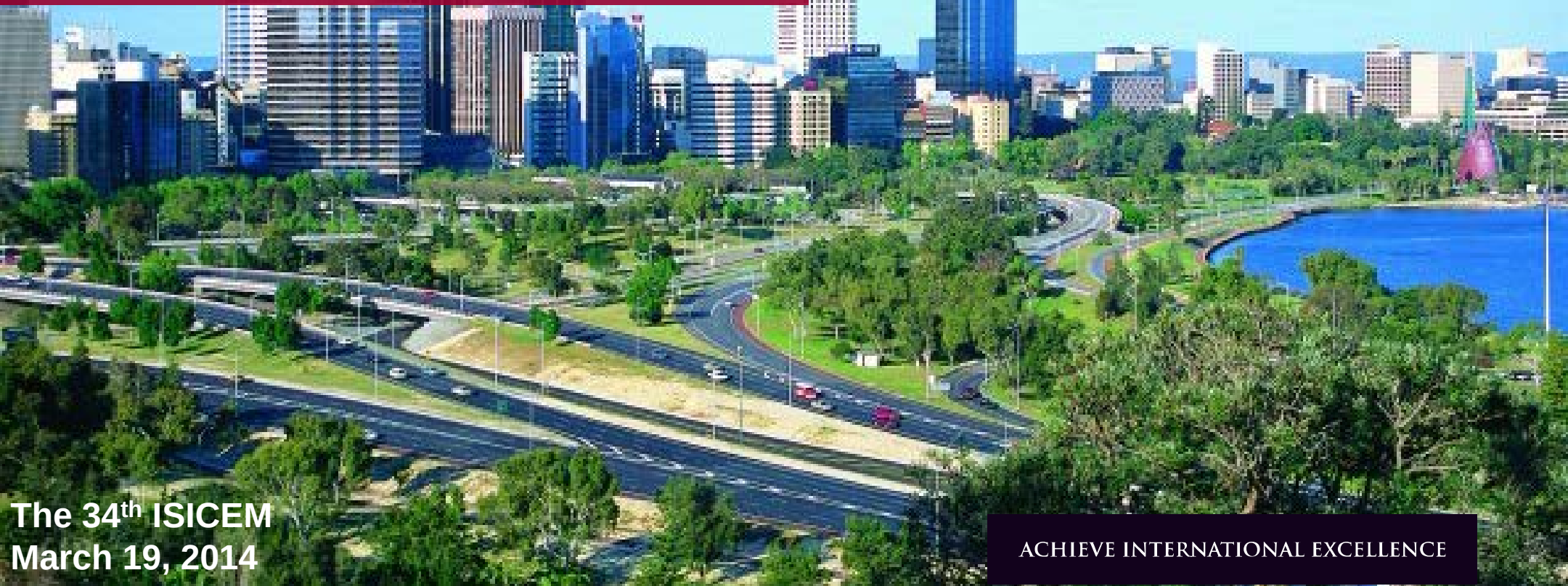
THE UNIVERSITY OF WESTERN AUSTRALIA

FACULTY OF MEDICINE, DENTISTRY AND HEALTH SCIENCES

Albumin Pharmacology – Molecular Structure to Physiological Properties to Therapeutic Function

ALBERT FARRUGIA PHD



The 34th ISICEM
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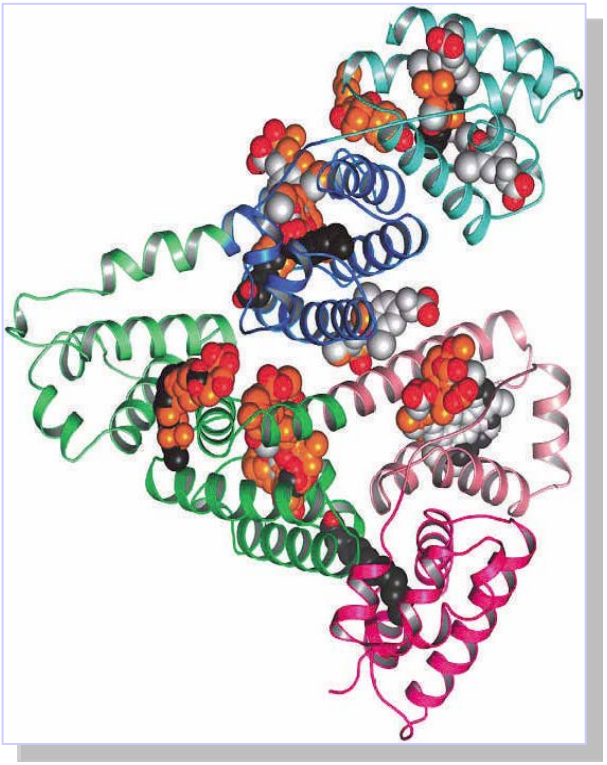
ACHIEVE INTERNATIONAL EXCELLENCE

Disclosures

I provide services to the pharmaceutical and biotechnology industry, including the manufacturers of therapies described in this presentation, who are also major sponsors of this Symposium

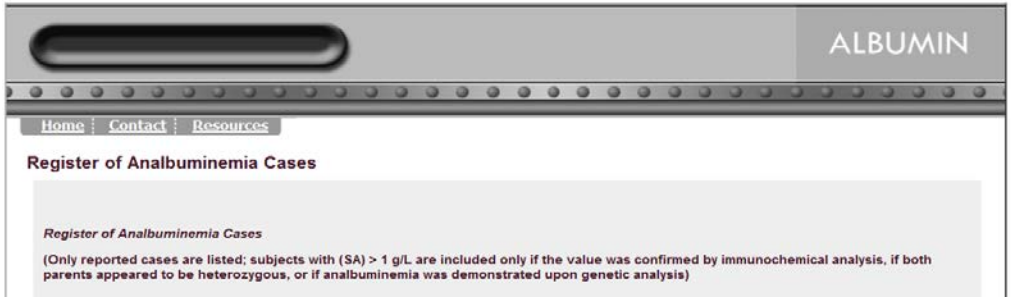
Physiologic Functions of Albumin

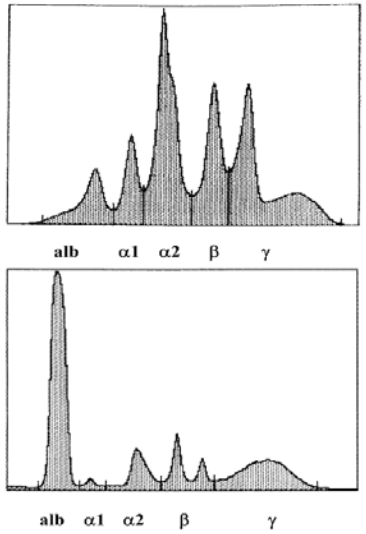


- Accounts for 50-60% of plasma proteins
- Creates 75% of colloid osmotic pressure
  - Colloid osmotic pressure (COP) ≈ 20 mm Hg for 4-5% albumin (5x = 100 mm Hg for 25% albumin)
- 60% of total albumin mass is extravascular
- Reversibly binds cations and anions
- Transport and inactivation of drugs, metals, dyes, fatty acids, hormones, enzymes, bilirubin

