Physiological Basis of the Radioisotope Renogram

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The *renogram*, a test of renal function introduced in 1956 by Taplin *et al.* (1956), is obtained by injecting some substance tagged with radioactivity which accumulates in a relatively selective manner in the kidney. Collimated counters placed over the two kidneys measure the accumulation of radioactivity, and its subsequent decrease. When the counter is connected to automatic recording devices, the curves produced begin at the origin, rise rapidly to a peak, and then fall in an approximately exponential manner. (fig. 3)

Blaufox, Orvis, and Owen (1963) have done a compartment analysis of Hippuran I^{131} in dogs and have suggested that characteristics of the radioisotope renogram may be elucidated by compartment analysis. The present paper is based on a similar compartment analysis. A different model, however, is proposed to describe the renogram. Estimates of the parameters are obtained by the *method of maximum likelihood* rather than by graphical means. In addition, certain implications and possible application of the model, not discussed by Blaufox *et al.*, are developed here.

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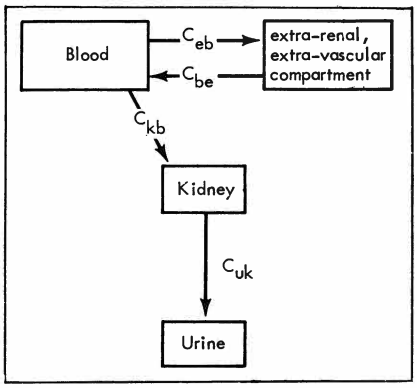

Fig. 1—Ortho-iodohippuran is imagined to mix very rapidly in the blood, and exchange with a non-vascular, non-renal space. It is assumed that a constant fraction of circulating hippuran is removed from the blood by the kidneys per unit time.

The compartment analysis to be done is schematized in figure 1. Berman, Weiss, and Shahn (1962) have published a general treatment of compartment analysis. Sapirstein *et al.* (1955) have proposed the particular analysis used here in deriving the blood curve for use in renal physiology.

The Blood Curve

Assume the injected substance is distributed principally into four compartments during the 20 minute duration of the experiment. These compartments are the blood, kidney, urine, and an extravascular, extrarenal space, and are designated by the subscripts b, k, u, and e, respectively. It is also assumed that:

a) Intravascular mixing takes place very rapidly, compared to exchanges between other compartments.

b) Compartment u exchanges only with k, k only with b and u, and e only with b.

c) The volumes of compartments b, k, and e are each constant.

We may write:

$$v_b\dot{Y}_b = -C_{kb}Y_b + C_{be}(Y_e - Y_b), \quad (1)$$

$$v_e\dot{Y}_e = C_{be}(Y_b - Y_e), \quad (2)$$

where:

v_i = volume of compartment i,

C_{ij} = the volume of compartment j cleared per unit time with transfer to compartment i. No assumptions are made concerning mechanisms of clearance except that $C_{be} = C_{eb}$; that is, there is no asymmetry of mechanism between compartments e and b.

Y_i = concentration of the injected substance in compartment i.

$\dot{Y}_b$ and $\dot{Y}_e$ are time derivatives of Y_b and Y_e, respectively. Equations (1) and (2) are satisfied by

$$Y_b = B_{1b}\exp(\gamma_1 t) + B_{2b}\exp(\gamma_2 t) \quad (3)$$

where t is time, and B_{1b} and B_{2b} are constants chosen to satisfy the initial conditions. γ_1 and γ_2 are the roots of a quadratic equation,

$$x^2 + ((C_{kb}/V_b) + (C_{be}/V_b) + (C_{be}/V_e))x + (C_{be}C_{kb})/(V_eV_b) = 0 \quad (4)$$

The choice of a two-compartment system to describe the blood curve is based on the suggestion of previous workers (Sapirstein *et al.*, 1955) but is here merely illustrative. More general systems might be used instead, and appropriate modifications made in the development which follows.

