sound theoretical basis for any methodology before simplification can be carried out, and I note with regret the authors' statement "we plan to do careful compartmental analysis in the future." It would seem more appropriate that before such a paper is written the careful compartmental analysis should be carried out. There are very well established methods for measuring glomerular filtration rate in the literature, and it is essential to compare a new and experimental method with a well known and accepted method rather than with estimates of expected renal function which can vary considerably from individual to individual and from moment to moment.

The use of the plasma volume in a given individual is in itself a highly variable entity, and most people who have had any significant experience with the measurement of plasma volume will attest to the great variation from individual to individual which makes an accurate prediction for any one person on the basis of height and weight alone well near impossible.

The authors have adopted a method that appears to be a compromise between the continuous-infusion technique and the single-injection technique with the gradual administration of the radiocompound so that a plateau is reached before the exponential portion of the curve is measured. For the single-injection technique a rapid bolus is essential so that mixing can take place rapidly, and this rapid bolus is essential to all mathematical assumptions in the technique. On the other hand, it is possible to achieve an equilibrium level by a gradual infusion, but for this to be an accurate method one must be sure that the material infused is distributed throughout its entire volume of distribution. The volume of distribution of sodium iothalamate probably is closer to the extracellular fluid than to the plasma volume.

Let me conclude by saying that attempts to apply radionuclides to the study of renal function require a firm foundation in renal physiology and tracer kinetics (*2,3*). The methodologies should be carefully tested out against well established techniques and should have a firm theoretical basis in fact. Methodology that makes use of the coincidental agreement of two sets of values can lead only to multiple errors in its application and to a general discontent for the use of radionuclides in the study of renal function.

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THE AUTHOR'S REPLY

The general impression gathered from this letter is that Dr. Blaufox is being a bit too dogmatic in his statements and is demanding in some respects an absolute accuracy that is applicable only to theoretical mathematics. By the same token even compartmental analysis, based on mathematical models which is itself a simplification, if rigorously confronted with the behavior of a living membrane of selective permeability, is to be dismissed on the same grounds. As in any other biological and medical problem, good judgment is essential and ample knowledge of the fundamental physiological facts is the prerequisite, as well as a good sense of proportion.

The first simplification is of a theoretical nature and based, as can be recognized easily on the principle of orders of magnitudes; to be more precise, the passage of an inulin-like substance into the interstitial space is of a much smaller magnitude than its passage through the renal glomeruli. For this reason, in the short time interval of observation the passage into interstitial space was considered small —in fact, negligible. No doubt, the latter assumption caused concern; admittedly it is a possible oversimplification in accord with the criteria now voiced by Dr. Blaufox.

I have talked over the facts with my colleagues in the physiology department at the Medical School concerning the possibilities of exploring in nephrectomized dogs the passage of sodium ^{131}I-iothalamate from the intravascular into the interstitial space. They justifiedly raised very serious objections about the validity of the results obtained. In spite of everything, successful studies in this direction (to be presented soon) have recently been possible. In a patient in whom both kidneys had to be removed (now under control with an artificial kidney) such a study was done by taking advantage of her arti-

ficial arterio-venous fistula. To obviate radiation hazards, however, another inulin-like substance had to be used—EDTA labeled with ^{113m}In (by the way, a very good agent to measure filtration rate).

A bolus is certainly necessary to measure very rapid phenomena as in cardiac outputs. But here again the mixing in blood of the experimental reagent takes place at a faster rate when compared with the renal filtration rate (this is graphically evidenced in the paper). For practical reasons (to get convenient values on the ratemeter and graph) a slow injection was used. This is by no means a compromise between a continuous infusion and a single injection. It is simply a single injection. Furthermore there is no reason to see a plateau where a plateau does not exist.

Briefly, something about the plasma volume: the first and fundamental table in the paper is based on a determination of plasma volume and it is preferable, as clearly stated, to use it. A direct determination of plasma volume should, however, be simultaneous and would require the use of a double-tracer technique. On the other hand, very competent workers have related weight and height with blood volume (The Tulane Tables—see also Nadler, S. B., Hidalgo, J. U. and Bloch, T. *Surgery* (St. Louis) **51**:224, 1962). (*1,2*).

The book *Basic Principles of the Tracer Method* by C. W. Sheppard is also very well known to us and in fact, gives a very similar method to the one used on pages 6–8 (see also Fig. 1) for dealing with a total-body water determination and its biological half-life.

To conclude, the criticism presented is not substantiated by numerical facts where essential, but instead is based on a series of assumptions and asseverations, making it rather too vague to be constructive.

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