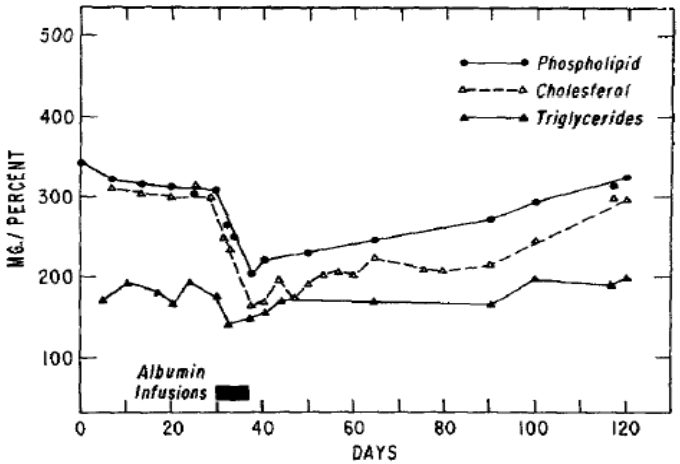
Quinlan, Martin, Evans. *Hepatology* 2005; 41: 1211-9.
Martin, Matthay, ATS Colloid Group. *AJRCCM* 2004; 170: 1247-59.

Congenital Analbuminemia





- Web based register of cases,50 cases as of June 2012
- Various mutations,autosomal recessive trait
- "Benign" BUT
  - Family histories indicate high sibling neonatal mortality
  - Lack of albumin in 2nd or 3rd trimester of fetal life may fail to protect against hyperbilirubinemia
  - Homozygotes may die *in utero*, survival to birth is rare
  - Survivors compensate through different protein composition



Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.

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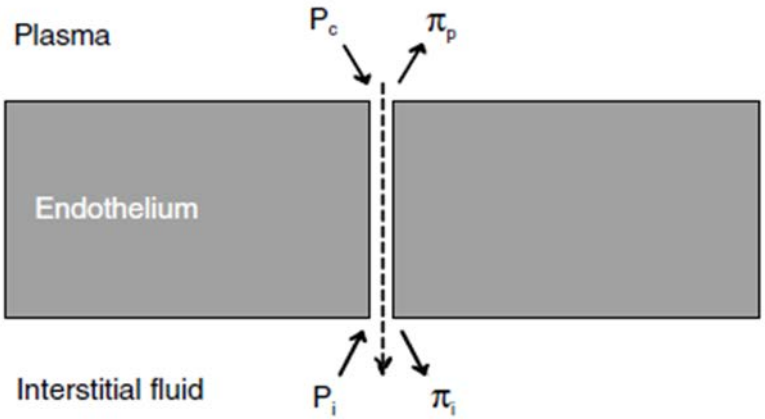
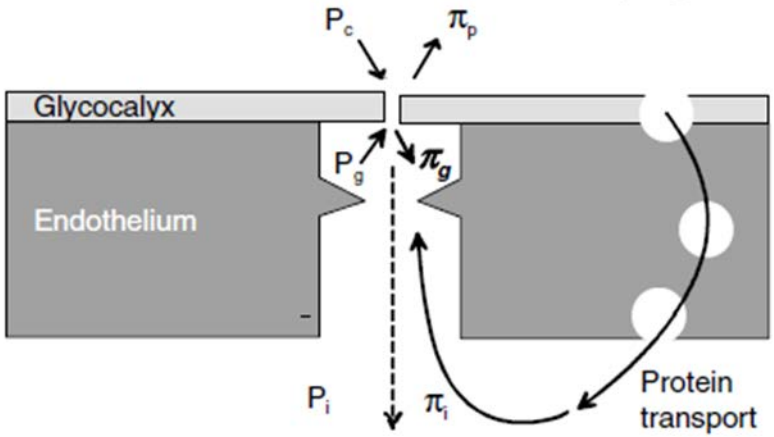
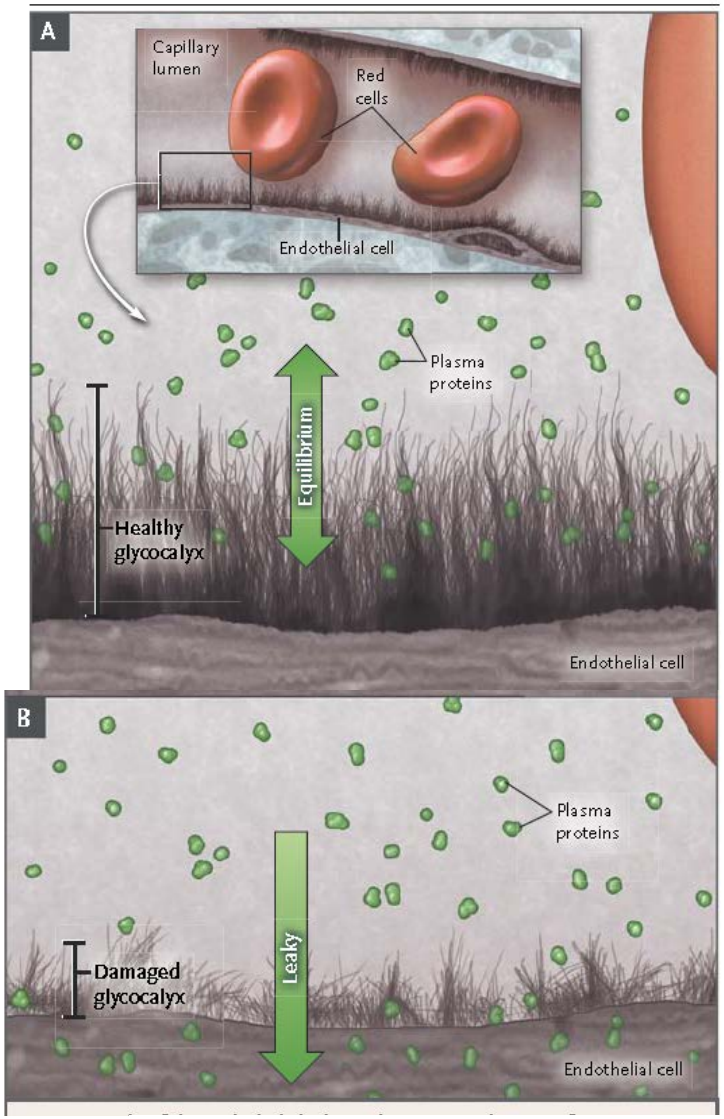
Classic Starling principle : $F = (P_c - P_i) - \sigma(\pi_p - \pi_i)$