The Renogram

We consider the total kidney count exclusive of contribution from other tissues over one kidney, y_r to be given by:

$$y_r = C_{kb}' \int_{\tau}^{t} Y_b(s)ds \qquad (5)$$

where s is a time variable of integration
C_{kb}' is the unilateral clearance, assumed to be constant.

$$\tau = \begin{Bmatrix} 0 \text{ for } 0 \leq t < a \\ t - a \text{ for } a \leq t \end{Bmatrix}$$

a is the appearance time of ortho-iodohippuran in the kidney.

The choice of limits of integration in (5) means that we imagine y to be simply accumulating within the kidney until $t - a$. At that time, y begins leaving the kidney and appears in the urine. If there is little or no longitudinal mixing of urine within the tubules, the successively excreted quantities of y in the urine will be just those quantities filtered $t - a$ minutes ago. Imagine an infinitely long train of microscopic box cars, each filled with an amount of y proportional to y_b as it enters the kidney. It takes each box car "a" minutes to leave the kidney. Thus if we want to measure y at some $t \geq a$, we sum up all the y which has entered, and subtract all that came in box cars which entered at some time, $t - a$, and has now left the kidney. That is,

$$y_R = C_{kb}' \left(\int_0^t y_b - \int_0^{t-a} y_b \right) \cdot ds, \; t \geq a, \qquad (6)$$

or

$$y_R = C_{kb}' \int_{t-a}^{t} y_b ds, \; t \geq a. \qquad (7)$$

If we substitute (3) into (5), and integrate, we obtain for $t \geq a$,

$$y_R = A_{1R} \exp(\gamma_1 t) + A_{2R} \exp(\gamma_2 t) \qquad (8)$$

A_{1R} and A_{2R} are constants determined by C_{kb}', γ_1, γ_2, B_{1b}, and B_{2b}. Since, in fact, we may count over tissue and blood as well as over kidney, the counting device will record,

$$Y_R = \alpha_1 y_b + \alpha_2 y_e + \alpha_3 y_R + \alpha_4 y_u \qquad (9)$$

where α_i are constants determined by the positioning of the detector, and the proportion of each compartment will appear in the counting field. Y_R, however, is still a linear combination of the same exponential terms. So we may rewrite (9) as

$$Y_R = B_{1R} \exp(\gamma_1 t) + B_{2R} \exp(\gamma_2 t) \qquad (10)$$

B_{1R} and B_{2R} are constants.

The Urine Curve

Since the ortho-iodohippuran removed from the blood appears a short time later in the urine, we write

$$(C_{uk} y_u)_t = (C_{kb}' y_b)_{t-a}, \qquad (11)$$

where C_{uk} is the urine flow rate. Sodium ortho-iodohippurate excretion (mg per minute) at time t is simply equal to the sodium ortho-iodohippurate cleared by the kidney (mg per minute) at $t - a$. The blood curve is evaluated at $t - a$ to predict the urine curve at t.

$$C_{uk} y_u = C_{kb}' \{ B_{1b} \exp[\gamma_1 (t - a)] + B_{2b} \exp[\gamma_2 (t - a)] \}, \qquad (12)$$

For convenience we rewrite (12) as

$$Y_u = C_{uk} y_u = B_{1u} \exp(\gamma_1 t) + B_{2u} \exp(\gamma_2 t) \qquad (13)$$

Experimental Methods

Experiments were performed on dogs anesthetized with intravenous sodium pentobarbital (30 mgm per kg body weight). Additional doses of anesthetic were given during the experiment as needed. Respiration was maintained with a motor-driven pump following intratracheal intubation. During the preparatory period and throughout the experiment, the animals received a constant intravenous infusion of isotonic saline, or a mixture of equal volumes of isotonic saline and 5% dextrose in water.

Renograms were obtained with a pair of matched scintillation counters (1 x 1 inch thallium-activated sodium iodide crystals), connected to pulse-height discriminators, ratemeters, and a dual linear recorder. A time constant of 10 seconds, and a full-scale setting of 10,000 counts per minute, were employed. All records were obtained with a paper speed of 12 inches per hour. The tracings were allowed to run for 15–20 minutes.

