This Week's Citation Classic®

Kety S S. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.* 3:1-41, 1951.
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Equations were derived describing various aspects of inert gas exchange, which made possible, inter alia, the visualization and measurement of regional cerebral blood flow in animals by calibrated autoradiography and in man by external counting, single photon, and positron emission tomography. [The *SCI*® indicates that this paper has been cited in over 1,000 publications.]

Visualization of Circulation and Functional Activity Throughout the Brain

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After the nitrous oxide technique was developed and the first values for cerebral blood flow and oxygen consumption were obtained in normal young men,[1] it was applied to a number of clinical problems, including essential hypertension, diabetic acidosis and coma, increased intracranial pressure, and senile dementia. When the technique was applied to the study of schizophrenia, the values for blood flow and oxygen consumption were within the normal range.[2] We pointed out that this did not rule out significant changes in particular regions of the brain, and the measurement and study of regional blood flow became my next objective.

In 1948 I had moved to the Graduate School of Medicine at the University of Pennsylvania, joining Julius Comroe's department, where I began to study the dynamics of the exchange of inert gases at the lungs. In fact, one of the early grants of the National Heart Institute enabled me to do this. What emerged in 1951 was an exhaustive review of earlier work and some new contributions of my own.

An expression was derived that described the uptake of inert gas at the lung in terms of pulmonary ventilation, cardiac output, and solubility of the gas in blood. This was of interest to many anesthesiologists since it appeared to be capable of explaining the different rates of induction and recovery of various volatile anesthetics and of predicting the course of the arterial concentration curve from measurable cardiopulmonary parameters. It was in the kinetics of exchange at the tissues, however, that the means of visualizing and measuring regional cerebral perfusion was found.

Both total and regional blood flow in an organ can be expressed as a relationship between three variable concentrations of an inert tracer: in tissue, in arterial blood, and in effluent venous blood. For the brain as a whole, arterial and cerebral venous blood was obtainable by direct sampling, and the mean brain concentration was indirectly evaluated from the venous blood as it approached equilibrium with the brain. For small regions of the brain, however, venous blood would be unobtainable, but if the tracer were radioactive, tissue concentrations could be measured by autoradiography in animals or external counting in man. By building on a derivation by Bohr for the exchange of oxygen at the capillary in a steady state, it was possible to develop an expression for the equilibration of an inert tracer in terms of capillary geometry, diffusion coefficients, and perfusion. This found usefulness as a measure of capillary permeability for a variety of tissues and substances[3] and, in the case of the brain, served to support an assumption that the concentration at the venous end of the capillary reached practical equilibrium with that in the surrounding tissue in each passage, for nonpolar tracers freely diffusible through the blood:brain barrier.

In 1952 I moved to the National Institutes of Health, and, shortly thereafter, William Landau asked to work with me because he wanted to measure regional blood flow in the brain. Here was an opportunity to put those equations to the test! We were joined by Louis Sokoloff, Lewis P. Rowland, and Walter H. Freygang in an exciting series of experiments, and in 1955 we were able to report the blood flow in 28 structures of the brain.[4] Other experiments followed, on the effects of CO_2 and on photic stimulation and anesthesia, where it was possible to demonstrate the coupling between blood flow and functional activity.[5] Others improved the method, substituting ^{14}C-antipyrine or ^{14}C-iodoantipyrine for the gaseous trifluor-iodomethane we first used, making the technique more generally applicable.

Lassen and Ingvar were the first to apply the clearance equation to man and to demonstrate in 1961 that in heterogeneous perfusion the initial slope of the clearance curve measured the weighted mean blood flow. External counting by collimated detectors eventually gave way to single photon tomography. With the development of positron emission tomography, Raichle and associates applied the equation used in the autoradiographic method[4] to the human brain in health and disease[6] and have begun what may become its most significant application—the study of cognitive function.

1. **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. (Cited 950 times.) [See also: **Kety S S.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986, p. 337.]
2. **Kety S S, Woodford R B, Harmel M H, Freyhan F A, Appel K E & Schmidt C F.** Cerebral blood flow and metabolism in schizophrenia. The effects of barbiturate semi-narcosis, insulin coma and electroshock. *Amer. J. Psychiat.* 104:765-70, 1948. (Cited 205 times.)
3. **Renkin E M.** Effects of blood flow on diffusion kinetics in isolated, perfused hindlegs of cats. *Amer. J. Physiol.* 83:125-36, 1955. (Cited 95 times.)
4. **Landau W M, Freygang W H, Rowland L P, Sokoloff 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. (Cited 275 times.)
5. **Sokoloff L.** Local cerebral circulation at rest and during altered cerebral activity induced by anesthesia or visual stimulation. (Kety S S & Elkes J, eds.) *Regional neurochemistry.* Oxford, England: Pergamon Press, 1961. (Cited 135 times.)
6. **Herskovitch P.** Measurement of regional cerebral hemodynamics and metabolism by positron emission tomography. (Boulton A A, Baker G B & Boisvert D P J, eds.) *Neuromethods.* Clifton, NJ: Humana Press, 1988. Vol. 8. p. 179-232.

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