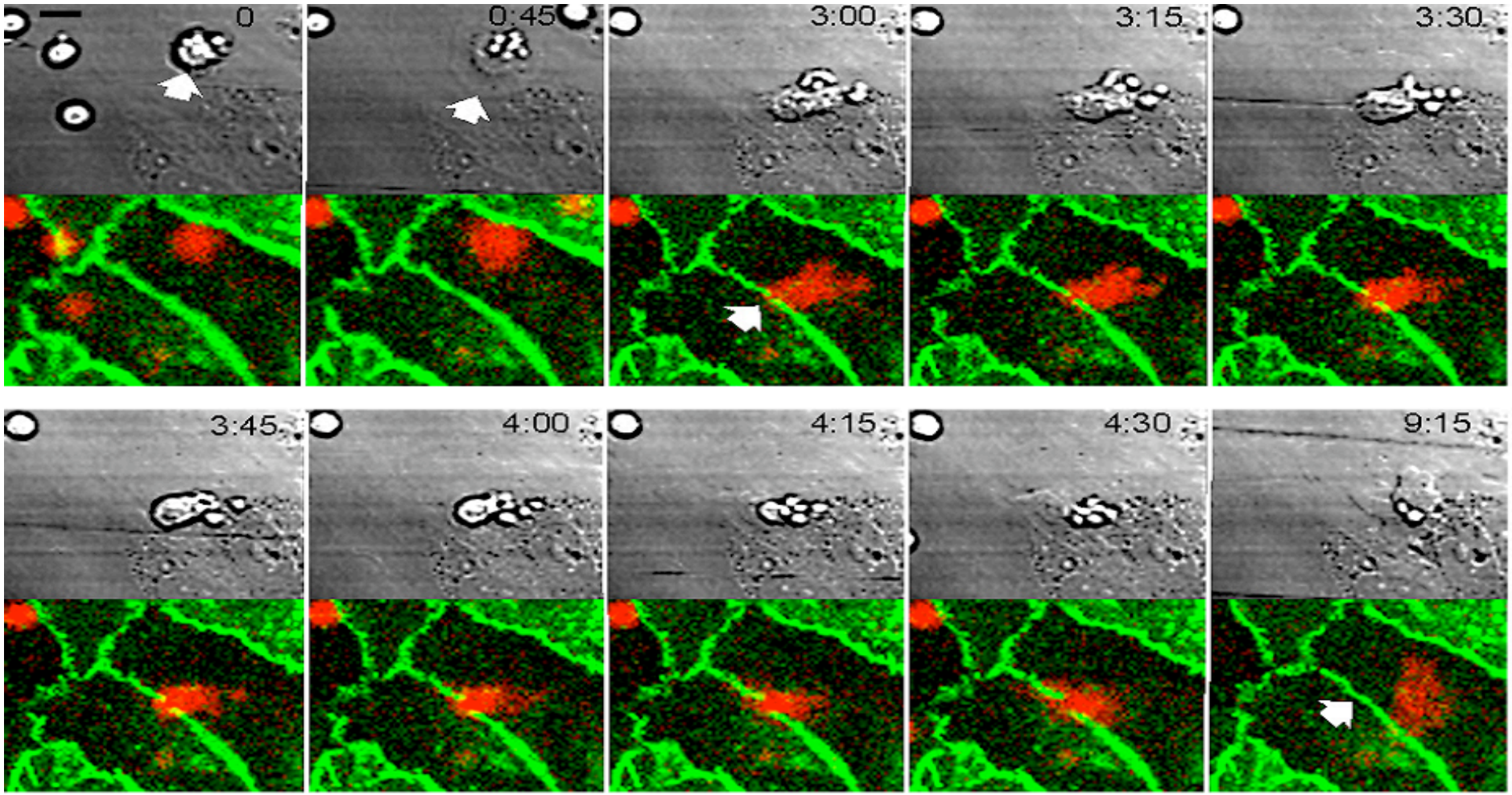
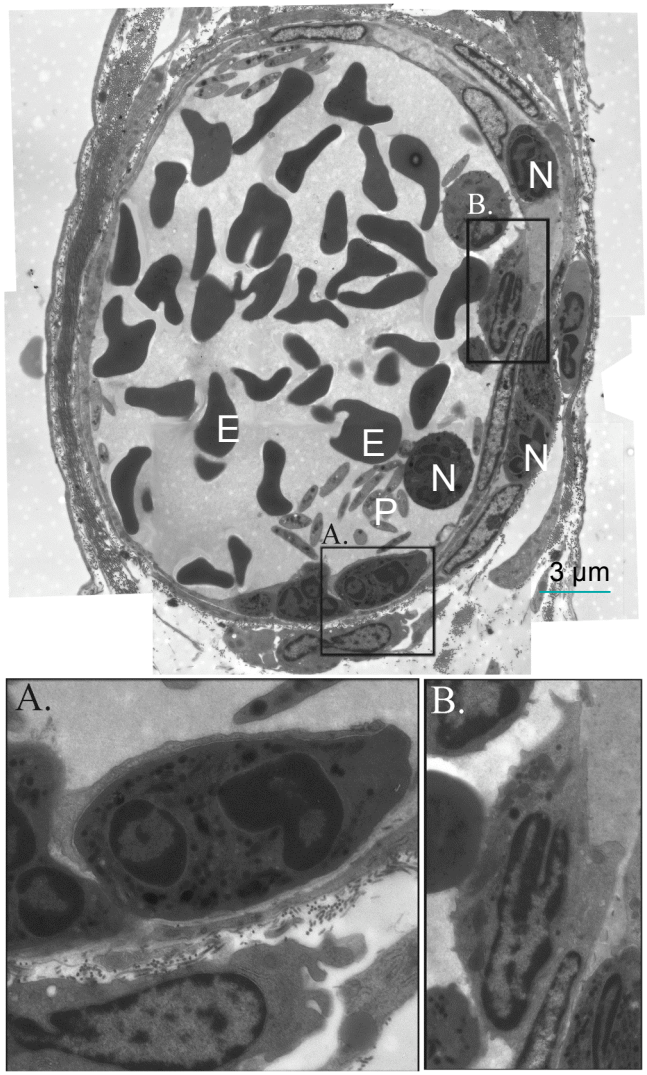
