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This Week's Citation Classics™

Crone C. The permeability of capillaries in various organs as determined by use of the 'indicator diffusion' method. *Acta Physiol. Scand.* **58**:292-305, 1963. [Institute of Medical Physiology, University of Copenhagen, Denmark]

The paper showed how permeability of blood capillaries could be determined quantitatively after a single passage of test solutes lasting a few seconds. The method was applied to different organs, with special emphasis on exchange between blood and brain. [The *SCI*® indicates that this paper has been cited in over 355 publications since 1963.]

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"Pappenheimer and associates[1] introduced quantitative studies of capillary permeability. Their method, however, required isolation and artificial perfusion of organs. Chinard and his collaborators[2] devised a principle which allowed organs to be studied *in situ* but their method was not quantitative. I solved this problem by making certain simplifying assumptions which made it possible to arrive at a simple mathematical expression from which capillary permeability could be calculated. The 'inaccessible' capillary membrane thus became accessible for quantification under *in vivo* conditions. The paper obviously filled a gap because very little was known about capillary permeability at that time. Interestingly, another solution to the same problem appeared almost in the same year from the other part of the globe, from Martin de Julián and Yudilevich[3] in Chile.

"I was doing my thesis work in the late 1950s. The peculiar fact that the blood-brain barrier has an extremely low permeability aroused my interest. How could this be reconciled with knowledge that D-glucose virtually pours into the brain from the blood? The blood-brain barrier had, so far, largely been characterized with semi-quantitative methods haying a very poor time resolution. The 'indicator diffusion' method now made it possible to approach this structure. However, it was necessary to cut through a lot of mystifications about the blood-brain barrier to postulate that it was just another capillary with properties of its own. This immediately made it possible to apply the strict analysis used in capillary physiology in general —a reductionist view which paved the way for an impressive development in this area.

"With the method established, I went on to assess brain capillary permeability—a true gold mine —and I was lucky enough to find a real piece of gold: the nonlinear, facilitated, glucose transport across the blood-brain barrier[4] —perhaps the best spin-off of the method.

"For quite a few years, there was considerable resistance against using the indicator diffusion technique, but things changed, and in the 1970s a surge of papers appeared based on this approach. The first to give the work full credit were my American colleagues, who chose me as the first recipient of the International Zweifach Award in 1979[5] —given for work in microcirculation."

1. **Pappenheimer J R, Renkin E M & Borrero L M.** Filtration, diffusion and molecular sieving through peripheral capillary membranes. *Amer. J. Physiol.* **167**:13-46. 1951. (Cited 495 times since 1955.)
2. **Chinard F P, Vosburgh G J & Enns T.** Transcapillary exchange of water and of other substances in certain organs in the dog. *Amer. J. Physiol.* **183**:221-34. 1955. (Cited 165 times since 1955.)
3. **Martin de Julián P & Yudilevich D L.** A theory for the quantification of transcapillary exchange by tracer dilution curves. *Amer. J. Physiol.* **207**:162-8. 1964. (Cited 80 times.)
4. **Crone C**. Facilitated transport of glucose from blood into brain tissue. *J. Physiol.—London* **181**:103-13. 1965. (195 cites.)
5. ..... Ariadne's threat—an autobiographical essay on capillary permeability. *Microvascular Res.* **20**:133-49. 1980.