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This Week's Citation Classic

Miller L L, Bly C G, Watson M L & Bale W F. The dominant role of the liver in plasma protein synthesis. A direct study of the isolated perfused rat liver with the aid of lysine-ε-C^{14}. *J. Exp. Med.* **94**:431-53.1951. [Depts. Radiation Biol. and Pathol.. Univ. Rochester Sch. Med. and Dentistry. Rochester, NY|

The need for a method allowing the protracted direct study of the liver uncomplicated by the contributions of other organs led to development of the isolated rat liver perfusion technique. The perfused rat liver closely simulated the physiological behavior of the liver *in vivo* with respect to metabolism of glucose and amino acids, synthesis of plasma proteins, and bile secretion. [The *SCI*® indicates that this paper has been cited over 600 times since 1961.]

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"From 1938 to 1946, in the laboratory of George H Whipple, I participated in studies of protein nutritional factors affecting the production of plasma proteins in intact dogs. Interpretation of results invoked the hypothesis that the liver was the site of albumin and fibrinogen synthesis, but there was no direct evidence to support this view.

"In 1948 I returned to Rochester to join William F. Bale in further studies of plasma protein biosynthesis with the new tool, ^{14}C-lysine, prepared by R. W. Helmkamp, an organic chemistry professor. The question of the liver's role in plasma protein synthesis became more challenging. A direct answer to that question seemed obtainable experimentally by isolating the liver and maintaining its circulation with an artificial pump oxygenator. The idea of isolated liver perfusion dated back to Claude Bernard' and to German physiologists.[2] Trowell[3] had perfused the rat liver with aqueous media in retrograde fashion and Lupton[4] briefly described an effect of vitamin K on prothrombin synthesis by the rat liver perfused for a few hours.

"Our first perfusion apparatus was a 'do it yourself project. The 'heart-lung' was made from the multi-bulbed tube of an Allihn condenser, hand-ground glass valves, and fingers of surgical gloves. Our first rat liver perfusions were encouraging, but short-lived because of blood clotting; a pre-liver filter made of a piece of nylon stocking removed small clots and extended perfusion time to six or seven hours. Within a short time, with ^{14}C-lysine, we demonstrated that the liver was producing ^{14}C-labeled albumin, fibrinogen, and plasma globulins. Collaborating in this early work were graduate students Chauncey G. Bly and Michael L. Watson. Bly's PhD thesis was based on these early studies.[5]

"There are two reasons for the frequent citation of this paper, (a) It afforded the first unequivocal demonstration of the dominant role of the liver in the biosynthesis of serum albumin, fibrinogen, and approximately 80% of the remaining plasma globulins. Several years later, by utilizing preparative zone electrophoresis to fractionate perfusates from liver perfusions[6] and from rat hindquarters,[7] we were able to document the view that the normal liver is the site of synthesis of virtually all of the plasma proteins with the notable exception of the gamma globulins. (b) It afforded a relatively inexpensive reproducible system for studying the direct interaction of various agents, on and with the liver, under conditions closely approximating the physiological, and with the aid of isotopically labeled metabolites. Over the intervening years the originally described operative technique and the apparatus have been substantially improved so that perfusions 24 hours in duration are routine.[8]

"The technique of isolated rat liver perfusion has been widely and fruitfully applied to problems in biochemistry, physiology, and pharmacology, it will continue to be used by those seeking to explore further the unknowns of liver metabolism and function."

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2. **Asp G.** Zur Anatomie und Physiologic der Leber. *Arbeiten aus der physiologischen Anslalt zur Leipzig* **8**.124-58. 1873.
3. **Trowell O A.** Urea formation in the isolated perfused liver of the normal rat. *J Physiology* **100**:432-58. 1942.
4. **Lupton A M.** The effect of perfusion through the isolated liver on the prothrombin activity of blood from normal and dicoumarol treated rats. *J Pharmacol Exp. Ther* **89**:306-12. 1947.
5. **Bly C G.** *Some studies in the biosynthesis of tissue and plasma proteins.* Unpublished PhD thesis. University of Rochester. 1952.
6. **Miller L L & Bale W F.** Synthesis of all plasma protein fractions except gamma globulins by the liver. *J. Exp. Med* **99**:125-32. 1954.
7. **Miller L L, Bly C G & Bale W** F. Plasma and tissue proteins produced by non hepatic rat organs as studied with lysine-ε-C^{14} *J. Exp Med.* **99**:133-53. 1954.
8. **Miller L L.** Technique of isolated rat liver perfusion. (Bartosek I. Guaitani A & Miller L L. eds) *Isolated liver perfuston and its applications* New York: Raven Press. 1973. p 11-52.