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This Week's Citation Classic

Kety S S & Schmidt C F. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. J. *Clin. Invest.* **27**:476-83, 1948. [Dept. Pharmacology, Univ. Pennsylvania, Philadelphia, PA]

Cerebral circulation and oxygen consumption of the human brain were measured, using a new method based upon the blood:tissue exchange of an inert gas. In normal young men, mean values of 54 ml and 3.3 ml per minute per 100 g of brain were obtained for blood flow and oxygen consumption, respectively. Assumptions on which the theory was based were examined experimentally and found to be tenable. [The *SCI*® indicates that this paper has been cited over 565 times since 1961.]

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"This paper presented the theory and validation of a new technique which permitted the first quantitative measurements of human cerebral blood flow and energy metabolism in physiological states and in disease. The method was based upon the uptake by the brain of a diffusible inert gas supplied by way of the arterial blood. The unique qualities of the human brain and the lack of appropriate animal models of human neurological and mental disease made the development of a method that could safely be applied to unanesthetized man particularly desirable.

"Earlier investigators had measured the arteriovenous oxygen difference across the brain as an index of blood flow or of oxygen consumption under a variety of conditions. What had limited the acceptance of that approach, however, was that the arteriovenous oxygen difference, being determined by both blood flow and oxygen consumption, was not a valid measure of either. The oxygen consumption of the brain could not be measured independently *or* even assumed to be constant, since it would be expected to vary with the states of activity or disease which were the object of investigation.

"The brain does, however, absorb by physical solution an inert gas such as nitrous oxide which reaches it by way of the arterial blood. The accumulation of such a tracer in the brain should be independent of mental state and neuronal function, since it would be determined instead by physical characteristics, such as its rate of diffusion or solubility in brain, which would not be expected to vary with functional activity. It seemed likely also that cerebral blood flow could be calculated by monitoring the concentrations of the inert gas in arterial and cerebral venous blood from the onset of its inhalation until equilibrium was achieved, at which time the partial pressure of the gas in the brain would be equivalent to that in its effluent blood.

"Then began a theoretical examination of the dynamics of distribution of diffusible, nonmetabolized substances,[1] reinforced by a number of experimental studies with many collaborators to test the assumptions involved, develop a practical technique validated by comparison with direct measurement in the monkey, and to employ the new technique in gaining some understanding of the circulation and energy metabolism of the human brain in a wide variety of physiological and pathological conditions. Later, with Landau, Freygang, Rowland, and Sokoloff,[2] I applied the theory to measurement of regional circulation in the brain of the cat, using an internally calibrated autoradiographic technique for measuring the regional distribution of a radioactive tracer.

"This early work has been cited probably because it made possible contributions by a large number of other investigators on the blood flow, vascular resistance, and oxygen and glucose utilization of the human brain in health and disease,[3] and because the theory on which it was based led directly or indirectly to the development of current methods for the measurement of regional blood flow, metabolism, and the visualization of functional activity throughout the human brain.[4,5] It has been the basis of several awards, the first being the Theobald Smith award in 1949 and the most recent, the Passano award in 1980."

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.
2. **Landau W M, Freygang W H, Rowland L P, Sokoioff L & Kety S S**. The local circulation of the living brain; values in the unanesthetized and anesthetized cat. *Trans. Amer. Neurol. Assn.* **80**:125-9, 1955.
3. **Lassen N A.** Cerebral blood flow and oxygen consumption in man. *Physiol. Rev.* **39**:183-238, 1959. [Citation Classic. *Current Contents/Clinical Practice* **23**(10):12, 10 March 1980.]
4. **Ingvar D H & Lassen N A.** Regional blood flow of the cerebral cortex determined by Krypton^{85} *Acta Physiol: Scand.* **54**:325-88, 1962.
5. **Sokoioff L**. Relation between physiological function and energy metabolism in the central nervous system. J. *Neurochemistry* **29**:13-26. 1977.