The radioactive material used was I^{131}-labeled sodium ortho-iodohippurate (Hippuran®), obtained from Abbott Laboratories. All renograms were obtained by injecting within 5 seconds 1.5 mc of radioisotope per kg body weight into the vein of a forelimb.

The experimental procedure was as follows: The animal was placed in the supine position and the peritoneal cavity was entered through a midline incision. The ureters were identified, divided at their upper part and their proximal, and cannulated with polyethylene tubing. To minimize dead space, the length of ureteral catheters was kept short and their tips were introduced into or very near to the renal pelvis. Then the right renal artery was dissected free and a Crutchfield clamp was placed around it without constricting the vessel. When urine flow became constant, the probes were placed immediately overlying the exposed kidneys, and control renograms were obtained. The position of the probes remained the same throughout the experiment.

Aortic blood was sampled through a catheter placed into the lower aorta, at 15 second intervals for the first 3 minutes following the injection of iodohippurate, and at 30 second intervals, subsequently. All urine excreted during the inscription of the renogram was collected. Collection periods lasted 15 seconds for the first 3 minutes following the administration of the radioisotope, and 30 seconds, subsequently.

Blood and urine specimens were counted in a scintillation-well counter, for periods long enough to give standard deviations not exceeding 1%. Background and blank counts were subtracted from each count rate.

The urine count rate per second of each specimen was divided by the duration of the period of collection in minutes to obtain the rate of excretion of radioisotope per minute. The data from

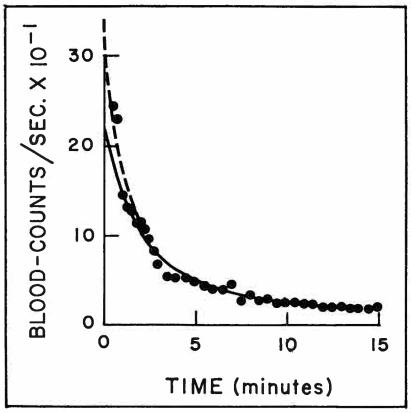

Fig. 2—Counts/sec in 1 ml of blood at various times after injection of I^{131} ortho-iodohippuran. Observed values are shown as points. Estimated values computed as $\hat{Y}_{bj}$ of Table 2 shown by dotted line. Solid line obtained as $\hat{Y}_{bj}(H_0)$ of table 2.

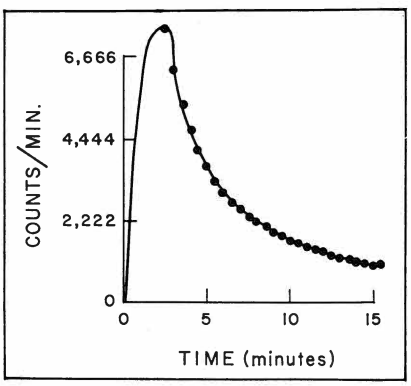

Fig. 3—The renogram from which the points shown in table 3 were obtained. Circled points are the estimates labeled $\hat{Y}_{Rj}(H_0)$ in table 3. The estimates labeled $\hat{Y}_{Rj}$ actually fit somewhat better, but this is not apparent graphically.

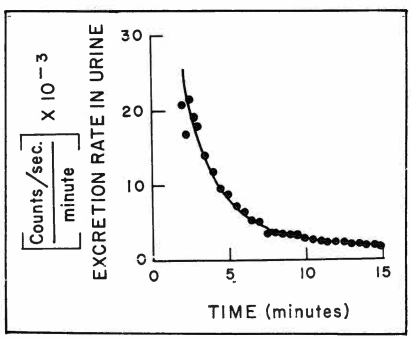

Fig. 4—Observed and estimated (counts/sec) $\times 10^{-3}$ excreted per minute at various times following the injection of I^{131} ortho-iodohippuran. Points are taken from Y_{uj} of table 4. The solid line is estimated in the same manner as $\hat{Y}_{uj}(H_0)$ of table 4.

one such experiment is used in this analysis.

