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This Week's Citation Classic

Grotte G. Passage of dextran molecules across the blood-lymph barrier. *Acta Chir. Scand.* **211**(Suppl.):**1**-84, 1956. [Institute of Physiology and Department of Clinical Chemistry, University of Uppsala, Sweden]

This paper was the first study of the passage of a **noncharged** *polymer* **(dextran) across capillary membranes from plasma to lymph. Here not only total concentration of a test substance was measured simultaneously in samples of plasma and lymph, but also the distribution of molecular sizes could be compared. This gave a quite clear view of the functional ultrastructure of capillary membranes in various regions of the body. [The** SCI® **indicates that this paper has been cited in over 295 publications since 1961.]**

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"During the years after World War II, surgical research in Sweden was much centered on surgical shock and blood volume restoration in surgery. During my surgical residency at the Sera-Timer Hospital in Stockholm, Sweden, where the surgeon, Gunnar Thorsén, was one of the leading scientists, I became interested in clinical trials of dextran as plasma 'substitute ' After a short first visit to the Mayo Clinic in Rochester, Minnesota, I went back there to work as a fellow in 1949. One evening, I was called to the home of Charles W. Mayo where one of the guests was one of the two inventors of dextran, B. Ingelman Walking back to the hotel that night we intensely discussed if it was ever possible that molecules penetrate capillary walls somehow in relation to their molecular size. At the same time, a new valuable technique in experimental surgery had been developed: a technique of cannulation of various lymphatics in the rat. With this new lymph sampling technique it would be possible to inject fractions of dextran of different molecular sizes and to follow their appearance in lymph. I then started a series of experiments with J L Bollman and the master of lymphatic calculation at the division of experimental surgery of the Mayo Clinic, Emery van Hook. This pilot study indeed showed that the transport of dextrans from plasma into lymph and urine was related to the molecular sizes of the test substance.[1]

"After my return to Uppsala University in Sweden in 1951, these studies were continued at the Institute of Physiology with T. Teorell, who was well known in permeability research, and with the other inventor of dextran, A Grönwall,[2] with whom G. Wallenius[3] at that time had developed a method for determination of molecular weight distribution of dextran in micro amounts. Wallenius then published the first permeability curves for the human glomerular membrane in his thesis of 1954.[3] The collaboration between these two institutions provided the necessary background and the work continued. The lymph cannulation technique was adapted for dogs and lymph could soon be collected from various regions of the dog, i.e., from the legs, heart, intestines, liver, and thoracic duct. Curves could soon be produced showing the different permeability characteristics of these various regions but the interpretation of these curves was still quite speculative.

"Much of the earlier work in this field had been done at Harvard's famous Institute of Physiology (by, among others, Drinker[4] and Landis[5]). Then in 1951, Pappenheimer and co-workers[6] at this same institution published their contribution to the pore theory of capillary permeability.[3] They suggested that capillary membranes have intercellular pores of 35-45 Å radius while my own investigation suggested a two-pore system with one set of pores of similar sizes as those suggested by Pappenheimer and co-workers, but also the presence of larger 'leaks,' probably situated at the venous ends of the capillaries. Then in 1953, Palade[7] suggested that macromolecules could be transported across capillary walls mainly by 'pinocytosis,' i.e., macromolecules are carried across the capillary membrane by small vesicles traversing endothelial cells.

"This experimental work on dextran was later confirmed and widely extended. A summary of this work was discussed at a symposium held in Uppsala, called Lymph Circulation,[8] in 1977 to commemorate both the 500 year jubilee of the University of Uppsala and also Olaus Rudbec k about 300 years after his discovery of the lymphatic circulation. A short summary of this complex problem is not possible "

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2. **Grönwall A.** *Dextran and its use in colloidal infusion solutions.* Uppsala: Almqvist & Wiksell. 1957. 156 p.
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4. **Drinker C K & Field M E.** *Lymphatics. lymph and tissue.* Baltimore. MD: Williams & Wilkins. 1933. 254 p.
5. **Landis E M.** Capillary pressure and capillary permeability. *Physiol. Rev.* **14**:404-81, 1934.
6. **Pappenheimer J R, Renkin E M & Borrero L M.** Filtration, diffusion and molecular sieving through peripheral capillary membranes. A contribution to the pore theory of capillary permeability. *Amer. J. Physiol.* **167**:13-46. 1951.
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8. **Lewis D H,** ed. Proceedings from the Symposium on Lymph Circulation. Basic morphological and physiological aspects of water and solute exchange in the microcirculation. (Whole issue.) *Acta Physiol. Scand.* **463**(Suppl.), 1979. 127 p.