Lassen N A, Lindbjerg J & Munck O. Measurement of blood-flow through skeletal muscle by intramuscular injection of Xenon-133. *Lancet* 1:686-9, 1964.
[Dept. Clin. Physiol., Bispebjerg Hosp., and Dept. Clin. Physiol. and Medical Dept. C, Glostrup Hosp., Copenhagen, Denmark]

The paper introduced the use of freely radioactive diffusible tracers for blood-flow measurements by local injection of Xenon-133 dissolved in saline with external monitoring. It was shown that patients with occlusion of the leg arteries have a subnormal and protracted muscle blood-flow response after exercise with proximal compression (reactive hyperemia). This agreed with plethysmographic data and tended to validate the method as well as to point to a clinical use. [The *SCI*® indicates that this paper has been cited in over 425 publications since 1964.]

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One day in 1963, our vascular surgeon came to visit the laboratory and asked if blood-flow methods existed for evaluating tissue blood flow in patients with intermittent claudication. We had at that time begun to use Xenon-133 dissolved in saline to measure cerebral blood flow by intra-arterial injection. We therefore applied the same tracer administered by intramuscular injection.

The local clearance principle for flow measurement had been used long before by others and had been formally described by S.S. Kety in 1951.[1] But until our study, the tracers used were hydrophilic, such as Sodium-24, and hence diffusion was limited at high blood-flow rates.

Our preliminary publication from a local symposium in Copenhagen actually dates from 1963. But we were very fortunate to be able to publish the first comprehensive presentation in *Lancet* in 1964. Certainly it has been helpful in getting the work known. As a curious coincidence, the distinguished research group from Johns Hopkins Hospital, Holzman, Wagner, Iio, Rabinowitz, and Zierler, in July 1964 published the very same technique in *Circulation*,[2] using both Xenon-133 and Krypton-85. But this publication has received much less attention. This is probably due to a number of "minor" factors: the Johns Hopkins group did not apply the method clinically; they mainly studied resting flow, where the method is least accurate; and perhaps *Circulation* has less circulation than *Lancet*.

Another factor has almost certainly been the fact that our group—and others thereafter—began to test the validity of the method and also to apply it to the study of flow in many other tissues, notably subcutaneous fat and myocardium. Thus, a long list of applications has been developed with the *Lancet* paper being the natural "first."

The local-clearance method using Xenon-133 continues to enjoy wide application. As a tool for routine clinical studies of occlusion of the leg arteries, it has been supplanted in particular by distal blood-pressure measurements using strain-gauge techniques. But as a research tool, it is very useful for studying blood-flow variations separately in the various peripheral tissues.

In many instances, advantage is taken of the control-test-control paradigm. This means one first records the clearance in the control state for a few minutes, then studies the test condition (say, the effect of sympathetic stimulation by lower body-negative pressure) for another period, and ends by a new control state for a further few minutes. By observing the percent change in fractional wash-out rate (k value $= 0.693/t_{1/2}$) relative to the average control value, blood-flow variations can be accurately recorded. This approach largely eliminates errors due to the unknown value of the tissue-to-blood partition coefficient.

With the continued vivid interest in peripheral tissue blood-flow regulation, it is likely that this fairly easy and practically atraumatic method will continue to be quite widely used in clinical research.

1. **Kety S S.** The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.* 3:1-14, 1951. (Cited 795 times since 1955.)
2. **Holzman G B, Wagner H N, Jr., Iio M, Rabinowitz D & Zierler K L.** Measurement of muscle blood flow in the human forearm with radioactive krypton and xenon. *Circulation* 30:27-34, 1964. (Cited 55 times.)