Estimation Procedures

The data obtained for estimating the blood curve (equation 6) consists of N_b points $(1, 2, \cdots, j, \cdots, N_b)$ recorded in counts per ml at successive time points $(t_1, t_2, \cdots, t_j, \cdots, t_{N_b})$.

$$Y_{bj} = B_{1b} \exp(\gamma_1 t_j) + B_{2b} \exp(\gamma_2 t_j) + \epsilon_{bj}\phi_b(t_j), \tag{14}$$

Y_{bj} = counts/ml at time t_j, and
$\epsilon_{bj}\phi_b(t_j)$ = "error;" the ϵ_{bj} are taken to be normally and independently distributed with mean zero and constant variance (for the blood curve) σ_b^2.

For the points on the descending portion of the renogram curve we have

$$Y_{Rj} = B_{1R} \exp(\gamma_1 t_j) + B_{2R} \exp(\gamma_2 t_j) + \epsilon_{Rj}\phi_R(t_j), \tag{15}$$

$\epsilon_{Rj}\phi_R(t_j)$ is as before the error; the ϵ_{Rj} are also taken to be normally and independently distributed with mean zero and constant variance σ_R^2. Because of the 10 second response time of the recorder, and the extremely rapid rise of the renogram curve in its initial phase, it was decided that this portion of the curve was unsuitable for analysis, and only the portion after the peak was used.

The urine data is in counts/min per minute of urine flow. Each datum has the dimensions of $(C_{uk}y_u)$.

$$y_u = \text{concentration of counts in the urine}$$
$$Y_{uj} = (C_{uk}y_u)_j + \epsilon_{uj}\phi_u(t_j), \tag{16}$$

$\epsilon_{uj}\phi_u(t_j)$ is the error and ϵ_{uj} has variance σ_u^2, but is otherwise like ϵ_{bj} and ϵ_{Rj}.

Equations (14), (15), (16) may be summarized as follows:

$$Y_{ij} = B_{1i} \exp(\gamma_1 t_j) + B_{2i} \exp(\gamma_2 t_j) + \epsilon_{ij}\phi_i(t_j); \tag{17}$$
$$i = b, R, u;$$
$$j = 1, 2, \ldots, N_i;$$
$$\phi_i(t_j) = \hat{\hat{y}}_{ij}$$

We will estimate the parameters by the method of maximum likelihood (5). The likelihood function is proportional to

$$e^L = \prod_{i=b}^{u} \prod_{j=1}^{Ni} (2\pi\phi_{ij}^2\sigma_i^2)^{-1/2} \cdot \exp\{-[\epsilon_{ij}\phi_i(t_j)]^2/2\phi_{ij}^2\sigma_i^2\}. \tag{18}$$

$\hat{Y}_{ij}$ is the estimated value of Y at t_j using the maximum likelihood estimates of the parameters appearing in equation (17). Taking the log of (18), and substituting into it ϵ_{ij} from (17), we obtain

$$L = \sum_{i=b}^{u} \sum_{j=1}^{Ni} (-\tfrac{1}{2} \log[2\pi\phi_{ij}^2\sigma_i^2]) - (Y_{ij} - B_{1i} \exp[\gamma_1 t_j] - B_{2i} \exp[\gamma_2 t_j])^2/2\phi_{ij}^2\sigma_i^2 \tag{19}$$

In order to find those estimates of the parameters which maximize L we take

$$0 = \partial L/\partial\gamma_1 = \partial L/\partial\gamma_2 = \partial L/\partial B_{1i} = \partial L/\partial B_{2i}.$$

Papers on fitting equations of compartment analysis have been published by Berman, Shahn, and Weiss (1962), and Berman. A more general approach, of which this problem is a special case, has been made by Turner, Monroe, and Homer (1963). Because equation (14) is non-linear in γ_1 and γ_2, these parameters must be estimated by an iterative procedure. The procedure used in the illustration presented here was as follows:

a) use trial values of $\hat{\phi}_{ij}$, $\hat{\gamma}_1$, $\hat{\gamma}$.
b) estimate $\hat{B}_{1i}$ and $\hat{B}_{2i}$.
c) obtain new estimate of $\hat{\phi}_{ij} = \hat{y}_{ij}$
d) obtain new trial values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.
e) Repeat the previous steps until one finds a $\hat{\gamma}_1$ and $\hat{\gamma}_2$ for which the sum of the squared errors given by

$$\sum_{j=1}^{Ni} = (\epsilon_{ij}\phi_i(t_j))^2 = SSE_i \tag{20}$$

is lower than for other values of γ_1 and γ_2 in the neighborhood of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.