Revised Starling principle : $F = (P_c - P_g) - \sigma(\pi_p - \pi_g)$





J Physiol 557.3 (3004) p704

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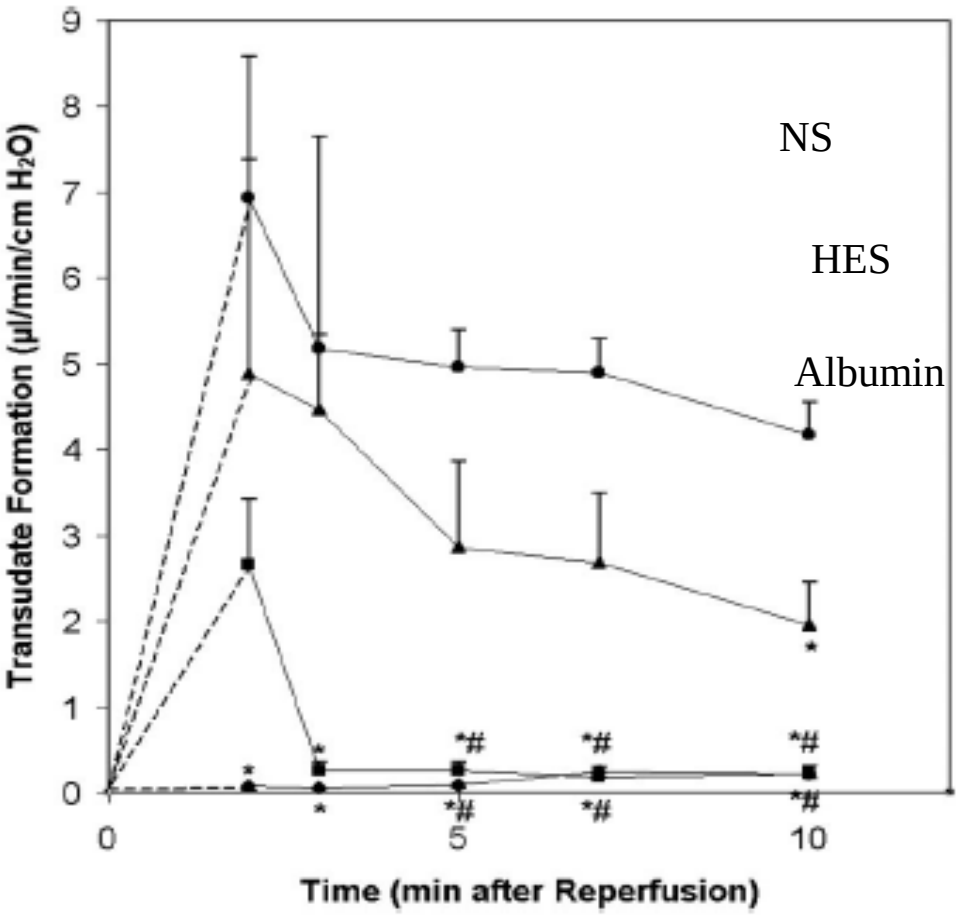
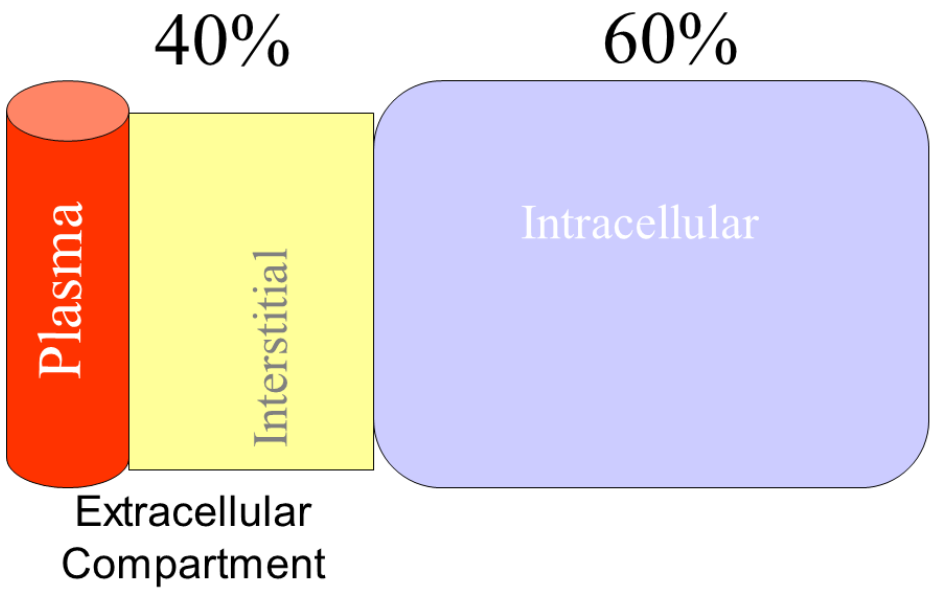
N Engl J Med 2013;369:1243-51.

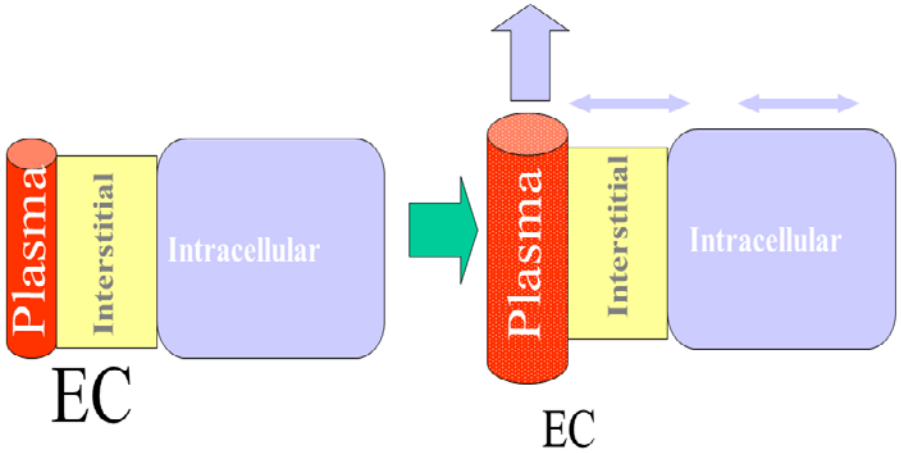
Filtration across vascular bed - Guinea pig heart model

- Study role of endothelial glycocalyx with respect to extravasation of fluid and development of tissue edema.
- Supplementing perfusate with albumin caused a significant decrease in transudate, also vs. HES (<0.05).
- Albumin also lowered edema formation vs. the other perfusion modes (<0.05).

