

This Week's Citation Classic

Tait J F. Review: the use of isotopic steroids for the measurement of production rates *in vivo*. *J. Clin. Endocrinol. Metab.* **23:1285-97, 1963.** [Worcester Foundation for Experimental Biology, Shrewsbury, MA]

Theoretical considerations and experimental procedures involved in the measurement of metabolic clearance rate (MCR) and blood production rate were compared and described, e.g., single injection and continuous infusion methods. Emphasis was placed on applications in endocrinology and particularly for steroid hormones. [The **SC[®]** indicates that this paper has been cited over 275 times since 1963.]

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"Applications in endocrinology of the experimental procedures and theoretical considerations for the estimation of metabolic clearance rate, largely originating from the work of Hamilton and co-workers,¹ were a feature of this review. The concept of blood production rate was also introduced.

"This concept arose because the labelled reagent methods for the estimation of nanomole amounts or less of biologically important substances in blood had become generally applicable. These originated in Bethesda with the radioactive pipsyl method and had been applied there and elsewhere to the estimation of steroid hormones using labelled pipsyl, acetic anhydride, and thiosemicarbazide reagents. These methods have now been supplanted by immunoassay procedures, but were the first practical methods in blood for important steroids such as aldosterone, androstenedione, and testosterone. Although laborious they were quite accurate and indeed it is doubtful whether some of the estimates of secretion rates for blood

production rates then made could have been achieved with the present accuracy of routine immunoassays.

"The blood production rate is the metabolic clearance rate multiplied by the blood concentration of hormone and represents its secretion rate plus the amount irreversibly converted to it from precursors. These concepts originated mainly from the general theoretical ideas of E. Curpide and co-workers.² The blood concepts, which proved to be more generally valid than those involving measurement of urinary metabolites, were largely evolved from the experimental work by myself and colleagues³ on aldosterone metabolism which presented a starting point for consideration of more complicated situations such as when steroids were converted peripherally. Their development also followed extensive discussions with J. Coghlan of the Florey Institute of Experimental Biology and Medicine, Melbourne, Australia, and S. Burstein, who worked, as did I then, at the Worcester Foundation for Experimental Biology, US. The S³⁵ thiosemicarbazide method, which was probably both the most difficult and sophisticated labelled reagent method ever developed, was vital for the critical estimation of androstenedione which first showed that concentrations of this prehormone in female and male plasma were similar. The use of this reagent was developed with the chemical advice of Marcel Cut at Worcester.

"If the review has been highly cited and has had some influence it is because it was timely and the concepts, although not completely original in general physiology, had not been appreciated generally in endocrinology. Appropriate experimental methods had also just become available.

"Later work at the Worcester Foundation followed this review when experimental collaborative studies with R. Horton, C. Longcope, and D. Baird⁴ exploited these concepts culminating in a presentation at the Laurentian Hormone Conference."

1. **Hamilton W F & Remington I W.** Comparison of the time concentration curves in arterial blood of diffusible and non-diffusible substances when injected at a constant rate and when injected instantaneously. *Amer. J. Physiol.* 148:35-9, 1947.
2. **Gurpide E, Mann I, VandeWiele R L & Lieberman S.** A discussion of the isotope dilution method for estimating secretory rates from urinary metabolites. *Acta Endocrinol.* 39:213-22, 1962.
3. **Tait J F, Little B, Tait S A S & Flood C.** The metabolic clearance rate of aldosterone in pregnant and nonpregnant subjects estimated by both single-injection and constant-infusion methods. *J. Clin. Invest.* 41:2093-100, 1962.
4. **Baird D T, Horton R, Longcope C & Tait J F.** Steroid dynamics under steady-state conditions. *Recent Progr. Hormone Res.* 25:611-64, 1969.