The best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ are found by this procedure for the blood, renogram, and urine, separately. When estimating one curve at a time, no value need be assigned to σ_i^2. After the best values of the parameters B_{1i}, B_{2i}, γ_{1i}, γ_{2i} have been obtained, SSE_i may

be computed, and an estimate of σ_i^2 is given by

$$\sigma_i^2 = SSE_i/(N_i - 4) \qquad (21)$$

Using the combined data to find the values of γ_1 and γ_2 which give the best fit for all three sets of data at once requires a slightly different procedure. First of all, as can be seen from equation (19), σ_i^2 is required. An alternative is to use estimates of σ_i^2 given by (21). This alternative introduces a substantial simplification into the numerical procedure at a cost of some information. ϕ_{ij} is kept constant instead of being re-estimated after each iteration as is done when analyzing the data separately. The values chosen are those used in the last iteration on each separate curve. This restriction is necessary in order to be able to compare SSE_i obtained using the combined estimates of γ_1 and γ_2. Finally a new criterion of fit must be chosen. The best pair of γ's for the combined data was that pair which minimized the weighted least squares criterion S, given by

$$S = \sum_{i=b}^{u} SSE_i'/\hat{\sigma}_i^2, \hat{\sigma}_i^2 = SSE_i/(Ni - 4);$$

SSE_i is the sum of the squared errors for i set of data using the best separate values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$, and SSE_i' is the sum of the squared errors for i set of data using the best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ from the combined data.

A program was written for the RPC 4000 computer to perform the calculations described, and to print out the estimates of the parameters, SSE_i and R^2. R^2 may be interpreted as the percentage of variation in Y_i, which can be accounted for by the hypothesis calculated by

$$R_i^2 = 1 - SSE_i \Big/ \left\{ \sum_{j=1}^{Ni} Y_{ij}^2/\phi_{ij}^2 - \left(\sum_{j=1}^{Ni} Y_{ij}/\phi_{ij}^2 \right)^2 \Big/ \left(\sum_{j=1}^{Ni} \frac{1}{\phi_{ij}^2} \right) \right\} \qquad (22)$$

Results

The data, estimates of parameters and estimates of Y_{ij}, are given in tables 1 to 4 and figures 2 to 4.

An approximate F test may be devised to test the hypothesis that $\gamma_{1b} = \gamma_{1k} = \gamma_{1u}$, and at the same time, that $\gamma_{2b} = \gamma_{2k} = \gamma_{2u}$. Using our previous notation, we have

TABLE 1

Estimates of the parameters and statistics measuring goodness of fit, $\hat{B}_1$, $\hat{B}_2$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ have the same meaning as in the text. Estimates obtained from fitting the γ's with pooled data and assuming $\gamma_{1b} = \gamma_{1k} = \gamma_{1u}$, and at the same time that $\gamma_{2b} = \gamma_{2k} = \gamma_{2u}$, are in the second line of each pair.

	$\hat{B}_1$	$\hat{B}_2$	$\hat{\gamma}_1$	$\hat{\gamma}_2$	Sums of Squares due to Error	Coefficient of Determination	No. of Observations
Blood	26.21	6.25	−.8178	−.0893	31.14	.967	35
	15.94	6.42	−.5517	−.0979	58.28	.939	35
Renogram	58.45	19.60	−.4915	−.1001	3.462	.994	27
	72.94	19.47	−.5517	−.0979	4.267	.992	27
Urine	47.50	3.60	−.4337	−.0489	15.32	.982	29
	55.27	7.22	−.5517	−.0979	18.74	.978	29