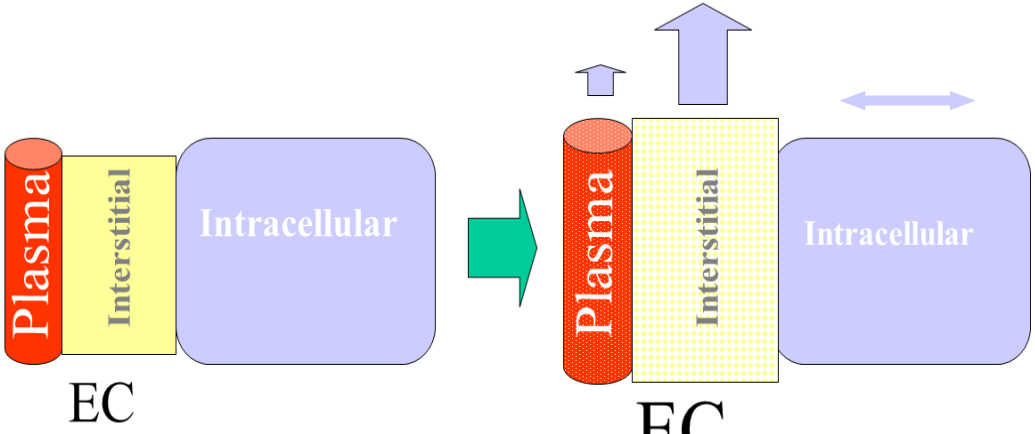


Body fluid distribution

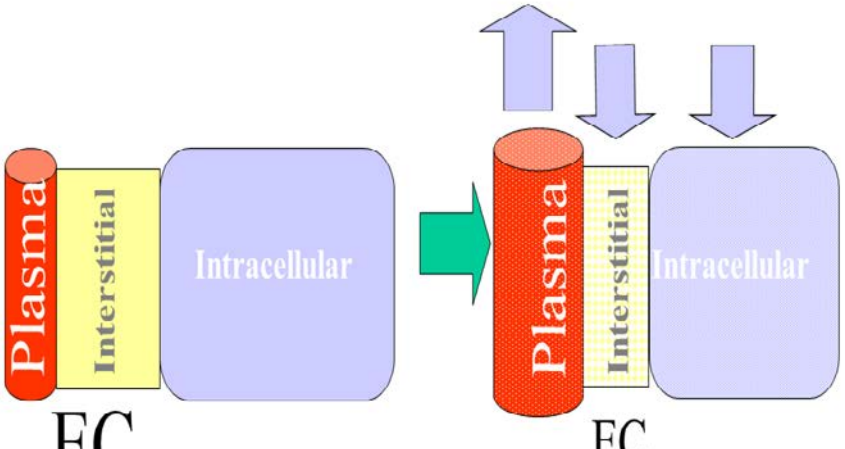




5% Albumin

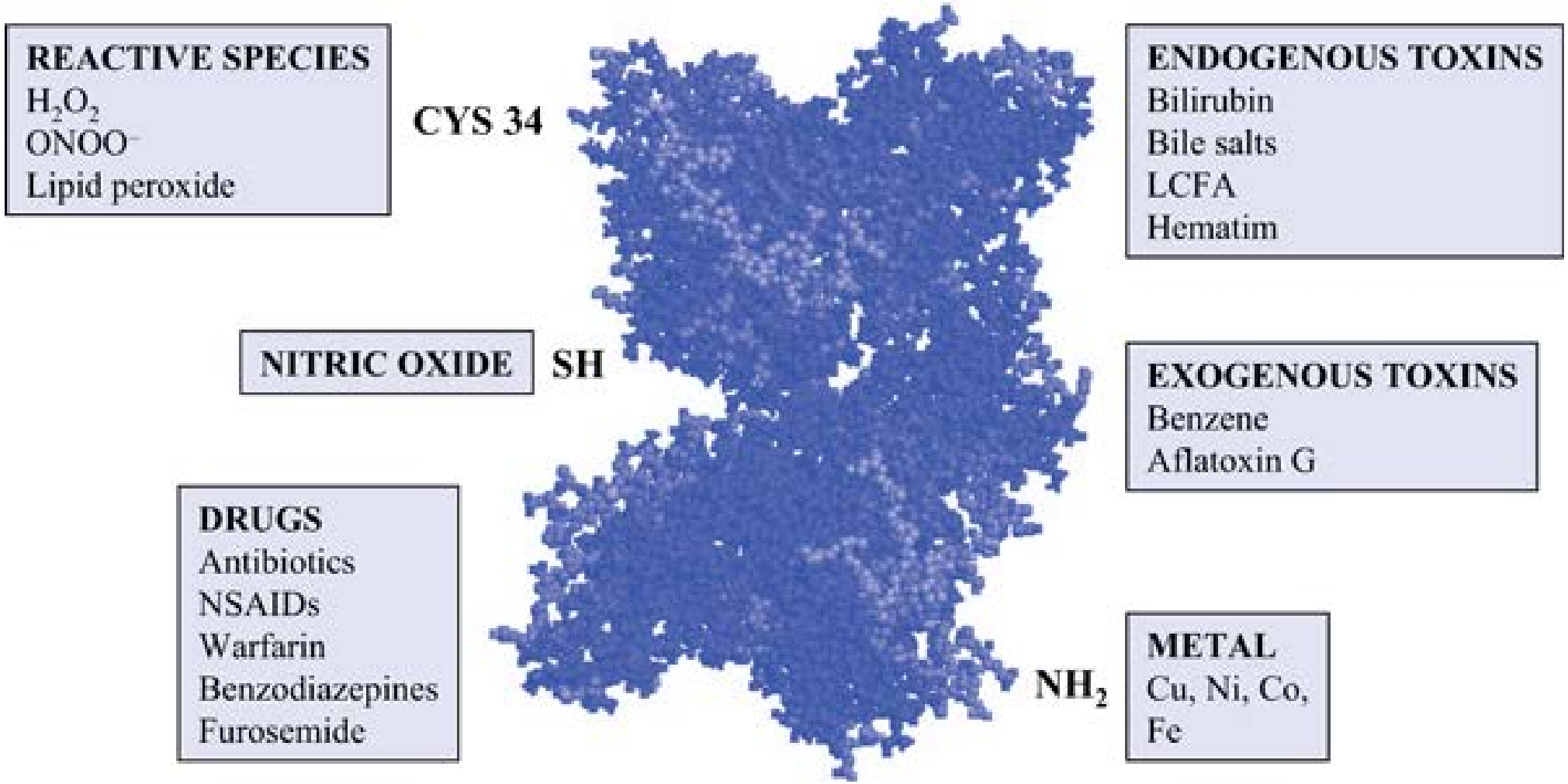


0.9 % NaCl



25% Albumin

Non-oncotic properties of human albumin: binding,transport and detoxification capacities.