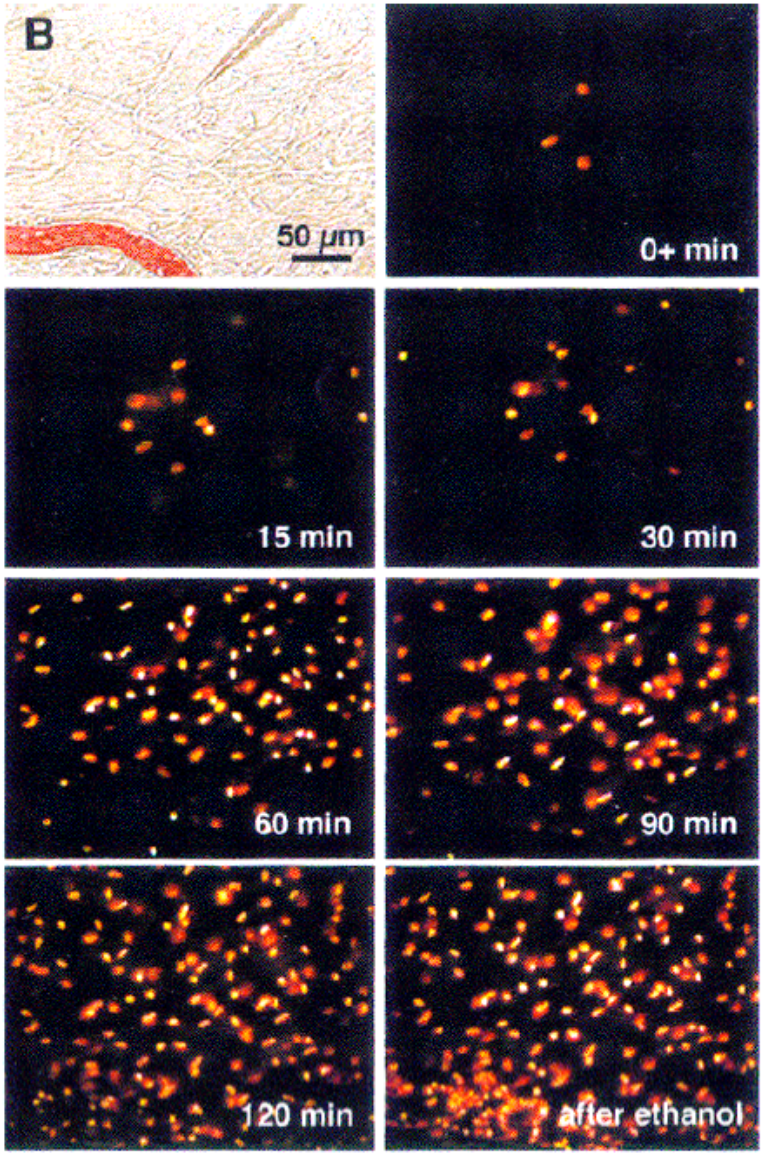


