CC/NUMBER 50
DECEMBER 14, 1987

This Week's Citation Classic®

Bradley S E, Ingelfinger F J, Bradley G P & Curry J J. The estimation of hepatic blood flow in man. *J. Clin. Invest.* 24:890-7, 1945.
[Evans Memorial, Massachusetts Memorial Hospitals, and Department of Medicine, Boston University School of Medicine, MA]

Bromosulfophthalein sodium (BSP) was used to estimate hepatic blood flow in normal humans by the Fick principle. Since extrahepatic BSP uptake is minimal, hepatic removal was taken as the rate of infusion needed to maintain flat peripheral blood levels (arterial and venous values are identical). Removal divided by the difference between BSP concentrations in the periphery and in blood taken from a hepatic vein by venous catheter yielded a value for hepatic blood flow. [The *SCI*® indicates that this paper has been cited in over 545 publications since 1955.]

Stanley E. Bradley
Department of Clinical Pharmacology
University of Berne
3010 Berne
Switzerland

July 15, 1987

When I arrived in Boston in July 1942 to begin the work that led to this paper, I had just finished two years of fellowship with Homer W. Smith at the Physiology Department of New York University. There I had been indoctrinated in the use of the clearance concept in studies of human renal hemodynamics. This experience was fortunately coupled with a close association with Andre Cournand and Dickinson W. Richards (Columbia Medical Division at Bellevue Hospital) in exploiting their newborn cardiac catheterization technique for renal and cardiocirculatory studies of patients with traumatic shock.

This preparation resulted in an invitation from Robert W. Wilkins to join him at Boston University for an investigation of the regional circulation. I was to measure cardiac output by the Fick principle and renal blood flow by renal clearances of sodium p-aminohippurate (PAH). A major problem lay in our assumption that PAH was completely removed from blood perfusing the kidneys. Since my colleagues and I in New York had repeatedly observed that the cardiac catheter frequently entered the inferior vena cava and the hepatic veins by chance, it seemed likely that it also could be introduced intentionally into the renal veins to obtain blood for measurement of PAH content in order to correct our calculation of renal blood flow. The ureteral (*sic*) catheters employed at that time were too short to reach the renal veins reliably. Hence, I designed and ordered extralength catheters soon after settling in Boston and, after their arrival several months later, found that they could easily be placed in the hepatic as well as the renal veins.

During this waiting period my wife and I set up our laboratory and looked about for the fluoroscope needed for precise catheter placement. We soon discovered just what we needed in the laboratory next door, which was presided over by a young gastroenterologist, Franz J. Ingelfinger. Ingelfinger had arrived a year earlier after training with T. Grier Miller and Osler Abbott in Philadelphia and was usually seen with a dangling Miller-Abbott tube he had popped in early each morning for study of his own esophageal motility. He assented at once to our sharing his apparatus, and a very happy collaboration ensued.

As I began computations of cardiac output and renal extraction of PAH, it became obvious that the Fick equation for cardiac output is identical with that for PAH extraction, except for the markers (oxygen vs. PAH). It was this perception that led to the idea that a nonmetabolizable substance that is rapidly excreted by the liver, such as bromosulfophthalein sodium (BSP), might serve as a means of measuring hepatic blood flow. It followed further that if BSP were removed exclusively (or almost so) by the liver, maintenance of a constant blood level by intravenous infusion would imply equality of the rate of input and the rate of hepatic removal. Since blood could be obtained from only one hepatic vein at a time, however, and not from a mixture of all effluent, the final value was referred to as *estimated* hepatic blood flow. The group of healthy young Army recruits who served as subjects for this and also for penicillin therapy of primary syphilis, under the aegis of John Curry, enjoyed, understood, and shared our enthusiasm.

In the course of the work evidence was obtained for a limited hepatobiliary transport system for BSP that was more intensively studied later. In fact, such "spin-off" publications (measurement of splanchnic blood volume, intrahepatic distribution of blood flow, and changes during exercise, shock, and disease)[1] may have had something to do with the frequency with which this paper has been cited. The method (using BSP or indocyanine green) is still useful for evaluating new approaches[2] and in studies of hepatic hemodynamics,[3] hypoxia,[4] and drug action,[5] or of metabolism of amino acids, lactate, and glucose.[6]

1. **Bradley S E.** The hepatic circulation. (Hamilton W F & Dow P, eds.) *Handbook of physiology—circulation.* Washington, DC: American Physiological Society, 1963. p. 1387-438. (Cited 135 times.)
2. **Kanstrup I-L & Winkler K.** Indocyanine green plasma clearance as a measure of changes in hepatic blood flow. *Clin. Physiol.* 7:51-4, 1987.
3. **Jensen L S, Krarup N, Larsen J A, Juhl C & Nielsen T H.** Effect of acute portal hypertension on hepatosplanchnic hemodynamics and liver function. *Scand. J. Gastroenterol.* 21:568-72, 1986.
4. **Winkler K, Keiding S, Tonnesen K & Tygstrup N.** Effect of short lasting hypoxia on the metabolic function of the perfused pig liver. Comparison of ischaemic and hypoxaemic hypoxia. *Eur. J. Clin. Invest.* 16:106-12, 1986.
5. **Tokics L, Brismar B & Hedenstierna G.** Splanchnic blood flow during halothane-relaxant anaesthesia in elderly patients. *Acta Anaesthesiol. Scand.* 30:556-61, 1986.
6. **Tinker D A, Brosnan J T & Herzberg G R.** Interorgan metabolism of amino acids, glucose, lactate, glycerol and uric acid in the domestic fowl (*Gallus domesticus*). *Biochemical J.* 240:829-36, 1986.