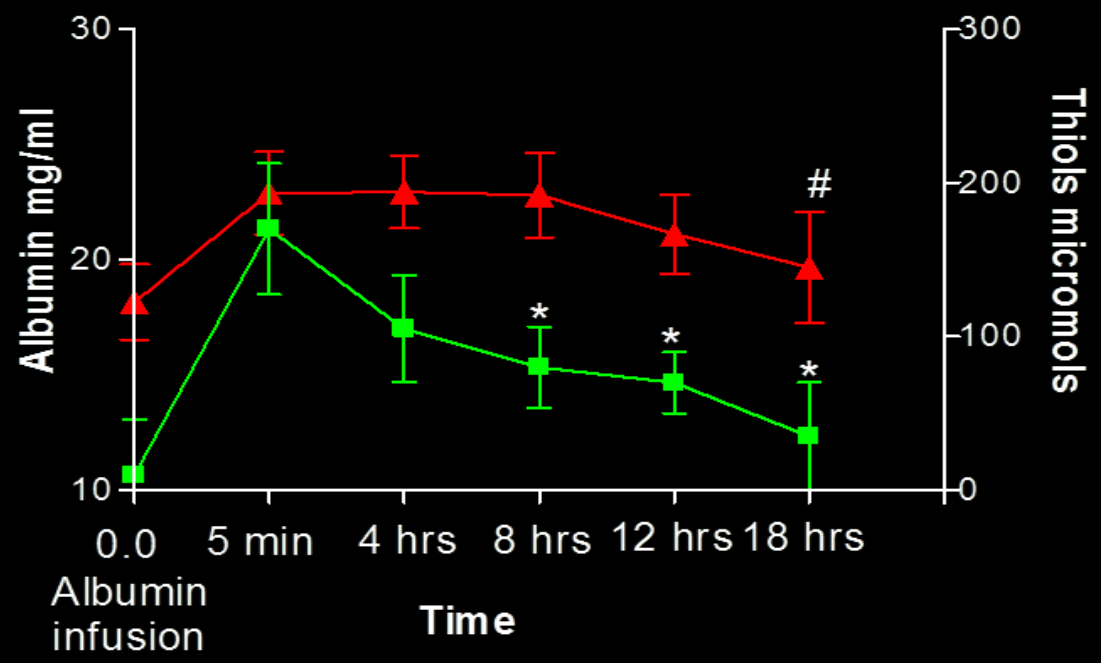


Antioxidant Properties of Albumin

- Albumin is the principal extracellular antioxidant found in human plasma †
- Cysteine-rich protein with a single exposed thiol
- Albumin increases intracellular GSH levels *in vitro* to levels sufficient to prevent H_2O_2–induced cytotoxicity and inhibit NF-κB activation *
- Dysfunctional oxidant-antioxidant "balance" in states of acute illness ‡

† Quinlan, Martin, Evans. *Hepatology* 2005; 41(6): 1211-1219.
* Cantin AM, et al. *Am J Respir Crit Care Med* 2000; 162: 1539-46.
‡ Jones DP, et al. *Free Radic Biol Med* 2002; 33(9): 1290-1300.

Plasma antioxidant capacity in patients given albumin



Plasma albumin levels (green) and total thiol levels (red) in patients with sepsis syndrome up to 18hr after albumin administration

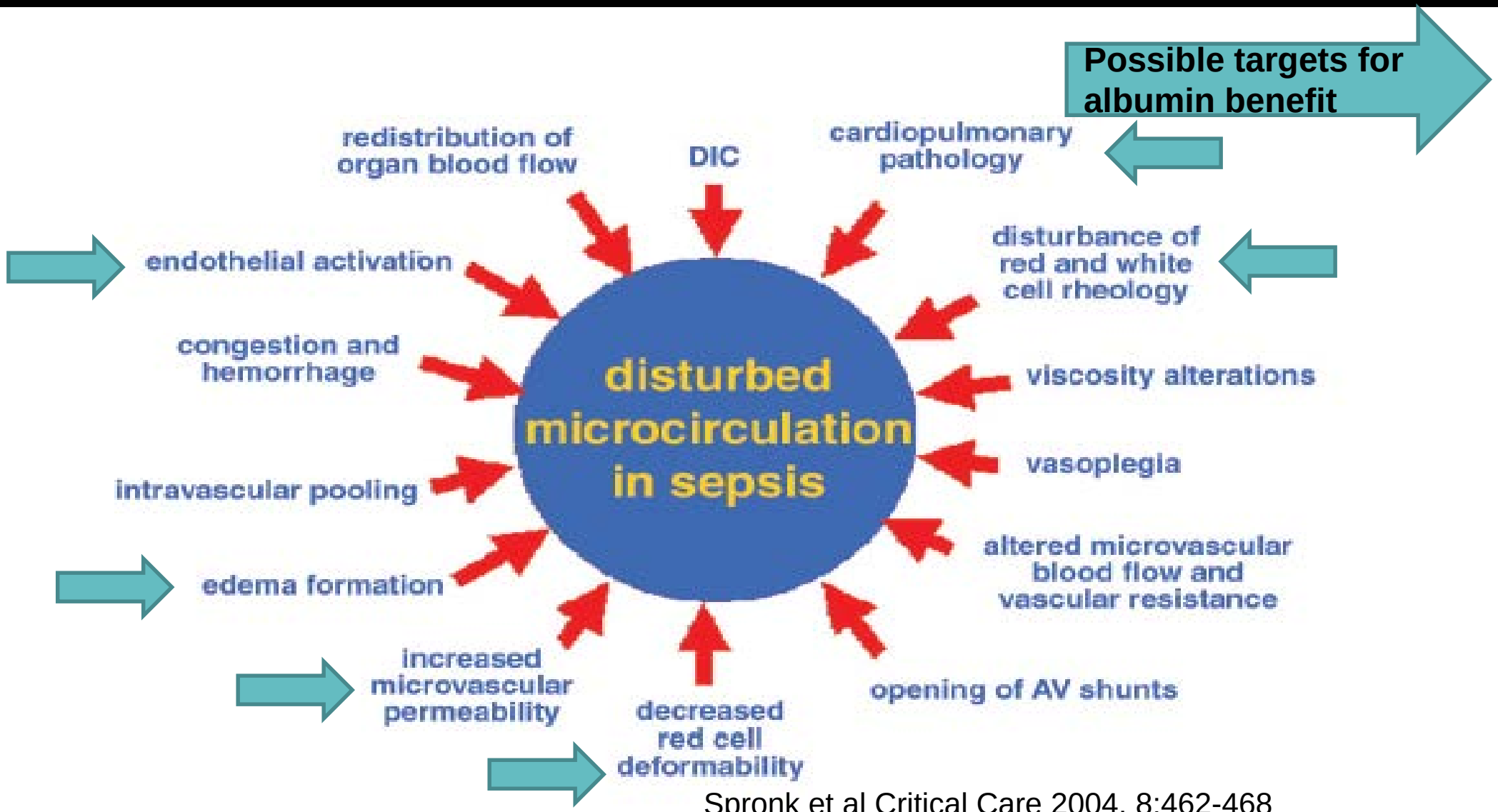
Quinlan G, et al. *Clin Sci* 1998; 95: 459-65.