Figure 9

Inflammation in the Microcirculation





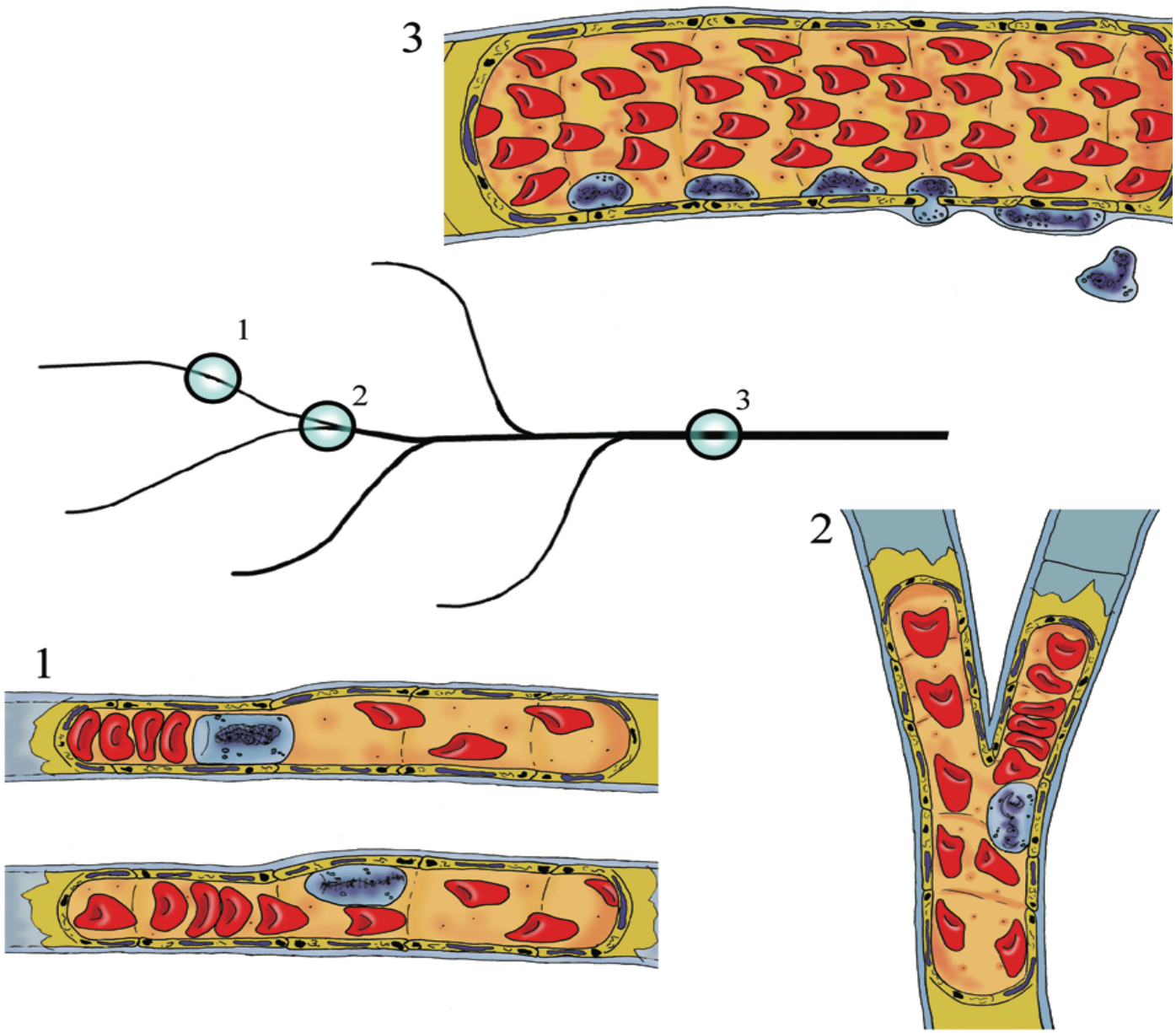
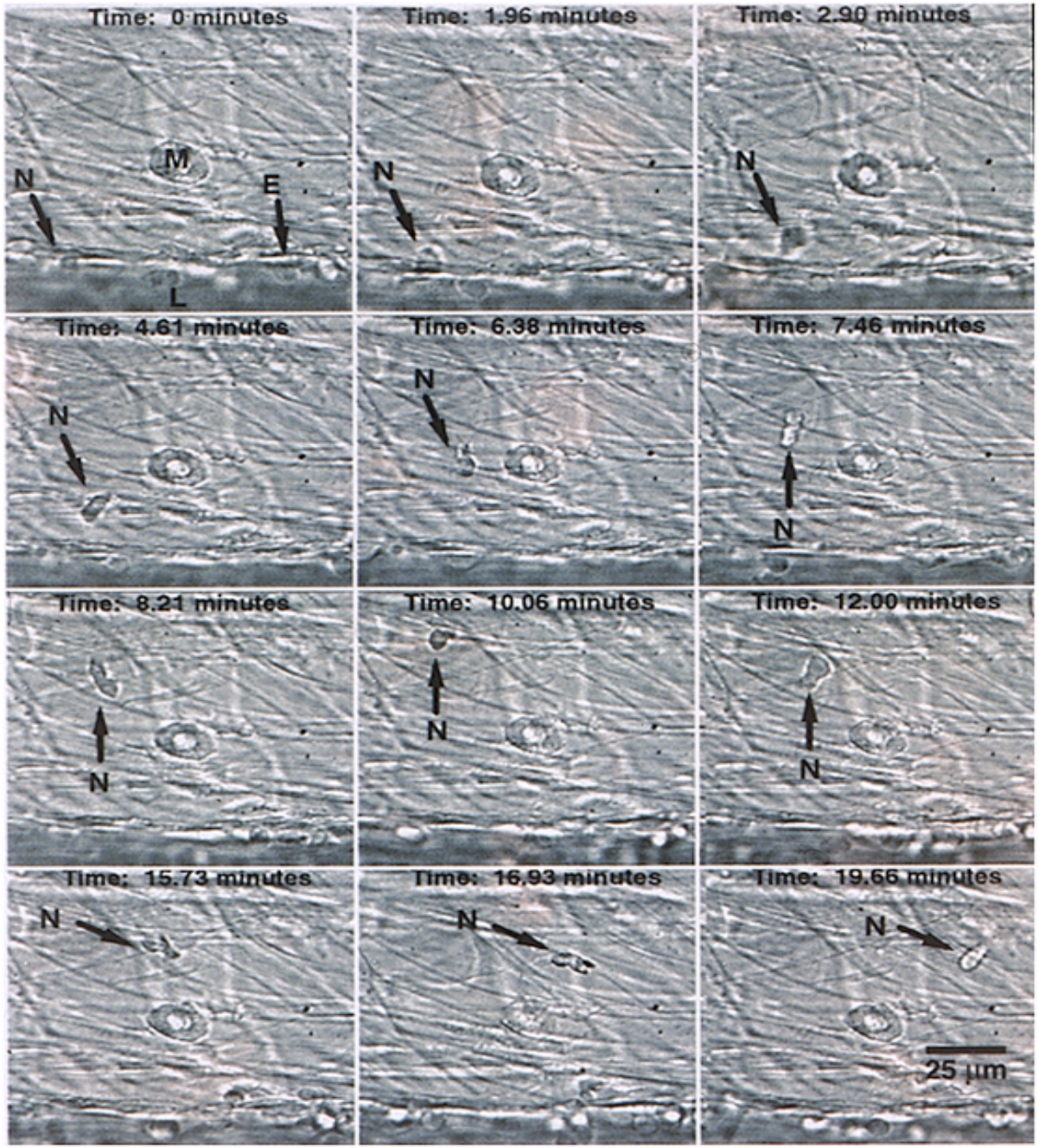