$$F = \left\{ \left[\left(\sum_{i=b}^{u} SSE_i'/\hat{\sigma}_i^2 \right) - \left(\sum_{i=b}^{u} SSE_i/\hat{\sigma}_i^2 \right) \right] \Big/ 4 \right\} \Big/ \left(\sum_{i=b}^{u} SSE_i/\hat{\sigma}_i^2 \right) \Big/ 79 = 9.5$$

with 4 and 79 degrees of freedom. We may reject the hypothesis with greater than 99.9% confidence ($P < .001$), in favor of a hypothesis in which some or all of the γ's are different. Attention is called to the high values of R^2. While fitting the γ's separately gives a significantly better fit, it is not much better from the standpoint of the value of R^2. The worst fit found has an R^2 of 0.94. Examination of tables 1 to 3 shows that, except for perhaps the first 5 points on the blood curve, the estimates of Y_i obtained with γ's from pooled data are very close to those obtained with the separately estimated γ's. Although the differences are quite significant, they are rather small. We can be relatively sure that the γ's differ but the differences may not be important.

Discussion

Clinical investigators have attempted to characterize the renogram by measuring the height of the maximum, the time of the maximum, and the "half time" of the descending slope (Stewart and Haynie, 1962). Our model predicts that these measurements are not related in any simple fashion to either the bilateral or unilateral renal clearance of ortho-iodohippurate. According to the model, the height of the maximum, disregarding contribution from other tissues, will be given by

$$Y_R(\max) = C_{kb}'\{ - (B_{1b}/\gamma_1 + B_{2b}/\gamma_2) + [B_{1b} \exp(\gamma_1 a)/\gamma_1 + B_{2b} \exp(\gamma_2 a)/\gamma_2]\}/v_k,$$

from equations (14) and (15). This maximum will depend on renal blood flow since C_{kb}' should approximate unilateral renal blood flow. $Y_R(\max)$ will also depend on the appearance time and bilateral renal blood flow. The relationship of the maximum and the appearance time to bilateral and unilateral clearance is not a simple one. For example, $Y_R(\max)$ might be unchanged in spite of a decrease in unilateral clearance if the appearance time were prolonged. The time required for the renogram to fall from its maximum to one-half the maximum is often referred to as the half-time of the renogram. Since the proposed hypothesis describes the renogram as the sum of two exponential functions, no simple interpretation of the meaning of this half time is possible in terms of the fundamental parameters.

Ortho-iodohippurate clearances are considered rather direct measures of renal blood flow. A scheme for analysing

TABLE 2

Observed and estimated counts/sec-ml in the blood at t_j minutes after injection of I^{131} ortho-iodohippuran. Y_{bj}, $\hat{Y}_{bj}$, and $\hat{Y}_{bj}(H_0)$ are reported in counts/sec $\times 10^{-1}$ for one ml of blood. Y_{bj} are the observed values. $\hat{Y}_{bj} = \hat{B}_{1b} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2b} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1b}$, $\hat{B}_{2b}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from the top line of table 1. $Y_{bj}(H_0)$ is computed as Y_{bj} except that B_{1b}, B_{2b}, γ_1, and γ_2 are taken from the second line of table 1.

t_j	Y_{bj}	$\hat{Y}_{bj}$	$\hat{Y}_{bj}(H_0)$
0.5	24.3	23.4	18.2
0.75	22.9	20.0	16.5
1.0	14.3	17.3	15.0
1.25	13.2	15.0	13.7
1.5	12.9	13.2	12.5
1.75	11.2	11.6	11.48
2.0	11.4	10.3	10.57
2.25	10.6	9.27	9.76
2.5	9.5	8.39	9.04
2.75	7.1	7.65	8.40
3.0	6.5	7.03	7.83
3.5	5.2	6.07	6.87
4.0	5.0	5.37	6.09
4.5	5.1	4.84	5.46
5.0	4.7	4.44	4.94
5.5	4.2	4.11	4.51
6.0	3.9	3.85	4.15
6.5	3.9	3.63	3.84
7.0	4.3	3.43	3.57
7.5	2.8	3.25	3.34
8.0	3.1	3.10	3.13
8.5	2.8	2.95	2.94
9.0	2.9	2.81	2.77
9.5	2.3	2.69	2.62
10.0	2.5	2.56	2.48
10.5	2.5	2.45	2.34
11.0	2.2	2.34	2.22
11.5	2.2	2.24	2.11
12.0	2.0	2.14	2.00
12.5	2.0	2.05	1.90
13.0	2.0	1.96	1.81
13.5	1.8	1.87	1.72
14.0	1.8	1.79	1.64
14.5	1.7	1.71	1.56
15.0	1.9	1.64	1.48