Albumin – Expander or drug?

- Albumin's use in shock is based on correction of hypovolemia through its ONCOTIC properties
- Albumin's range of physiological properties and roles lends itself to HYPOTHESES BUILDING for other, pharmacological effects
  - Sepsis
  - Hepatology
  - Pulmonology
  - CABG
  - Burns…….

Microcirculatory perfusion in sepsis

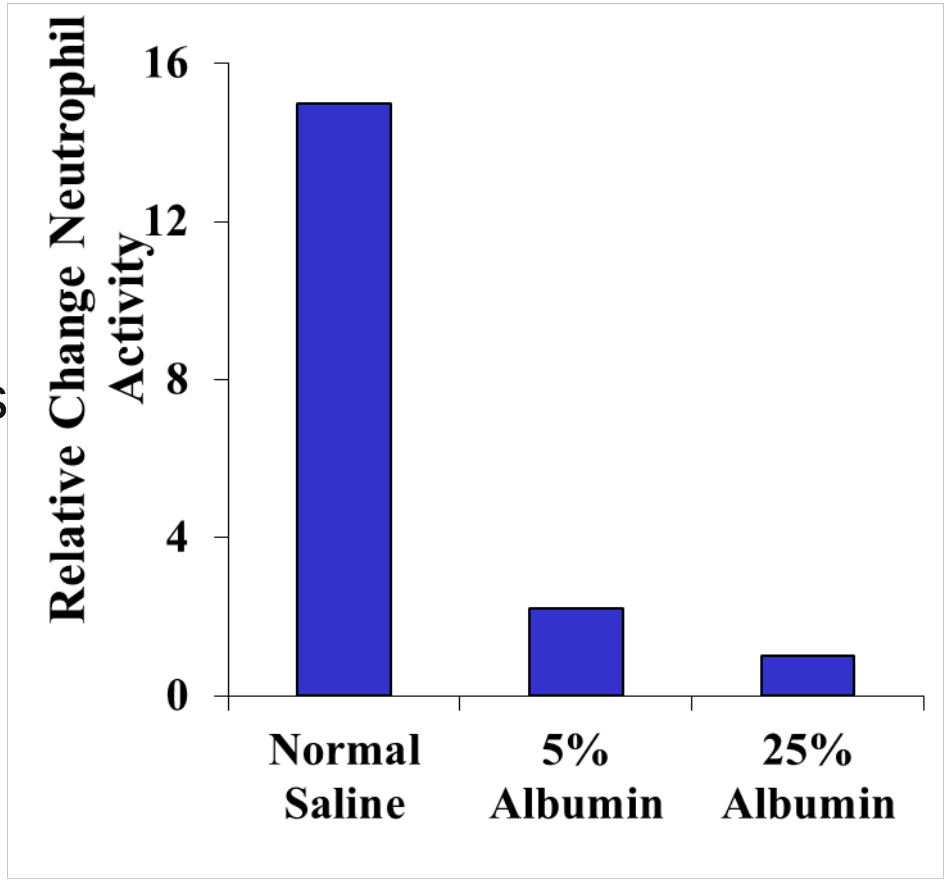
Potential impairing factors



Spronk et al Critical Care 2004, 8:462-468

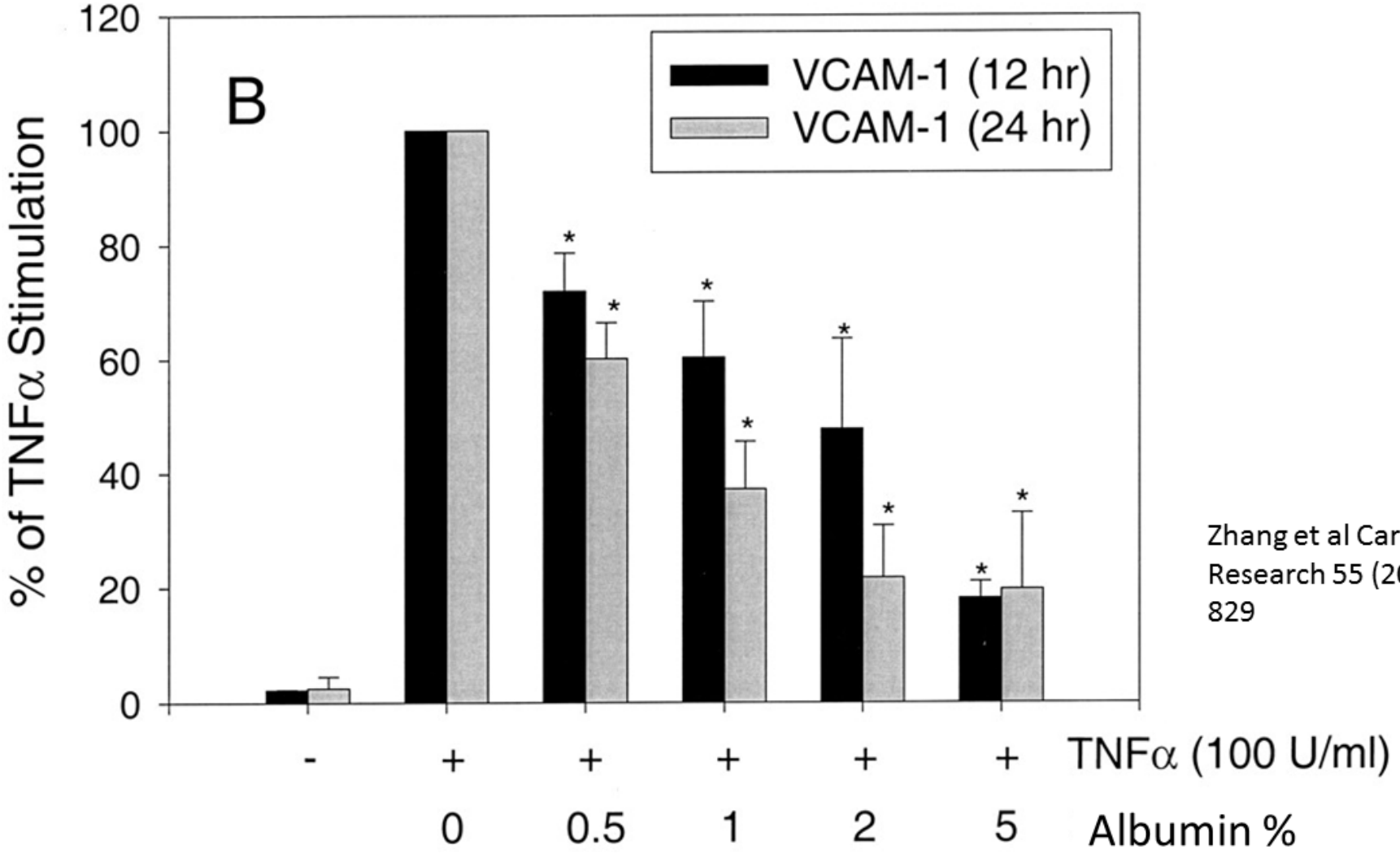
Anti-Inflammatory Effects of Albumin

- Neutrophils from healthy human subjects
- Dilution with various intravenous fluids
- Crystalloids and synthetic colloids increased neutrophil activation (intracellular oxidative burst activity) and adhesion (CD18 expression)



Rhee P, et al. *Crit Care Med* 2000; 28(1): 74-78.