Figure 6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Figur
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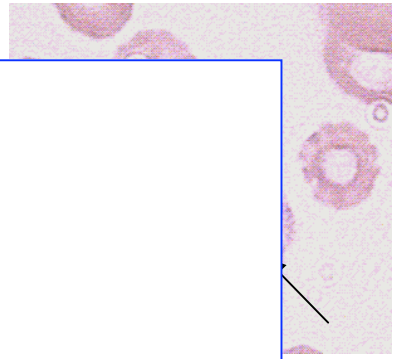
Trigger Mechanisms for Cardiovascular Cell Activation

- Inflammatory mediators (bacterial/viral/fungal sources, endotoxins, cytokines, histamine, oxidized products, complement fragments, LTB_4, PAF, etc.)
- Depletion of anti-inflammatory mediators (nitric oxide, IL-10, glucocorticoids, albumin, etc.)
- Fluid stress
- Transients of Gas Pressure or Temperature
- Juxtacrine Activation
- Bio-Implant Interfaces

Plasma Derived Inflammatory Mediators in Hemorrhagic Shock



Leukotaxin Peptide

Myocardial Depressing Factor

Clastogenic factor

T-Lymphocyte proliferation depression factor

Neutrophil activating factor

Leukocyte Chemotactic Factor

Neurin

Inflammatory Mediators in Hemorrhagic Shock