TABLE 3

Observed and estimated (counts/min)/222.2 of renogram t_j minutes after injection of I^{131} ortho-iodohippuran. Y_{Rj} are obtained from the renogram in figure 3. $\hat{Y}_{Rj} = \hat{B}_{1R} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2R} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1R}$, $\hat{B}_{2R}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from line 3 of table 1. $\hat{Y}_{Rj}(H_0)$ is obtained using the estimates in line 4 of table 1.

t_j	Y_{Rj}	$\hat{Y}_{Rj}$	$\hat{Y}_{Rj}(H_0)$
2.5	32.5	32.3	33.6
3.0	27.5	27.9	28.4
3.5	23.8	24.2	24.4
4.0	22.3	21.3	21.1
4.5	19.2	18.9	18.6
5.0	17.0	16.9	16.6
5.5	14.9	15.2	14.9
6.0	13.4	13.8	13.5
6.5	12.4	12.6	12.3
7.0	11.4	11.6	11.3
7.5	10.6	10.7	10.5
8.0	10.2	10.0	9.8
8.5	9.7	9.3	9.1
9.0	9.0	8.7	8.6
9.5	8.4	8.1	8.1
10.0	7.3	7.6	7.6
10.5	6.9	7.2	7.2
11.0	6.6	6.8	6.8
11.5	6.3	6.4	6.4
12.0	6.2	6.1	6.1
12.5	6.0	5.7	5.8
13.0	5.8	5.4	5.5
13.5	4.9	5.2	5.2
14.0	4.7	4.9	5.0
14.5	4.3	4.6	4.7
15.0	4.5	4.4	4.5
15.5	4.4	4.2	4.3

renograms which would permit estimates of these clearances to be made might prove of great clinical value. Using the model presented here, we are able to suggest several different approaches to the analyses of the renogram which should provide such information. While the analyses suggested involve procedures more complicated than merely measuring the "half time," the appearance time, or the height of the maximum, much is to be gained in simplicity of interpretation since the analyses provide estimates of bilateral and unilateral clearances, while no such fundamental information may be easily obtained from the simple measurements referred to above. It is hoped that the more precise and more easily interpreted information thus obtained from the renogram would be of sufficient clinical importance to justify somewhat more complicated analyses than have been previously attempted.

Bilateral renal function may be assessed with γ_1 and γ_2. From the relationship of equation (4)

$$\gamma_1\gamma_2 = C_{kb}C_{be}/v_e v_b\,, \qquad (23)$$

$$\partial(\gamma_1\gamma_2)/\partial C_{kb} = C_{be}/v_e v_b\,. \qquad (24)$$

The left member of (24) is always positive so that a decrease in C_{kb} should be reflected in a decrease in $\gamma_1\gamma_2$. Perhaps persons having decreased total renal blood flow will have unusually low values of $\gamma_1\gamma_2$. Also from equation (4) we have,

$$\gamma_1 + \gamma_2 = -(C_{kb}/v_b + C_{be}/v_e + C_{be}/v_b), \qquad (25)$$

$$\partial(\gamma_1 + \gamma_2)/\partial C_{kb} = -\frac{1}{v_b} \qquad (26)$$

As C_{kb} decreases, $\gamma_1 + \gamma_2$ increases (becomes less negative). Thus, in general, persons with low renal blood flows might be expected to have values of $\gamma_1 + \gamma_2$, less negative than persons with higher renal blood flows.