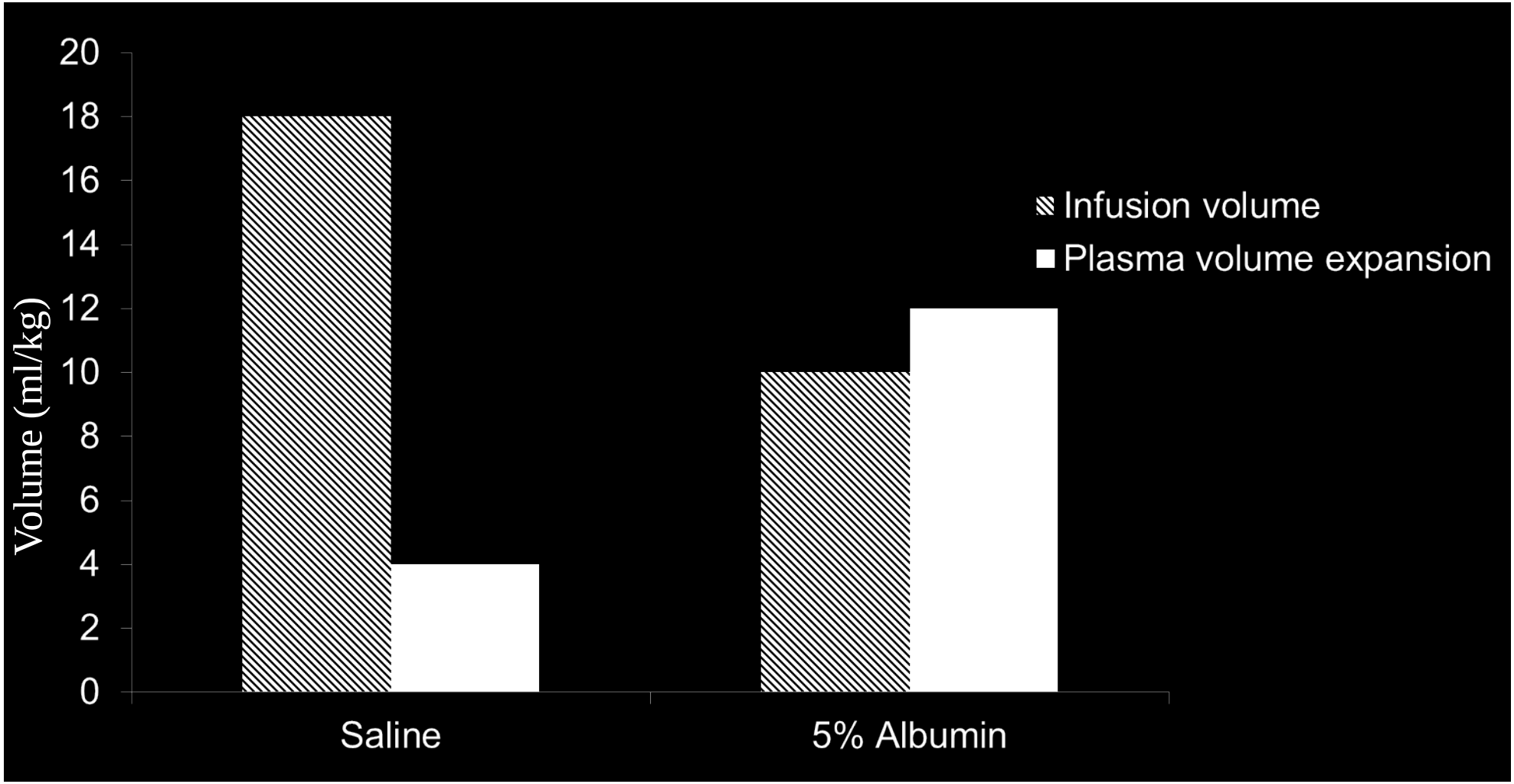
Albumin effect on endothelium
Inhibition of TNFa-induced VCAM-1 expression



Zhang et al Cardiovascular Research 55 (2002) 820–829

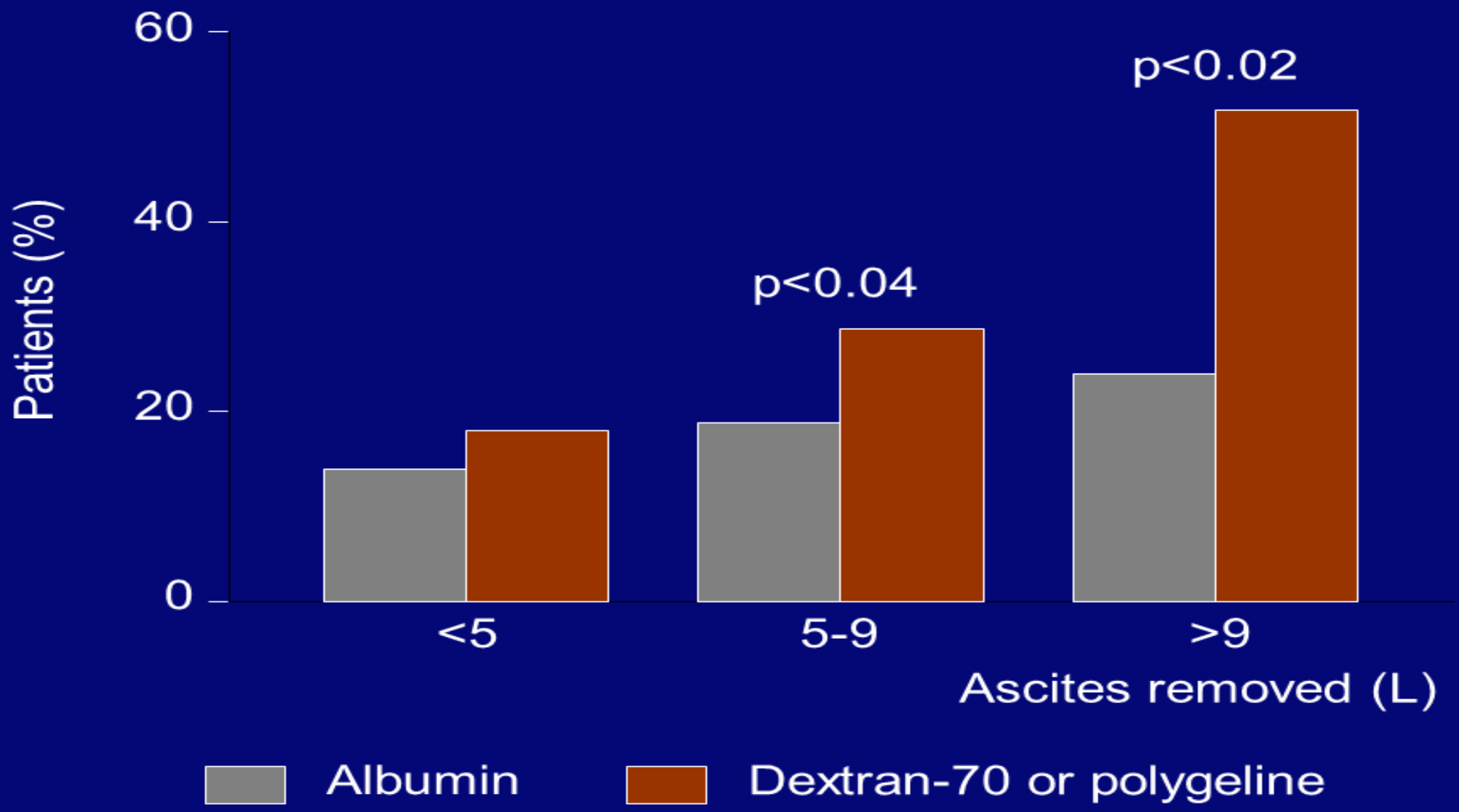
Fluid Therapy in Septic Patients

Albumin retains its plasma expansion capacity



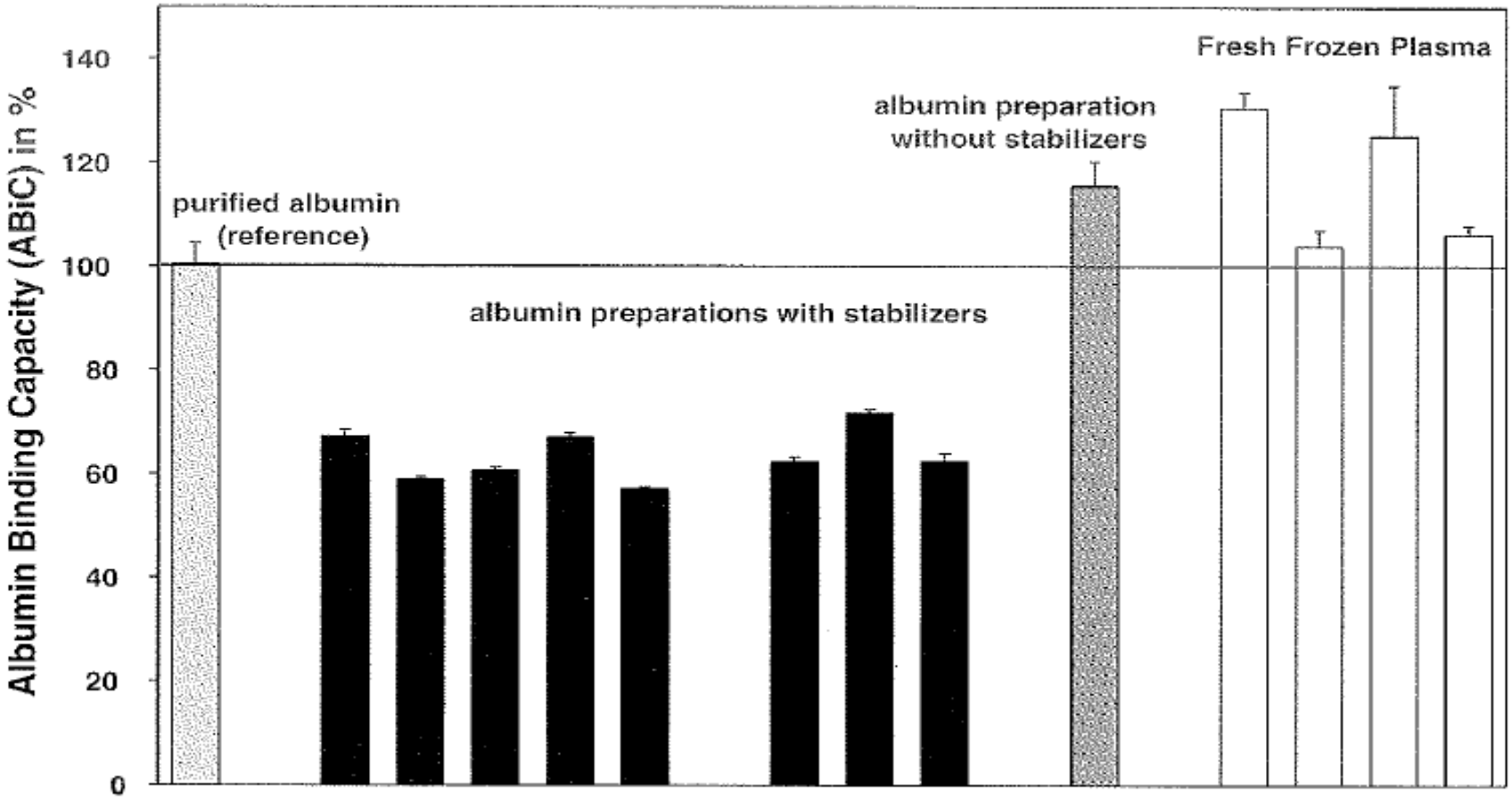
Ernest et al Critical Care Medicine:Volume 27(1)January 1999 pp 46-50

ALBUMIN vs OTHER COLLOIDS
POST-PARACENTESIS CIRCULATORY DYSFUNCTION



Sort et al NEJM 1999

Heterogeneity in albumin products
Binding site II for diazepam



Klammt et al Zeitschrift für Gastroenterologie 2001;39 Suppl 2():24-7

Heterogeneity in clinical effect
Batch specific within one manufacturer

- Herringlake et al Intensive Care Med 2000
- Hypertensive reaction to one batch
- Different bottles from same batch had effect
- No bacterial or other contaminants
- Other batches from same manufacturer had no effect

The company stated that such a "slight adverse drug reaction might be ascribed to the variability in reactions to biological products"

Summary

- Albumin is an essential multifaceted natural protein
- A historical focus on its oncotic effects is being overtaken by an interest in other pharmacologic properties
- These allow hypotheses building in relation to certain disease states
- Clinical data in sepsis and cirrhosis indicates that these pharmacologic effects can lead to clinical benefit
- Albumin preparations show heterogeneity, with uncertain effects in the clinic
- More investigations exploring albumin’s role in illness are merited