The two parameters γ_1 and γ_2 could be determined in "normal" patients, and changes in $\gamma_1\gamma_2$ and $\gamma_1 + \gamma_2$ might be simply interpreted as changes in clearance. If the blood curve were also determined, it would be possible to obtain numerical estimates of bilateral renal blood flow, compartment volumes, and compartment exchange rates, using

TABLE 4

Observed and estimated (counts/sec) $\times 10^{-3}$ excreted each minute in the urine t_j minutes after the injection of I^{131} ortho-iodohippuran. $\hat{Y}_{uj}$ are the observations. $\hat{Y}_{uj} = \hat{B}_{1u} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2u} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1u}$, $\hat{B}_{2u}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from line 5 of table 1. $\hat{Y}_j(H_0)$ was calculated using the estimates in the last line.

t_j	Y_{uj}	$\hat{Y}_{uj}$	$\hat{Y}_{uj}(H_0)$
2.0	20.8	23.2	24.3
2.25	16.8	21.1	21.8
2.5	21.5	19.2	19.6
2.75	19.1	17.6	17.6
3.0	18.0	16.0	15.9
3.5	14.0	13.4	13.1
4.0	11.82	11.3	11.0
4.5	9.68	9.63	9.26
5.0	7.87	8.24	7.93
5.5	7.05	7.12	6.87
6.0	6.36	6.20	6.03
6.5	5.24	5.45	5.35
7.0	5.07	4.83	4.80
7.5	3.51	4.33	4.35
8.0	3.72	3.91	3.97
8.5	3.63	3.56	3.64
9.0	3.33	3.27	3.38
9.5	3.24	3.03	3.14
10.0	2.86	2.82	2.93
10.5	2.79	2.65	2.75
11.0	2.46	2.50	2.59
11.5	2.35	2.37	2.44
12.0	2.34	2.26	2.30
12.5	2.14	2.16	2.18
13.0	2.03	2.07	2.06
13.5	2.03	1.99	1.96
14.0	1.98	1.92	1.86
14.5	1.87	1.86	1.76
15.0	1.69	1.80	1.68

the equations of Sapirstein *et al.* (1955). With the additional information from the renogram, unilateral renal blood flows could also be computed.

Because of the contribution from adjacent tissues to renogram counts, the value of B_{1R} and B_{2R} in evaluating unilateral function is a more complicated matter. Some investigators (Block, Hine, and Burrows, 1960) have already found Y_R(right)/Y_R(left) to be a useful index of differences in function between the two sides. This suggests that B_{iR}(right)/B_{iR}(left) might also be useful.

As already said, the F test assures us that the best fitting γ_{1i}'s and γ_{2i}'s are not identical, as the model requires. There are several possible explanations for this. The rejection is largely due to difficulties with the early part of the blood curve (fig. 2), and thus might be partly explained by difficulties in exact timing, where a very few seconds may make a large difference in the activity of the blood sample in a period. Also to be explored are the possible effects of changing blood flow (C_{kb}, C_{kb}' not constant), and changing appearance time. If the model fitted to available data is indeed such a sensitive measure of variations in renal blood flow or urinary appearance time, it may prove to be a valuable tool in studying these variations, and in studying relationships between these two parameters.

Summary and Conclusions

A model elucidating the relationships between blood radioactivity, the renogram curve, and urine radioactivity, as a function of time, is derived. Estimation procedures have been devised which use the data from three curves at once to estimate parameters common to the three curves, and which also estimate parameters unique to the individual curves. A program has been written for the RPC 4000 computer to perform the estimation.

It was found that some model in which six different exponential parameters could be justified instead of the two proposed by the model could provide a significantly better fit of the data ($P < .001$), but that the fit under the hypothesis was still quite good. It is proposed that the model be retained for further evaluation and study for the following reasons:

1. It is based on soundly established principles of physiology, and hence provides a link between the renogram curve and those principles.

2. The model fits the descending part of the curve well.

3. On the basis of the model we are able to suggest several improvements in the analysis of renograms for clinical evaluation of renal function.

4. The model leads to reasonable estimates of the time of the renogram peak.

5. The model provides a framework for further study of the renogram and its relations to physiologic function in general. More specifically, it may prove to be a sensitive instrument in studying rapid variations in urinary appearance time and renal blood flow, and the relations between blood flow and appearance time.

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